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## **Physical activity and stroke among women - a non-linear relationship**

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## ***Abstract***

Studies have identified non-linear inverse relationships between physical activity and the risk of stroke. A U-shaped response has been observed between haemorrhagic stroke and physical activity. The objective of this study was to investigate the associations between physical activities on stroke. We used data from the E3N cohort study, a French prospective study of women initiated in 1990. From the women in the study, we included those without cardiovascular disease or cancer at baseline, resulting in 94,169 women. We assessed total physical activity in 1993, grouped as quartiles. Cox models adjusted for potential confounders were used to assess the relationship with stroke, considering cases until 2008. Splines were used to assess the shape of the response. Similarly, we then considered high and low-intensity physical activity grouped as tertiles.

Among the included women, with a mean age of  $51.2 \pm 6.7$  years, 592 cases of stroke were identified over an average follow-up time of 16.2 years. Total physical activity was associated with a lower stroke risk ( $HR_{Q1-Q4} = 0.38 [0.30, 0.49]$ ). An inverse relationship was observed between physical activity and all stroke sub-types. A non-linear (L-shaped) relationship was observed for all-stroke, and ischemic stroke, and a U-shaped response for sub-arachnoid and intracerebral haemorrhage. High-intensity activities were associated with a U-shaped response for haemorrhagic stroke types. Low-intensity activities were associated with a linear response for all stroke types

Our results support other observations that physical activity may reduce stroke risk. U-shaped responses were observed between physical activity and haemorrhagic stroke.

**Keywords: Stroke, Physical exercise, Epidemiology**

## **Introduction**

Stroke is a leading cause of death and disability [1,2], with a higher burden in females than males, partly due to their higher longevity. Up to 20 % of women will have a stroke during their lifetime, and women typically suffer poorer outcomes than males, with a 1.25 times higher risk of fatal stroke [3].

Previous studies and meta-analysis have identified a non-linear relationship between the risk stroke and total physical activity [4,5]. Physical inactivity is one of the major risk-factors for stroke [1,3,6–8], and small amounts of activity can reduce the risk. However, some studies have reported a U-shaped response for haemorrhagic stroke [9], with diminishing returns from very high levels of physical activity. The type of physical activity may be important in this setting, as it is unclear how the intensity of these activities may be related to stroke risk, and to stroke sub-types.

We aimed to assess the shape of the relationship between physical activity and stroke, and to assess the associations for both high and low-intensity physical activity.

## **Methods**

### **Study Population**

The E3N ([www.e3n.fr](http://www.e3n.fr)) [10] is a French prospective cohort started in 1990 comprising 98,995 women aged 40-65 years at baseline and insured by the MGEN, a health insurance plan for employees of the French education system and their families. The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom (Commission Nationale Informatique et Libertés), and all participants in the study signed an informed consent form. Participants returned questionnaires every 2 to 3 years

(1992, 1993, 1995, 1997, 2000, 2002, 2005, 2008). The average response rate at each questionnaire cycle was 83 %, and the total loss to follow-up was 3%.

We excluded women with prevalent stroke or cardiovascular disease (n = 1345, including 136 cases of stroke) at baseline, those who did not complete questionnaires after baseline (n = 728), and women with unrealistic physical activity (99<sup>th</sup> percentile of the distribution in the population, n= 918), or BMI (1st and 99th percentile of the population (n = 1835)). The final study population included 94,169 women.

### **Physical activity estimates**

We assessed total physical activity with a questionnaire in 1993 that included questions on weekly hours spent walking, cycling, and performing light and heavy household chores, or recreational activities and sports (e.g., swimming and tennis) considering the winter and summer seasons. It included questions on the time spent walking (to work, shopping, and leisure time), cycling (to work, shopping, and leisure time), housework, and sports activities (such as racket sports, or swimming).

Each activity was assigned a Metabolic equivalents (METs) value based on values from the Compendium of Physical Activities [11]. These included MET values of 3.0 for household activities and cleaning, 3.0 for walking, 6.0 for cycling, and 6.0 for sports. For analysis, total physical activity was considered as quartiles based on the population distribution. Sub-types of physical activity were considered as high-intensity (i.e. sports), and low-intensity (i.e. walking, gardening, and housework/cleaning, cycling), and grouped as tertiles. For high-intensity activities/sports, those reporting none (zero hours per week) were assigned as the first tertile, and the remaining women placed into the remaining two depending on their level

of activity. Cycling was considered non-vigorous due to the low number of women reporting cycling, and the relatively low values reported for those who did.

### **Stroke assessment**

Stroke was self-reported at each questionnaire by the study participants. Following the identification of a self-reported event, both the participant and the general practitioner of the study participant were contacted in order to acquire additional information and documentation (hospital discharge reports, medical imaging reports, reports of other ancillary exams conducted in relation with the event) needed to validate and characterize the event. Causes of death were obtained from the French National Service on Causes of Death, and strokes were identified according to ICD-9/10 codes. Fatal stroke were considered if the primary cause of death was stroke. Fatal and non-fatal strokes were validated by certified stroke neurologists working in the group. We considered cases as ischaemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage, and stroke of unknown type if information was insufficient. Specific details of the validation process are presented in the supplementary material.

### **Assessment of covariates**

Covariates were assessed at the 1992 questionnaire, in order to temporally separate them from the physical activity assessment, and reduce the likelihood that they introduce bias to this estimate. Self-reported height and weight from the 1992 questionnaire were used to calculate body mass index (BMI), defined as weight (kg) divided by squared height (m<sup>2</sup>). Family history of hypertension (yes/no), education (no high school diploma, high school diploma), and smoking (ever smoker, current smoker, or never smoker) were based on self-reports, and for diabetes (yes/no) we used cases which had been later validated through the

use of a detailed algorithm and a drug reimbursement database at 2004 [12]. From a dietary questionnaire in 1993, mean daily intakes of energy (excluding energy from alcohol), alcohol, and macro- and micronutrients were estimated. A Mediterranean dietary score was determined using principal component analysis [13].

The use of menopausal hormone therapy (MHT) was assessed at baseline, using a booklet containing photos of all types of oestrogens and progestogens. Age at menopause was defined as either age at last menstrual period, age at bilateral oophorectomy, self-reported menopause, age at start of MHT, or the age at the start of menopausal symptoms.

### **Statistical analysis**

Cox proportional hazard models with age as the timescale and total physical activity quartiles as the exposure, considering the lowest group as the reference, were used to assess the risk of incident stroke, including subtypes (ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage). Time at entry was the age at the beginning of follow-up (1993), exit time was the age when participants were diagnosed with stroke, died (dates of death were obtained from the participants' medical insurance records), were lost to follow-up, or were censored at the end of the follow-up period (June 30, 2008), whichever occurred first. P-values for trends were calculated using the quartile median value as a pseudo-continuous variable in the model. Models were initially adjusted for hypertension at baseline (yes/no), dyslipidaemia at baseline (yes/no), diabetes at baseline (yes/no), smoking status (current/ex/never), family history of cardiovascular disease (yes/no), education level (high-school/no high-school), menopause and MHT usage at baseline (both yes/no), and on BMI (continuous). The proportional hazards assumption was assessed graphically, by plotting the Schoenfeld residuals. We then considered total physical activity as a penalised spline term with three degrees of freedom in a cox model. The relationship between physical activity and

all-stroke was then visualised by plotting the spline term against the estimated hazard from the cox model, which was adjusted as previously described. We then conducted analysis grouping activities as vigorous (i.e. sports), and non-vigorous (i.e. walking, gardening, housework/cleaning, and cycling) in tertiles as a secondary analysis (mutually adjusted).

In a sensitivity analysis, we included only women who responded to a dietary questionnaire in 1993 (n resting = 70,975 , cases = 456), and controlled the models for total calories consumed, alcohol, and Mediterranean diet score. We also excluded cases occurring within 2 and 5 years to explore the possibility of reverse causality.

All statistical analyses used R version 3.5.1 ([www.r-project.org](http://www.r-project.org)) and the survival package ([www.github.com/therneau/survival](http://www.github.com/therneau/survival)), with an alpha of statistical significance equal to 0.05. Data are reported as mean (standard deviation), or as percentages.

## **Results**

At baseline, the 95,405 women in the study were on average 51.2 (6.7) years old, 35.2 % had hypertension, 5.6 % had dyslipidaemia, and 0.9 % had diabetes. Average physical activity in the cohort was 50.2 (28.1) MET-h/week at baseline, and BMI was 22.8 (3.3) kg/m<sup>2</sup>.

Characteristics based on the physical activity groups are presented in table 1. Over an average of 16.2 (0.7) years of follow-up, 592 cases of incident stroke were identified and verified, occurring at an average age of 64.5 (8.1) years (min: 44.3, max: 83.4). These included 196 cases of fatal stroke (90 cases of intracerebral haemorrhage, 35 subarachnoid haemorrhage, 21 ischemic events, 50 of unknown aetiology), and 396 non-fatal strokes ( 255 cases of ischemic events, 41 cases of intracerebral haemorrhage, 50 cases of subarachnoid haemorrhage, and 49 events of unknown aetiology).



Considering physical activity in quartiles, the fourth was associated with a lower risk of stroke than the first quintile ( $HR_{Q1-Q4} = 0.38 [0.31: 0.49]$ ). Results were consistent when considering all stroke subtypes (Ischaemic stroke  $HR_{Q1-Q4} = 0.30 [0.20: 0.41]$ , Intracerebral haemorrhage  $HR_{Q1-Q4} = 0.50 [0.30: 0.81]$ , Subarachnoid haemorrhage  $HR_{Q1-Q4} = 0.50 [0.27: 0.89]$ ).

In spline regression (figure 1), the association was non-linear and L-shaped, with a higher rate of risk reduction in the lower levels of physical activity, and flattening for higher levels of physical activity. The same L-shaped curve was observed as for ischemic stroke, but both types of haemorrhagic stroke showed a U-shaped response.

In sensitivity analysis, considering women who completed the dietary questionnaire, controlling for calories, alcohol and Mediterranean dietary score, results were similar (All stroke  $HR_{Q1-Q4} = 0.39 [0.30: 0.51]$ ). When excluding cases within 2 and 5 years of baseline, results were consistent (excluding 2-years  $HR_{Q1-Q4} = 0.38 [0.30: 0.49]$ , excluding 5-years  $HR_{Q1-Q4} = 0.39 [0.31: 0.50]$ ).

For high-intensity physical activity the lowest risk was observed in the second tertile ( $HR_{Q1-Q2} = 0.67 [0.54: 0.83]$ ,  $\leq 1.3$ h of sport weekly or 7.6 METS-h/wk), with a non-significant reduction of risk in the third tertile ( $HR_{Q1-Q3} = 0.87 [0.72: 1.06]$ ,  $> 1.3$ h of sport weekly or 7.6 METS-h/wk). Low-intensity activities were associated with a reduced risk of stroke risk only in the third tertile ( $HR_{Q1-Q3} = 0.45 [0.36: 0.55]$ ,  $> 50.2$  METS-h/wk).

When considering specific types of stroke, high-intensity activities were associated with a reduced risk of ischaemic stroke ( $HR_{Q1-Q3} = 0.73 [0.55: 0.98]$ ) and u-shaped response for subarachnoid haemorrhage ( $HR_{Q1-Q2} = 0.30 [0.15: 0.59]$ ,  $HR_{Q1-Q3} = 0.70 [0.43: 1.15]$ ), but no association with intracranial haemorrhage ( $HR_{Q1-Q2} = 0.97 [0.63: 1.50]$ ,  $HR_{Q1-Q3} = 1.28 [0.85:$

1.93]). Low-intensity activities were associated with a reduction of all stroke sub-types (ischaemic stroke:  $HR_{Q1-Q3} = 0.35$  [0.26: 0.48], sub-arachnoid haemorrhage:  $HR_{Q1-Q3} = 0.48$  [0.28: 0.82], intracranial haemorrhage:  $HR_{Q1-Q3} = 0.47$  [0.30: 0.73]).

## **Discussion**

Physical activity was inversely associated the risk of stroke in this large cohort of women. The association was L-shaped for overall, and ischaemic stroke, showing a steep reduction in risk for medium levels of physical activity, which levelled off at around 50 MET-h / week. For intracerebral haemorrhagic the response was U-shaped and was U-shaped, but less pronounced for subarachnoid haemorrhage. Low-intensity activities made up the majority of METS-h in this population, and despite relatively low partaking in sport in this cohort, participation at around one hour per week was associated with a modest reduction in stroke risk. High levels of low-intensity activities (i.e. much higher METS values) such as walking and gardening were associated with an even lower risk of stroke. These results suggest that medium levels of high-intensity activities, in combination with high levels of other lower-intensity activities could be optimal for reducing stroke risk in middle aged and elderly women.

This study confirms the non-linear associations previously observed between stroke risk and total physical activity [4,5]. As reported in other studies [9], we observed a U-shaped relationship between haemorrhagic stroke and total physical activity as demonstrated in spline modelling, and an L-shaped response for ischaemic stroke. The U-shaped response for haemorrhagic stroke types was likely driven by high-intensity activities.

Physical activity is one means of increasing energy expenditure, which can result in weight loss, helping control one of the major stroke risk factors – obesity [14]. Physical activity is

also a means of reducing blood pressure [15], and improving glucose metabolism and blood lipid profiles[16], which aids in the control of the other major stroke risk factors. High-intensity physical activity is known to cause acute increases in blood-pressure [17]. Previous studies have suggested that high-intensity physical activity could trigger intracerebral and subarachnoid haemorrhage through increases in blood pressure [9,18], which could explain our observations. Similarly, physical activity can cause the rupture of atherosclerotic plaques [19,20], which could explain the u-shaped associations between high-intensity activity and ischaemic stroke.

Kubota et al [9] observed no apparent benefit from high-intensity activity on haemorrhagic stroke. Similarly, our results showed no apparent benefit from high-intensity activities on intracranial haemorrhage, and a U-shaped association with sub-arachnoid haemorrhage. Those women undertaking a lot of low-intensity activities were observed to have a lower risk of all stroke sub-types. These results would suggest that for elderly and late middle aged women, partaking in some sports, and maintaining a high-level of physical activity in day to day life could be an effective way to reduce stroke risk. This could be obtained by regular walking or cycling in replacement of driving for short trips, as well as one session of sports per week. These observations may not be applicable to younger women, who would presumably have fewer cardiovascular risk-factors.

The strengths of this study include its prospective design, large cohort, and detailed validation algorithm for stroke events. We obtained estimates of total physical activity before the onset of stroke, and controlled for a number of confounding variables. A unique strength of this study is the ability to separate physical activity and BMI measurements by 1 year, reducing the likelihood that BMI is affecting physical activity and introducing bias to the hazard ratio estimates. Similarly, as controlling for BMI may introduce collider bias through

calorific intake, the sensitivity analysis controlling for nutritional variables reduces the suspicion of this bias having occurred. This study does however have a number of limitations including the use of self-reported measures of physical activity, which may be inaccurate. Only a single measurement of physical activity was used, which may be subject to change as the participants age. Future work can consider changes in physical activity or cumulative means of activity over time. Previous studies have found that decreases in activity are associated with worse cardiovascular risk profiles [21], and increases are associated with a reduced risk of cardiovascular disease [22]. Another limitation is the low number of stroke cases, given such a large population. This can be partly explained by the low-risk profile of women in this cohort, and by the strict validation procedure used for cases. The proportion of fatal strokes was high, at around 30 %, which is likely due to a number of non-fatal cases not being considered due to lacking information for validation. There is the possibility of residual confounding, but it is unlikely to account for the strong associations observed, given we observed consistent results in various sensitivity analysis. As mentioned, these results may not generalise to younger populations.

In conclusion, high levels of total physical activity are associated with a lower risk of stroke, with the associations offering diminishing returns for the very high levels of physical activity, especially for haemorrhagic stroke types. Partaking in around 1 hour of sport or vigorous exercise per week, in combination with other forms of less-vigorous exercise could be optimal for reducing stroke risk in elderly and middle-aged women.

## **Declarations**

We gratefully acknowledge the contribution of all the participants in the E3N study for their diligence and their answers. We thank Nassira Allili and Sabrina Schilling for their precious assistance in the stroke validation procedure.

The authors have no conflicts of interest to declare.

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Table 1

Participant characteristics of whole cohort, and depending on physical activity at baseline

	Whole cohort (n = 94,169)	Physical activity (METS-h / week)			
		Q1 (< 29.8) (n = 23,663)	Q2 (29.8 – 44.8) (n = 23,587)	Q3 (44.8 – 66.5) (n = 23,514)	Q4 (> 66.5) (n = 23,405)
Age (years)	51.2 (6.6)	50.6 (6.3)	50.7 (6.5)	51.3 (6.7)	52.3 (7.0)
BMI (kg/m <sup>2</sup> )	22.8 (3.0)	22.9 (3.1)	22.7 (2.9)	22.7 (2.9)	22.8 (2.9)
Sports (hours / wk)	1.1	0.4 (0.6)	0.9 (0.9)	1.3 (1.4)	2.0 (2.0)
Walking (hours / wk)	4.0	1.7 (1.5)	3.0 (2.3)	4.5 (4.0)	6.7 (4.6)
Gardening (hours / wk)	1.7	0.5 (0.7)	1.1 (1.1)	1.8 (1.8)	4.6 (4.0)
Housework/cleaning (hours / wk)	6.6	2.6 (2.0)	4.8 (2.9)	7.1 (4.2)	8.9 (4.9)
Cycling (hours / wk)	0.5	0.1 (0.3)	0.3 (0.5)	0.5 (0.9)	0.9 (1.4)
Menopausal at baseline (%)	48.4	44.6	44.8	49.1	55.1
Ever use of MHT(%)	42.7	42.6	43.6	43.3	41.3
Hypertension (%)	35.0	34.5	32.8	35.4	37.3
Dyslipidaemia (%)	5.6	4.4	4.7	6.1	7.2
Diabetes (%)	0.9	0.9	0.7	0.9	1.0
Family history of CVD (%)	30.3	27.6	29.6	31.7	32.2
University education (%)	34.8	38.9	35.8	33.6	30.8

Current smoker (%)	14.4	15.6	14.4	14.2	13.3
Ex-smoker (%)	32.0	32.0	33.1	32.3	30.7
Never smoker (%)	53.6	52.4	52.5	53.5	56.0

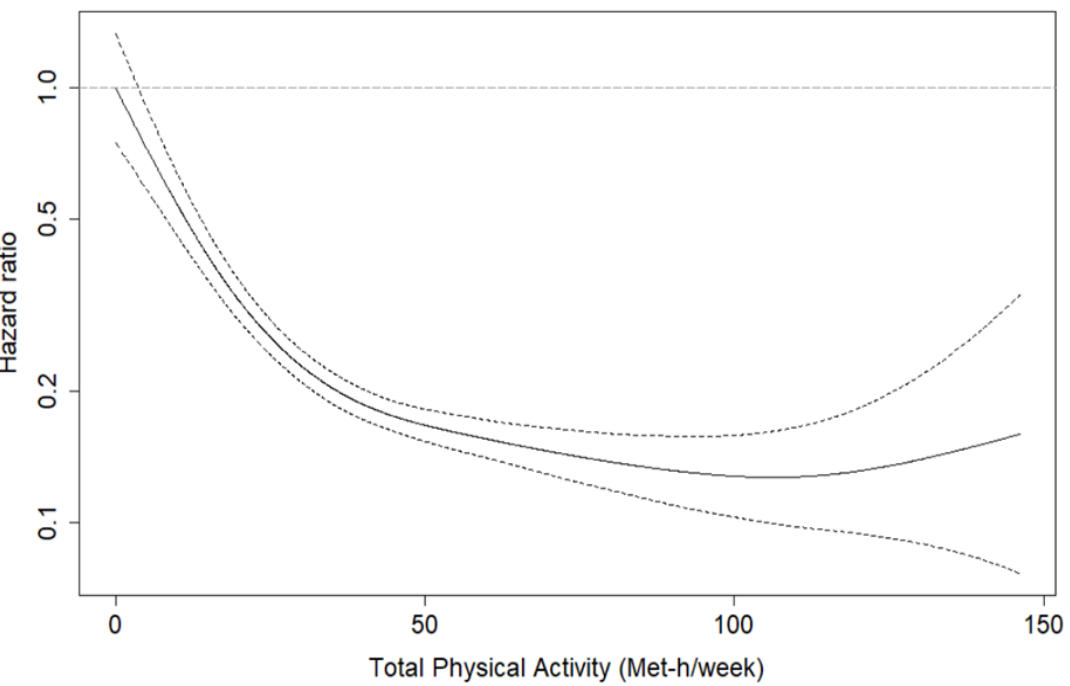
## Figures

### Figure 1

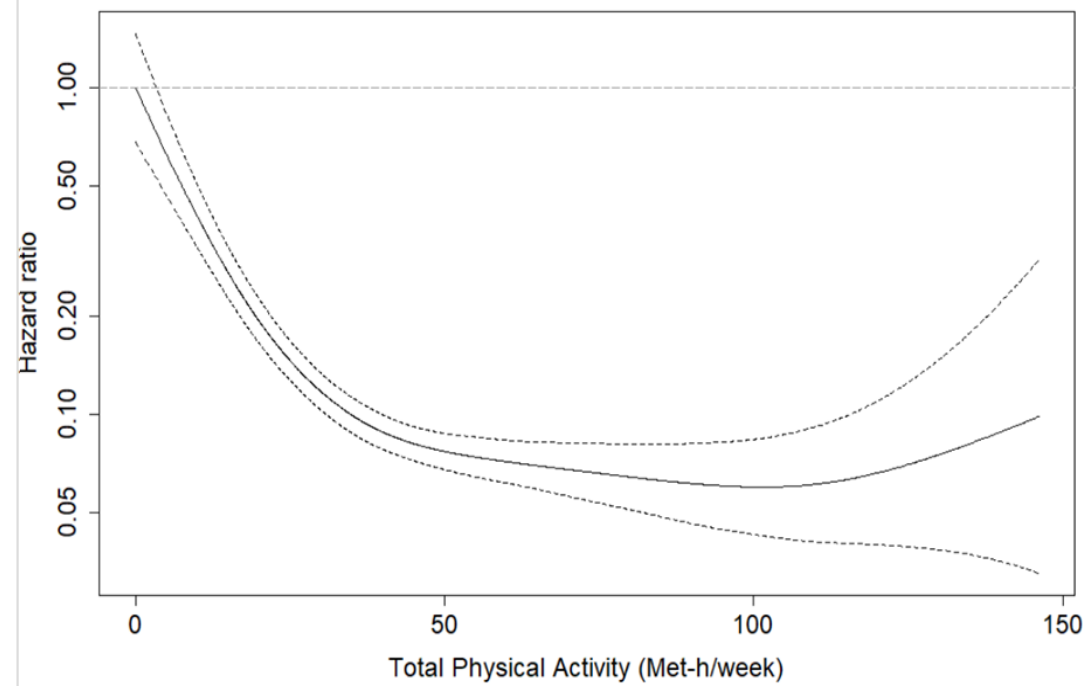
Spline analysis showing the relationship between total physical activity and total stroke (A), ischaemic stroke (B), and intracerebral haemorrhage (C), and subarachnoid haemorrhage (D).



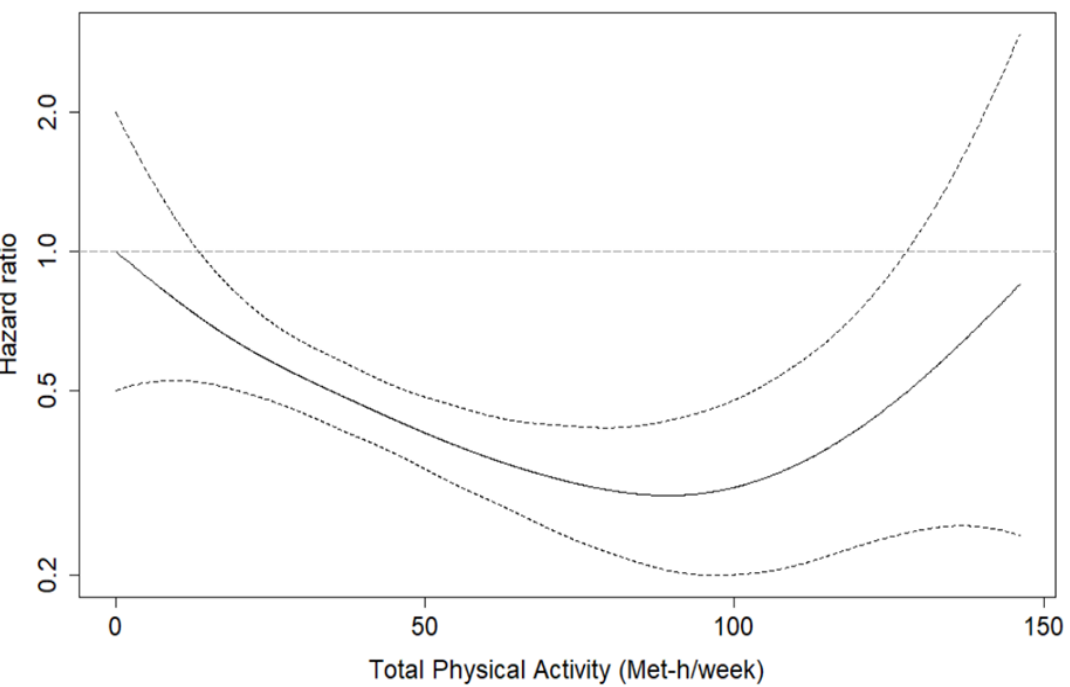
(A) All stroke



(B) Ischaemic stroke



(C) Intracerebral haemorrhage



(D) Subarachnoid haemorrhage

