Systematic review

Risk of stroke with different levels of leisure-time physical activity: a systematic review and meta-analysis of prospective cohort studies

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2023-332457).

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Received 20 August 2023
Accepted 10 December 2023

To cite: De Santis F, Romoli M, Foschi M, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2023-332457

ABSTRACT

Background Leisure-time physical activity (LTPA) protects against vascular diseases. Whether and to what extent different levels of LTPA, including lower ones, benefit stroke prevention is still unclear.

Methods We searched prospective cohort studies, indexed on PubMed and Scopus, published in English up to 22 April 2023, that investigated, in a general healthy population, the relationship between different predefined LTPA levels, compared with inactivity, and the risk of any type of stroke. We applied random effect modelling for meta-analyses and meta-regression to control for the impact of age and sex.

Results Out of 3064 screened articles, 15 articles on 16 cohorts of subjects were included in meta-analyses, with a total of 752 050 followed-up subjects. Mean follow-up was 125.7±77.5 months. Included studies identified three (none, below target and ideal) to five (none, insufficient, low, moderate and intense) levels of LTPA. In the five studies identifying three levels of LTPA, compared with no LTPA, below target (risk ratio (RR)=0.82, 95% CI=0.75 to 0.88) and ideal LTPA significantly reduced stroke risk (RR=0.71, 95% CI=0.58 to 0.86).

Lower levels of LTPA also mitigated stroke risk in studies reporting on four (n=6; RR=0.73, 95% CI=0.62 to 0.87 favouring moderate LTPA over no LTPA) and five levels (n=2; RR=0.71, 95% CI=0.58 to 0.88 favouring moderate LTPA over no LTPA). The benefits of LTPA were independent of age and sex.

Conclusions According to our results, all levels of LTPA can be beneficial for stroke prevention, including levels currently regarded as low or insufficient. People should be encouraged to be physically active even at the lowest levels.

PROSPERO registration number CRD42023425302.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Moderate to high leisure-time physical activity decreases the risk for stroke. However, research gaps exist in understanding the protective effects of low leisure-time physical activity and its association with stroke subtypes, age, and sex.

WHAT THIS STUDY ADDS

⇒ Our study showed that even low levels of leisure-time physical activity can prevent stroke in the long term and that the effect of physical activity is independent of sex and age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our data might contribute promoting campaigns to encourage physical activity in the general population and even in subjects who can meet the goals of physical activity only in part.

INTRODUCTION

Stroke represents a leading cause of morbidity and mortality in the worldwide population resulting in significant individual, social and economic burden[1]; therefore, primary stroke prevention remains an important goal in the worldwide agenda.

Despite some conflicting results, most observational studies have demonstrated that physical activity (PA) is associated with reduced stroke risk. PA can be performed in a wide range of intensities, duration and frequency. To compute the level of PA, studies mainly considered leisure-time physical activity (LTPA, or structured PA or properly called exercise), excluding or separating the occupational PA (also called incidental, as the result of daily activities at work and home).[2–4] There is a clear benefit of moderate–high level of LTPA to prevent both stroke incidence and mortality.[4] The magnitude of the effect is considerable: highly active individuals have a 21% lower risk of ischaemic stroke and a 34% lower risk of haemorrhagic stroke when compared with low-active individuals.[3 4] Several biological mechanisms can explain the beneficial role of PA in preventing stroke, including increased levels of neurotrophins (such as brain derived neurotrophic factor and insulin-like growth factor 1) involved in neuroprotection, promotion of neoangiogenesis, synaptic plasticity, neurogenesis, anti-inflammatory and antithrombotic processes.[5] PA has been also shown to have indirect beneficial effects by counteracting common cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes and obesity.

International recommendations suggest ≥150 min per week of moderate activity or ≥75 min per week of vigorous activity to prevent all cardiovascular diseases, including stroke.[6] There is evidence of a dose–response effect of LTPA for the primary prevention of ischaemic stroke[7]; the higher level of LTPA provides the better prevention. However, a dose–response effect of LTPA was found for stroke only, as the association between LTPA and cardiac disease is most likely U-shaped and too much LTPA might increase cardiovascular risk.[8] Besides, despite the beneficial effects of PA on the risk of stroke and many other diseases, there are several reports showing that adequate levels of LTPA are not met by the general population.[9] According to the American Heart Association 2023 report, only one healthy adult out of four achieves the minimum LTPA level recommended by guidelines.[10] The potential benefits of smaller than the recommended target amounts of LTPA is unclear. Previous systematic reviews compared moderate and high levels of PA to lower levels,[3 4] showing their protective role, but did not take into account low LTPA levels or inactivity. Demonstrating that also a low level of LTPA has a protective role against stroke is relevant for public health perspective as not all people can achieve moderate–high levels of LTPA because of psychophysical or social limitations. Besides, there are no thorough accounts on the association between LTPA levels and the risk of stroke subtypes—ischaemic or haemorrhagic—and on the modifying effect of age and sex.

The aim of the present systematic review and meta-analysis is to provide updated data on the effect of each level of LTPA compared with inactivity and to specifically address if low levels of LTPA can have a beneficial effect on stroke prevention. Additionally, the present study aimed to assess the effect of different levels of LTPA on stroke subtypes and to assess whether age and sex modify the association between LTPA and the risk of stroke.

MATERIALS AND METHODS

Search strategy and selection criteria

The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[11] guidelines and the *Cochrane Handbook for Systematic Reviews of Interventions*.[12] The protocol was registered in PROSPERO with code CRD42023425302. We formulated the clinical question and planned search strategy according to the Population–Intervention–Comparison–Outcome scheme reported in table 1.

We made a literature search on articles published in English language up to 22 April 2023 on PubMed and Scopus, using these main keywords: 'physical activity' OR 'exercise' OR 'cardiorespiratory fitness' OR 'motor activity' OR 'leisure-time activity' OR 'physical conditioning' AND 'stroke' OR 'cerebrovascular disease' OR 'cardiovascular disease' AND 'cohort'.

Table 1 Population–Intervention–Comparison–Outcome chart

Population	General population/healthy subjects.
Intervention	Physical activity/physical fitness/physical conditioning/motor activity/leisure-time activity/aerobic activity.
Comparison	Inactivity/very low level.
Outcome	Stroke/cerebrovascular diseases/ischaemic stroke/haemorrhagic stroke.

We selected articles that fulfilled the following inclusion criteria: prospective cohort studies on a general adult healthy population, comparing, as exposure variable, different levels of PA to inactivity or insufficient LTPA, having as outcome the incidence of any type of stroke. LTPA could be reported through any validated method, from self-reported questionnaires to in-person interviews to wearable devices. Adjusted relative risk (RR) estimates and 95% CIs were required for inclusion. The exclusion criteria were wrong design (not cohort studies, not comparing exercise with no-less exercise), wrong exposure (not physical exercise), wrong outcome (no stroke), wrong population (not general population) and wrong publication type (letters, editorials, comments, narrative reviews). We excluded, for the quantitative meta-analysis, the studies that identified PA levels in tertiles, quartiles and quintiles. The main findings of those studies were reported as a qualitative synthesis. For clarity, we used throughout the text the term 'articles' referring to papers retrieved from the literature search and the terms 'cohort' or 'cohort study' or 'study' when referring to the populations of subjects considered for quantitative (meta-analysis) or qualitative synthesis.

As a first step, four authors (RO, FDSantis, MF, FDScriancalepore) independently screened for title and abstracts all the records, using Rayyan Systematic Reviews web-based tool.[13] Then the same authors selected the articles after examining the full text. Disagreements on eligibility were resolved by consensus among all the authors involved.

Quality assessment

The quality of the cohort studies included in meta-analyses was assessed with the ROBINS-I tool.[14] According to the recommendations of the tool, we evaluated five aspects: confounding domains, selection criteria, classification of intervention, missing data and measurement outcome. By applying those criteria, the tool attributes low, moderate or high risk of bias to each of the considered studies.

Data extraction

Data extraction was conducted by two authors, independently and blinded and thereafter compared, (RO and MF) using an electronic spreadsheet with the following prespecified variables: first author's name, publication year, country where the study was conducted, study period, number of subjects, months of follow-up, sex proportion, mean age, race/ethnicity, confounders considered for statistical adjustment, type of stroke (any, ischaemic, haemorrhagic) and effect sizes with 95% CIs for each LTPA category. Cohort studies included in the articles were grouped across comparable definitions of LTPA, despite some slight discrepancies due to heterogenous methods of measure (most frequently American Heart Association PA categories or the number of minutes/hours per week of moderate or vigorous intensity activity based on Metabolic Equivalent of Task) or cut-offs of PA intensity and frequency. We distinguished, in three subgroups of studies, up to five levels of LTPA comparing all of them to a reference level called 'none' corresponding to complete inactivity or very insufficient level (details in the online supplemental tables 1–5). Cohort studies applying relative measures of LTPA—tertiles, quartiles or quintiles—were excluded as those categories were not predefined and referred to the characteristics of each population, thus decreasing comparability.

When an article reported more than one analysis on the same cohort study, we included in meta-analyses all cohorts, provided that their populations did not overlap.

Statistical analysis

Meta-analysis was performed according to random effects modelling[15] to take into account unmeasured confounders and differences in setting across studies.

Heterogeneity across cohort studies was assessed with Cochrane's Q statistics and I^2 statistics.

Random effects models were used to estimate summary risk ratio (95% CIs) using Cochrane's Review Manager (RevMan V.5.3) software and R studio V.4.2.2 (RStudio PBC) for meta-regression. Subgroup analysis was performed basing on the number of PA levels of intensity and stroke subtypes (ischaemic, haemorrhagic), when available. We classified the studies into three subgroups according to the number of LTPA categories (from three to five levels of LTPA intensity) according to the number of categories, irrespective of the definition of the different categories. Where applicable, we performed subgroup analyses according to stroke subtype (ischaemic and haemorrhagic).

Meta-regression was performed by grouping participants into three predefined activity strata: none, low to moderate and high or vigorous. Studies with three LTPA categories were all included in meta-regression, while those with four or five categories were included if three of those categories fit the definitions of 'none', 'low' or 'moderate' and 'high' or 'vigorous', respectively. Age and gender were tested for their impact on the relationship between variables.

In addition to subgroup analyses by stroke subtype and meta-regression analyses, we performed sensitivity analyses grouping studies with homogeneous definitions of LTPA levels to consider the heterogeneity of those definitions. Where applicable, we also performed sensitivity analyses by excluding studies with moderate or high risk of bias.

Forest plot for meta-analyses were generated with Cochrane Review Manager, V.5.3, while meta-regression was performed with R statistical software (V.4.2.2).

RESULTS

Literature search

Our search identified a total of 3064 articles. After removal of duplicates, 2785 articles remained for title and abstract screening; 445 were eligible for full-text screening. After full-text assessment, 15 articles, on a total of 16 cohorts (because on 1 article reporting on 2 cohorts), were included in the meta-analyses; additionally, 6 articles were included in the qualitative analysis. Figure 1 shows the PRISMA flowchart for literature search.

The 16 cohorts selected for the meta-analysis included overall 752 052 followed-up subjects, with a mean follow-up length of 125.7±77.5 months. 14 cohort studies reported cumulative RR data of any stroke[16–29] either ischaemic or haemorrhagic; 3 cohort studies reported the RR for ischaemic[17 25 30] and 2 the RR for haemorrhagic stroke.[17 25] The main characteristics of the cohort studies reporting stroke incidence are summarised in table 2 (details on the comparison of different levels of LTPA in each subgroup of cohort studies are accessible in the online supplemental tables 1–5). Notably, all cohort studies included in meta-analyses measured LTPA with self-report questionnaires, while two studies[21 23] performed in-person interviews to ascertain LTPA levels. All studies included in meta-analyses used self-reported measures of LTPA; only one study[31], which was included in the qualitative synthesis as it contained data stratified in tertiles, used an accelerometer as an objective measure of LTPA. Among the 15 articles included in the meta-analysis, we judged 4 (26.6%)[16 17 19 22] to be at moderate risk of bias, while no article was at high risk of bias. We judged the remaining to be at low risk of bias (figure 2).

In table 3, we summarised the characteristics of the articles included in the qualitative synthesis.

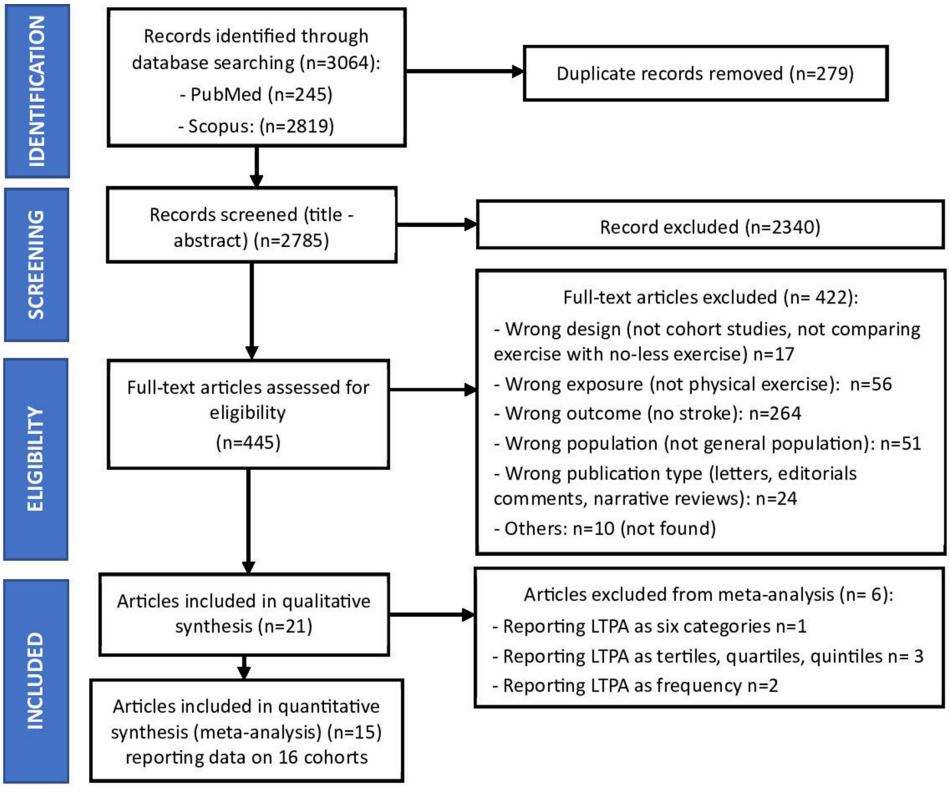

Figure 1 Flow chart of the systematic review process of study selection. LTPA, leisure-time physical activity.

Table 2 Characteristics of cohort studies included in meta-analyses

Author (ref)	LTPA measure	Country	First year observation	Follow-up (months, n)	Subjects (n)	Women (n, %)	Outcome measure	Stroke cases, n	Age (min–max)	Mean age	Race/ethnicity
Three LTPA levels											
Bell *et al*[16]	Q	USA	1987–1998	132	10018	5441 (54.3%)	Discharge diagnosis codes independently reviewed by study investigators	N.A.	45–64	53.8±5.6	Caucasian
Bell *et al*[16]	Q	USA	1987–1998	132	3707	2296 (61.9%)	"	N.A.	45–64	53.6±5.8	Black
Cao *et al*[17]	Q	UK	2006–2010	132	354 976	194 038 (54.7%)	Electronic health records (ICD-10 codes 160–164)	N.A.	40–70	56.2±8.2	Mixed (black, white, Asian, other)
Håheim *et al*[19]	Q	Norway	1972–1973	144	14403	0	Stroke incidence from hospital registry—no revision	81	40–49	N.A.	Caucasian
Kulshreshtha *et al*[23]	Q+T	USA	2003–2007	58.8	22914	13290 (58.0 %)	WHO clinical diagnostic criteria of stroke applied to medical records by experts	432	45	65	Mixed (black, white)
Motamed-Gorji *et al*[25]	Q	Iran	2004–2008	103.2	47008	27418 (58.3%)	Clinical data reviewed and ICD-10 codes	1135	N.A.	57±8.8	Caucasian
Nagata *et al*[26]	Q	USA	1985–1986	360	5114	2787 (54.5%)	Patients interview+clinical records and expert revision	N.A.	22–28	N.A.	Mixed
Willey *et al*[30]*	Q	USA	1993–2001	109.2	3298	2072 (62.8%)	Annual phone screening+medical records+expert review	N.A.	N.A.	69.2±10.3	Mixed (black, white)
Four LTPA levels											
Chomistek *et al*[18]	Q	USA	1992–1995	229.2	27536	27536 (100%)	WHO clinical diagnostic criteria of stroke applied to medical records by experts	650	45	N.A.	Caucasian
Hamer *et al*[20]	Q	UK	1994–2008	112.8	65093	35541 (54.6 %)	National Health Service Central Registry diagnosis	633	40	58±12.0	Caucasian
Huerta *et al*[21]	Q+I	Spain	1992–1996	12.3	32992	19416 (58.9%)	Hospital databases diagnostic codes and clinical data reviewed by expert	N.A.	29–69	N.A.	Caucasian
Liu *et al*[24]	Q	China	1998–2001	87.6	100560	60193 (59.8%)	Patient Interview+check of ICD-10 codes by medical record review	2850	N.A.	51.5±12.0	Asian
Soares-Miranda *et al*[27]	Q	USA	1989–1992	120	4207	2566 (61.0%)	Patients interview+clinical records and expert revision	563	65	72.5±5.5	Mixed (black, white)
Tikk *et al*[28]	Q	Germany	1994–98	152.4	23927	12865 (53.7%)	Patients interview+clinical records and expert revision	551	35–64	N.A.	Caucasian
Five LTPA levels											
Jefferis *et al*[22]	Q	UK	1978–1980	130.8	3357	0	Clinical diagnosis from hospital and primary care databases	195	40–59	68.3	Caucasian
Zhao *et al*[29]	Q	China	2010–2018	82.08	32942	17495 (53.1%)	Annual check-up+linkage to hospital admission diagnosis	2240	60	69.49±7.4	Asian

*Includes data only on ischaemic stroke subtype.
I, in-person interview; ICD-9, International Classification of Diseases, 9th Edition; ICD-10, International Classification of Diseases, 10th Edition; LTPA, leisure-time physical activity; N.A, not available; Q, self-reported questionnaire; T, telephone interview.

Figure 2 Data on the risk of bias judgment in each domain for the outcome of stroke.

Figure 2 Data on the risk of bias judgment in each domain for the outcome of stroke.

Meta-analysis of risk of any stroke: studies with three LTPA levels

Five studies[16 17 19 23 25 26] identified three levels of LTPA (none, below target and ideal). As compared with no LTPA, below target LTPA had a pooled RR for any stroke of 0.82 (95% CI 0.75 to 0.88; I^2=16%, not important heterogeneity) and ideal LTPA had a pooled RR for any stroke of 0.71 (95% CI 0.58 to 0.86; I^2=81%, considerable heterogeneity) (figure 3).

Meta-analysis of risk of any stroke: studies with four LTPA levels

Six studies[18 20 21 24 27 28] identified four levels of LTPA (none, low, moderate and intense). As compared with no LTPA, low LTPA had a pooled RR of any stroke of 0.76 (95% CI 0.63 to 0.90; I^2=77%, considerable heterogeneity), moderate LTPA had a pooled RR of 0.73 (95% CI 0.62 to 0.87; I^2=73%, considerable heterogeneity) and intense LTPA a pooled RR of 0.75 (95% CI 0.61 to 0.92; I^2=78%, considerable heterogeneity) for any stroke (figure 4).

Meta-analysis of risk of any stroke: studies with five LTPA levels

Two studies[22 29] identified five levels of LTPA (none, insufficient, low, moderate and intense). As compared with no LTPA, insufficient LTPA had a pooled RR of 0.89 (95% CI 0.79 to 1.0; I^2=0%, not important heterogeneity) with limited statistical significance, low LTPA had a pooled RR of 0.87 (95% CI 0.77 to 0.98; I^2=0%, not important heterogeneity), moderate LTPA had a pooled RR of 0.71 (95% CI 0.58 to 0.88; I^2=0%, not important heterogeneity) and intense LTPA a pooled RR of 0.98 (95% CI 0.73 to 1.32; I^2=12%, not important heterogeneity) for any stroke compared with no LTPA (figure 5).

Meta-analysis of risk of ischaemic stroke

Three studies[17 25 30] reported the risk of ischaemic stroke with three levels of LTPA. As compared with no LTPA, below target LTPA had a pooled RR of 0.87 (95% CI 0.80 to 0.95; I^2=0%, not important heterogeneity) and ideal LTPA had a pooled RR of 0.80 (95% CI 0.64 to 1.01; I^2=71%, considerable heterogeneity) (figure 6).

Meta-analysis of risk of haemorrhagic stroke

Two studies[17 25] reported the risk of haemorrhagic stroke with three levels of LTPA. As compared with no LTPA, below target LTPA had a pooled RR of 0.84 (95% CI 0.68 to 1.04; I^2=12% not important heterogeneity) and ideal LTPA ha a pooled RR of 0.87 (95% CI 0.72 to 1.04, I^2=0%, not important heterogeneity) compared with no LTPA (figure 7).

Qualitative synthesis risk of any stroke in studies with more than five categories

Only one study[32] reported six LTPA categories and was not included in meta-analyses. The characteristics of the study are reported in online supplemental table 6). Overall, the study showed a significant effect of LTPA on stroke prevention only in the highest category (online supplemental table 6).

Table 3 Characteristics of cohort studies included in qualitative synthesis

Author (ref)	LTPA measure	Country	First year observation	Follow-up (months, n)	Subjects (n)	Women (n - %)	Outcome measure	No. stroke cases	AGE (min-max)	Mean age	Race/ ethnicity	Narrative summary
Hamer *et al*[20]*	Q	UK	1994–2008	112.8	65 093	35 541 (54.6 %)	National Health Service Central Registry diagnosis	633	40	58±12.0	Caucasian	LTPA stratified into quintiles. Decreased risk of stroke in second, fourth, and fifth, but not in third quintile compared with the first one
Hooker *et al* [31]	A	USA	2003	88.8	7607	4145 (54.5%)	Patient contact, medical records review for clinical definition.	286	N.A.	63.4±8.0	Mixed	LTPA stratified into tertiles. Moderate-to-vigorous LTPA linked to decreased risk of stroke in both second and third tertiles compared with the first one. Low-intensity LTPA not linked to decreased risk of stroke in either the second or third tertiles compared with the first one
Hummel *et al*[34]	Q	Sweden	1997	214.8	31 580	20 855 (66.0%)	ICD codes on medical discharge reports	707	N.A.	N.A.	Caucasian	LTPA stratified into tertiles. No decreased risk of stroke in the second or third tertiles compared with the first one
Jeong *et al*[36]	Q	South Korea	2002–2013	43.2	336 326	164 645 (48.9%)	ICD codes on medical discharge reports	2213	N.A.	N.A.	Asian	LTPA stratified according to frequency. Any LTPA frequency linked to decreased risk of stroke compared with no activity, except from the highest one ('almost every day')
Kim *et al*[35]	Q	South Korea	2002–2015	156.0	257 854	49.5%	ICD 10 codes on hospital and death reports	16 134	N.A.	50.7±8.7	Asian	LTPA stratified according to frequency. Any LTPA frequency linked to decreased risk of stroke compared with no activity
MacDonald *et al*†[33]	Q	France	1990	194.4	95 169	95 169 (100%)	Self-reporting followed by analysis of medical reports by experts	592	N.A.	51.2±6.7	N.A.	LTPA stratified into tertiles. Decreased risk of stroke in the second, but not in the third tertile of LTPA compared with the first one
Wannamethee *et al*[32]	Q	UK	N.A.	114.0	7735	0	ICD codes on death reports and clinical diagnosis on medical records.	128	40–59	N.A.	Caucasian	LTPA categorised in six levels. Decreased risk of stroke only in the highest level of LTPA compared with the lowest level

*The cohort data expressed in tertiles.
†It includes three different analyses of the same cohort.
A, accelerometer; I, in person interview; ICD-9, International Classification of Diseases, 9th Edition; ICD-10, International Classification of Diseases, 10th Edition; N.A, not available; Q, self-reported questionnaire; T, telephone interview.

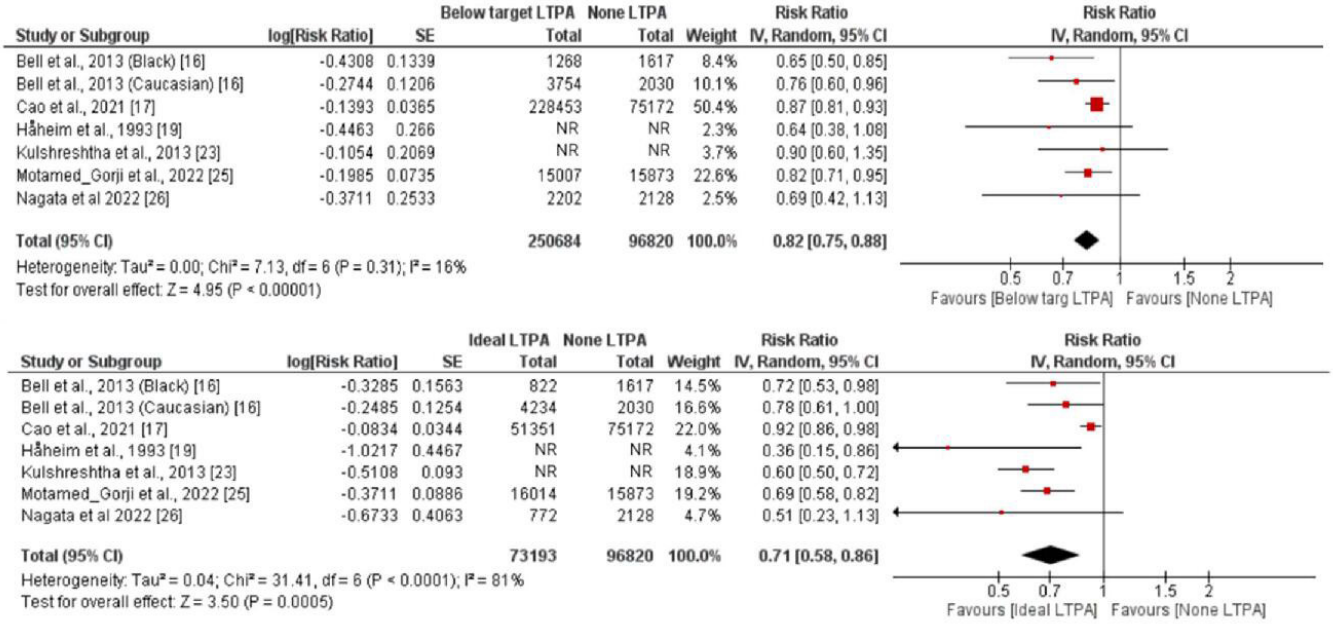

Figure 3 Forest plots of the pooled risk ratio for any stroke, from the three LTPA levels studies, comparing below target and ideal LTPA versus none. NR, not reported; LTPA, leisure-time physical activity.

Qualitative synthesis of studies reporting relative measures of LTPA (tertiles, quartiles, quintiles)

The characteristics of studies reporting LTPA according to relative measures—tertiles,[3133 34] quartiles[33] and quintiles[20]—are reported in online supplemental tables 7–9. Evidence from studies was conflicting. None of the cohorts clearly found a dose–dependent relationship between the levels of LTPA and the decrease in the risk of stroke (online supplemental tables 7–9).

Qualitative synthesis of studies reporting the risk of stroke according to the weekly frequency of LTPA

Two studies reported the risk of stroke according to LTPA weekly frequency,[35 36] without information on the total duration (online supplemental table 10). The results of those two studies could not be pooled in a meta-analysis due to differences in the reporting of frequency of LTPA. No clear weekly frequency pattern of LTPA was associated with a more relevant decrease in the risk of stroke, all patterns had a comparable protective effect on stroke incidence, compared with no LTPA (online supplemental table 10).

Meta-regression

Meta-regression analysis revealed no impact of age on the advantage of moderate versus no exercise ($p_{meta\text{-}regression}=0.5$) and high versus moderate exercise in terms of incident stroke ($p_{meta\text{-}regression}=0.4$) . The male/female ratio did not impact the benefit of activity ($p_{meta\text{-}regression}=0.6$ for moderate vs none, $p_{meta\text{-}regression}=0.5$ for high vs moderate) (see online supplemental figure 1).

Sensitivity analyses

The sensitivity analysis, grouping studies with homogeneous definitions of LTPA, could be applicable to studies with three levels of LTPA. It showed similar point estimates to those derived in the main analysis and confirmed the advantage of any LTPA level over none LTPA for the risk of stroke (online supplemental figure 2).

The sensitivity analysis by excluding studies with moderate risk of bias was possible only for studies with three LTPA categories. Studies with four categories of LTPA all had a low risk of bias, while among those with five categories of LTPA one had a low risk and the other a moderate risk of bias, thus preventing the possibility of a sensitivity analysis. The analysis excluding studies with moderate risk of bias did not change the direction of association between LTPA levels and the risk of stroke (online supplemental figure 3).

DISCUSSION

The main finding of our systematic review and meta-analysis of prospective cohort studies is that all levels of LTPA, irrespective of categorisation across different studies, were associated with a reduced risk of stroke (in the range of 18% to 29% lower risk) as compared with no activity. It is worth noting that even low levels of LTPA resulted in reduced stroke risk and that the effect of LTPA on primary stroke prevention was independent of age and sex. These findings have important implications and allow to conclude that LTPA is an effective measure to prevent stroke and that even a very low level of LTPA is better than being completely inactive.

According to global reports, more than one quarter of the world population is physically inactive,[37 38] contributing to about 8% of global mortality.[39] In this context, campaigns such as Life's Essential 8[38 40] are important to favour a healthy lifestyle in the population, including an adequate level of PA. However, there is no consensus about the minimum level of LTPA helpful to decrease the risk of stroke in the long term. This information would be relevant for individuals affected by socioeconomical, psychological and physical limitations in their PA capacity. According to the results of our systematic review and meta-analysis, even small amounts of LTPA are able to decrease the risk for stroke in the long term, even if we did not

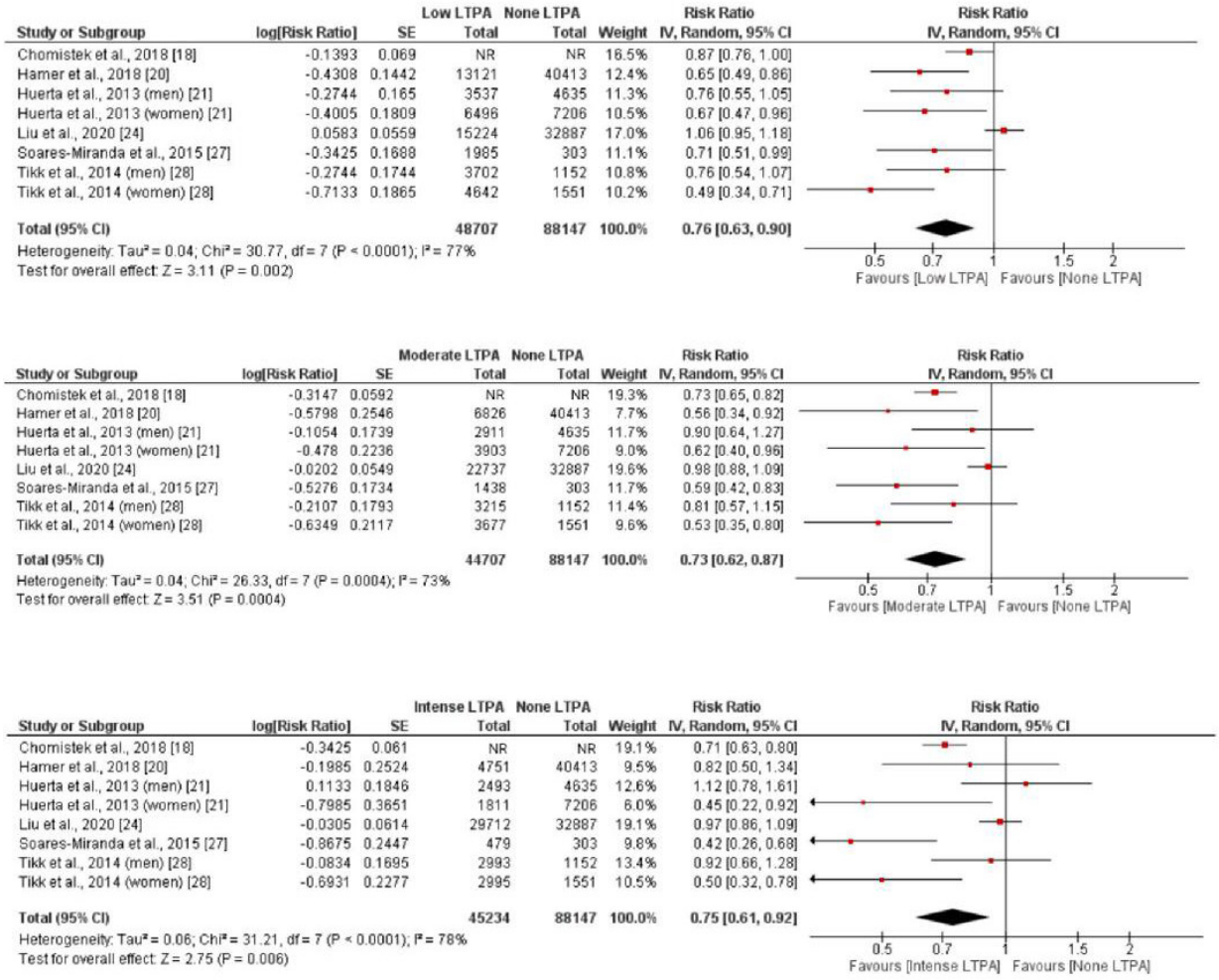

Figure 4 Forest plots of the pooled risk ratio of any stroke comparing, from the four LTPA levels studies, low, moderate and intense PA versus none PA. NR, not reported; LTPA, leisure-time physical activity.

make a network meta-analysis between different levels, therefore allowing an extended recommendation of being as active as possible only for individuals who cannot attain the recommended levels of LTPA, without falling in the mistake of encouraging to practice the slightest useful activity in sedentary people.

Our results are in line with a key principle of the 2020 WHO evidence-based recommendations for PA,[41] that is, that some PA is better than none. The same recommendations underlined some knowledge gaps, including the precise shape of the dose–response curve between PA and health outcomes, the health benefits of light-intensity PA and the health effects of different types and domains of PA.[42] In that regard, we aimed at quantifying the contribution of low levels of LTPA in decreasing the risk of stroke. We could not retrieve the shape of any dose–response curve of LTPA in relation to stroke risk as data from the retrieved studies did not allow such an estimate. A dose–response curve was retrieved, with some approximation estimating both occupational and recreational activity, by a previous meta-analysis of the Global Burden of Disease on the risk of ischaemic stroke and other diseases.[7] That previous meta-analysis concluded that increasing levels of total daily PA are associated with decreasing risk of ischaemic stroke. However, small amounts of PA were associated with a steep decrease in the risk of ischaemic stroke, while the decrease was less pronounced with higher amounts of PA.[7]

Our systematic review also included two studies[35 36] that reported the association between the frequency of LTPA and the risk of stroke. There is much debate about the best pattern of PA that can prevent disease and mortality. The findings of the two included studies,[35 36] which reported that stroke is prevented by LTPA of any frequency, are in line with previous studies that found that a 'weekend warrior' pattern of PA—ie, infrequent and intense—was associated with disease prevention as well as a more distributed PA pattern.[43]

Our analyses also addressed the effect of sex and age on the relationship between LTPA and the risk of stroke. Interestingly, there is a gender imbalance in LTPA levels, in that women are usually less active than men.[44] Our meta-regression analysis found that the preventive activity of LTPA over the risk of stroke was independent of sex. Therefore, our results strengthen the importance of promoting any level of PA to reduce the risk of stroke in both sexes. We also found that the preventive effect of LTPA on the risk of stroke was independent of age, which suggests that LTPA is beneficial for stroke prevention at any age.

Our systematic review and meta-analysis included a large number of individuals from studies that were strictly selected

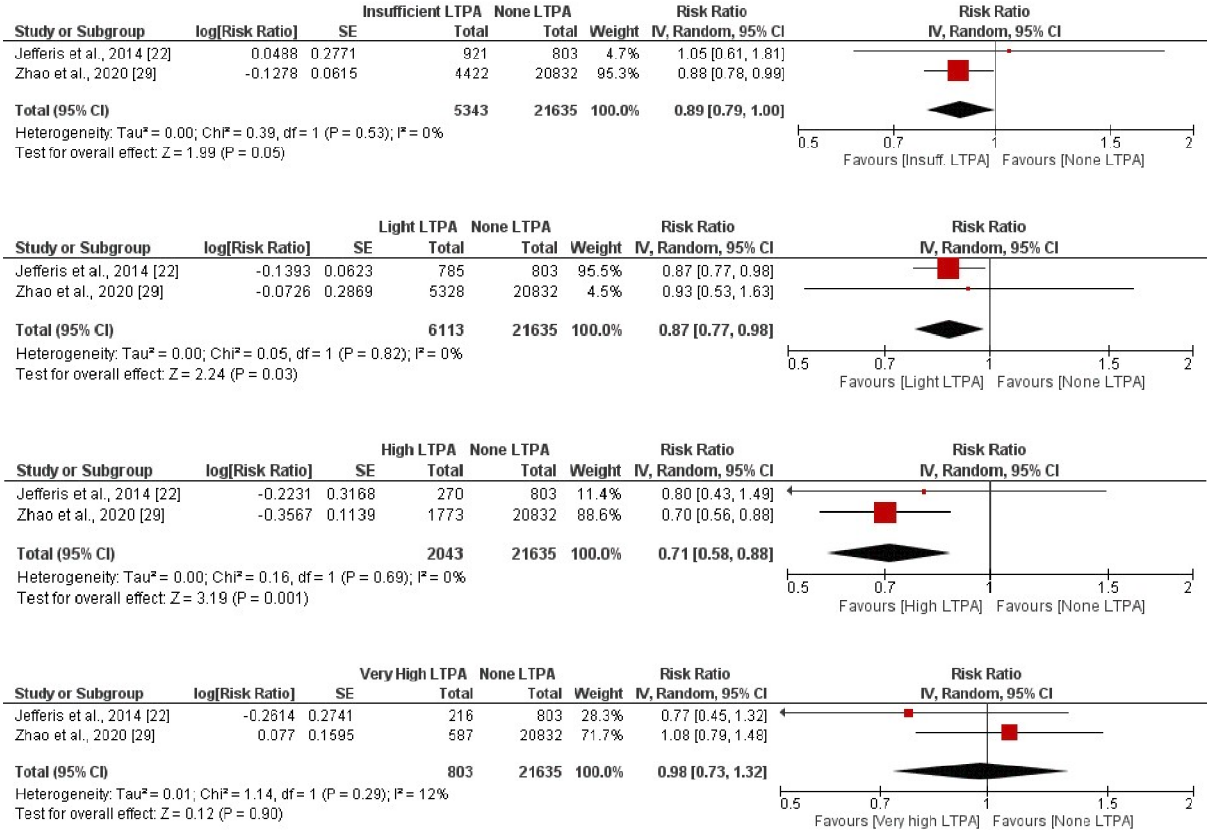

Figure 5 Forest plot of the pooled risk ratio of any stroke comparing, from the five LTPA levels studies, insufficient, light, high, very high LTPA versus none LTPA. NR, not reported; LTPA, leisure-time physical activity.

to represent the general population. A few studies discriminated between stroke subtypes, the meta-analysis showed a protective role of two levels of LTPA against ischaemic and haemorrhagic stroke, despite it is supposable that LTPA affects haemorrhagic and ischaemic stroke differently, due to different aetiologies. Besides, to our knowledge, this one of the first meta-analysis that consider the risk of haemorrhagic stroke in relation to LTPA. Indeed, a previous work,[45] matching both cohort and case–control studies, also found that the protective effects of PA were similar in both haemorrhagic and ischaemic stroke.

We recognise that our study has several limitations. Studies were included based on the number of categories of LTPA, regardless of their specific definitions which were highly heterogeneous about unit measure types and cut-off. Methods for reporting LTPA levels were also heterogeneous: under the term 'none' we included also minimal levels for some studies,[18 21 24 26] not reporting a true 'none' level; only one study[28] reported a cumulative index on both LTPA and occupational PA. Most cohort studies in the meta-analysis only (13/16) used periodic self-report questionnaires during follow-up, while only two used interviews

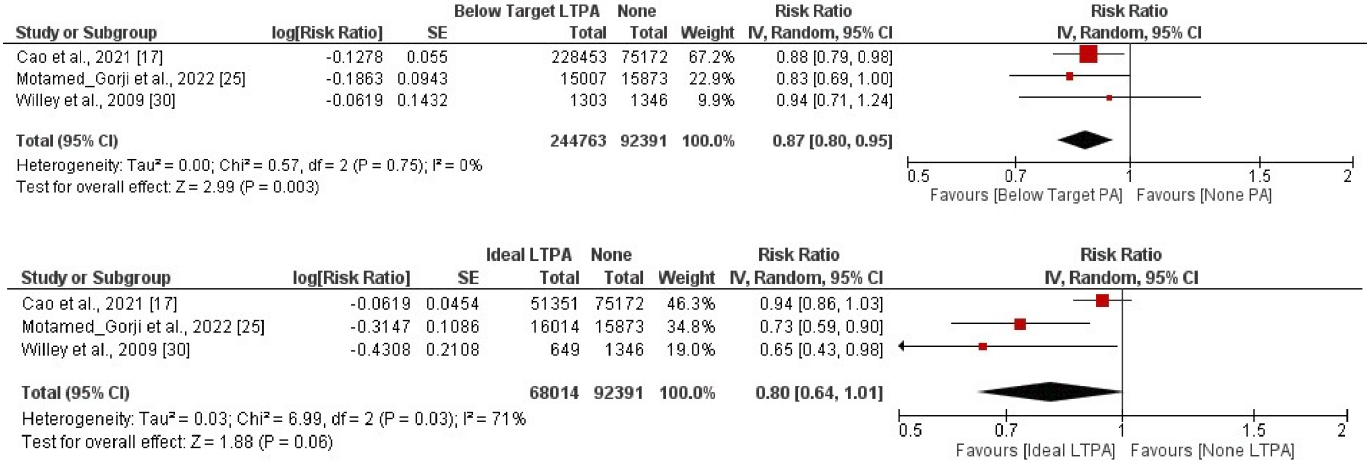

Figure 6 Forest plot of the pooled risk ratio of ischaemic stroke comparing in two levels below target and ideal LTPA versus none LTPA and ideal LTPA versus none. NR, not reported; LTPA, leisure-time physical activity.

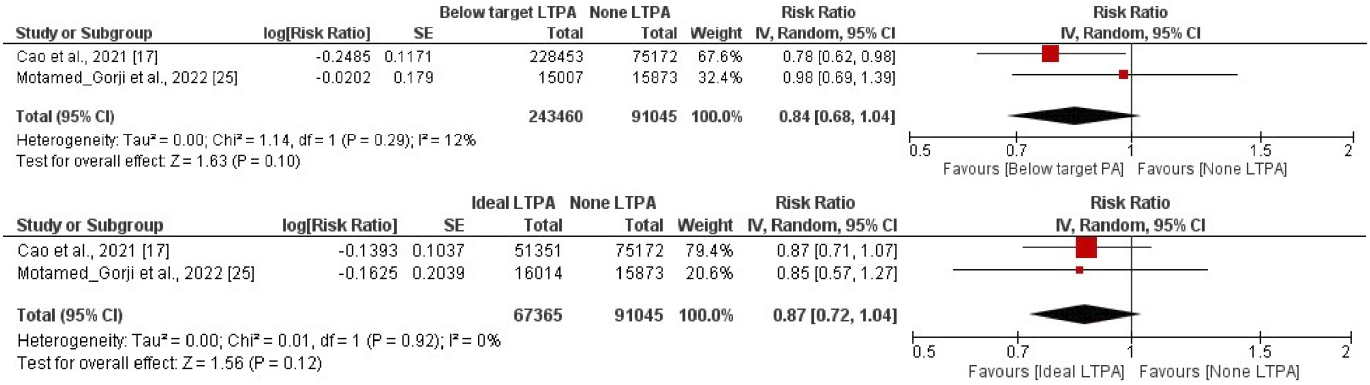

Figure 7 Forest plot of the pooled risk ratio of haemorrhagic stroke comparing, in two levels, below target and ideal LTPA versus none LTPA. NR, not reported; LTPA, leisure-time physical activity.

and none confirmed self-reports with objective methods, thus exposing to recall bias. Only one study[31], included in the qualitative synthesis, used an accelerometer, as objective method to measure total light-intensity physical activity and total moderate-to-vigorous intensity PA, concluding that both levels of PA were significantly and independently associated with a reduction in the risk of incident stroke compared with sedentary behaviour. Besides, stroke outcomes were adjudicated by experts in only 10 out of 16 studies (table 2). Many studies were also excluded from meta-analyses because they reported LTPA with relative measures such as tertiles, quartiles and quintiles that were not prespecified. Together with statistical heterogeneity, clinical and methodological heterogeneity of the included studies were also high, due to the different population size, race/ethnicity, age ranges, sex prevalence and lengths of follow-up. We focused on studies reporting LTPA, while other types of PA can influence the risk of stroke, including occupational PA which is more difficult to measure and standardise objectively. In the future, it will be interesting to collect comprehensive data on all types of PA from wearable devices,[46] increasingly used in the general population and probably capable to promote people's propensity to higher exercise levels.[47] Therefore, we could not fill one of the knowledge gaps of the WHO recommendations, which asked for a more complete assessment of the different types of PA.[42] Lastly, while we could perform some subgroup analyses and meta-regressions, we could not perform analyses on race/ethnicity due to the small number of studies with available data. Therefore, we could not assess one of the possible disparities in the relationship between LTPA and stroke.

In conclusion, although limited by methodological heterogeneity between the studies, our results, including updated data from the most recent studies, demonstrated that each level of recreational PA could be protective against stroke (considering also the ischaemic and haemorrhagic subtypes) as a non-pharmacological primary preventive measure, suggesting that even small amounts of LTPA can prevent stroke in the long term and that the effect of LTPA is independent of sex and age. Our data encourage campaigns to overcome sedentary lifestyle and to strive to do the best level of LTPA that people can achieve according to their possibilities, an approach that will pay in terms of stroke prevention even if LTPA goals are met only in part.

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Contributors RO conceived the study, supervised the overall work and is responsible for the overall content as guarantor. FDSantis, RO, MR, LD and MF drafted the manuscript and created tables and figures. RO, FDSantis, MF and FDSciancalepore contributed to the search process, data extraction and synthesis. FDSantis, MR, MF and RO performed the statistical analyses. FDSantis, LD, SA-R, LB and SS revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests RO reports grants from Novartis and Allergan; compensation from Teva Pharmaceutical Industries, Eli Lilly and Company, Pfizer and Novartis for other services. SS reports compensations from Novartis, Nordisk, Allergan, AstraZeneca, Pfizer Canada, Eli Lilly and Company, Teva Pharmaceutical Industries, H. Lundbeck A/S and Abbot Canada for consultant services; employment by University of L'Aquila. The other authors have no conflicting interests relevant to the manuscript.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request to the corresponding author.

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