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Prestroke physical activity is associated with admission haematoma volume and the clinical outcome of intracerebral haemorrhage

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ABSTRACT

Background Prestroke physical activity (PA) has been linked to improved outcomes after intracerebral haemorrhage (ICH), but its association with ICH volume is unknown. We aimed to investigate associations of prestroke PA with location-specific haematoma volume and the clinical outcome of ICH.

Methods All patients with primary ICH, admitted to three hospitals between 2014 and 2019, were included. Patients performing light PA ≥4 hour/week the year before stroke were considered physically active. Haematoma volumes were assessed from admission brain imaging. Adjusted associations were estimated using multivariate linear and logistic regression models. Haematoma volume was explored as mediator to the relationship between prestroke PA and mild stroke severity (0–4 points on the National Institutes of Health Stroke Scale), a good 1-week functional status (0–3 points on the modified Rankin Scale) and 90-day survival. Average direct effects (ADE) and average causal mediation effects (ACME) were computed.

Results Of 686 primary ICH cases, 349 were deep, 240 lobar and 97 infratentorial. Prestroke PA predicted smaller haematoma volumes in deep ICH (β=−0.36, SE=0.09, p<0.001) and lobar ICH (β=−0.23, SE=0.09, p=0.016). Prestroke PA was also associated with mild stroke severity (OR 2.53, 95% CI 1.59 to 4.01), a good 1-week functional status (OR 2.12, 95% CI 1.37 to 3.30) and 90-day survival (OR 3.48, 95% CI 2.06 to 5.91). Haematoma volume partly mediated the relationships between PA and stroke severity (ADE 0.08, p=0.004; ACME 0.10, p<0.001), 1-week functional status (ADE 0.07, p=0.03; ACME 0.10, p<0.001) and 90-day survival (ADE 0.14, p<0.001; ACME 0.05, p<0.001).

Conclusions Light PA ≥4 hour/week prior to ICH was associated with smaller haematoma volumes in deep and lobar locations. Physically active patients with ICH had a higher likelihood of mild stroke, a good 1-week functional status and 90-day survival, in part mediated by smaller haematoma volumes on admission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prestroke physical activity has been linked to a favourable poststroke prognosis. However, the association between physical activity and the volume of intracerebral haemorrhage remains unexplored.

WHAT THIS STUDY ADDS

⇒ Engaging in regular, light physical activity prior to experiencing an intracerebral haemorrhage is independently associated with reduced haematoma volumes in deep and lobar locations. This finding partly explains the link between prestroke physical activity and favourable clinical outcomes following intracerebral haemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study adds to the current understanding of the health benefits associated with increased physical activity and presents new incentives for investigating the neuroprotective mechanisms of physical activity in relation to intracerebral haematoma volume and haematoma expansion.

INTRODUCTION

Non-traumatic intracerebral haemorrhage (ICH) primarily occurs owing to hypertensive vasculopathy or cerebral amyloid angiopathy[1] and is considered the deadliest type of stroke.[2] Nearly half of all patients with ICH die within 30 days, and only one-fifth live independently at 6 months.[3] The prognosis is largely determined by the haematoma volume, which remains one of the most important predictors of mortality and functional outcomes.[4 5] However, modifiable determinants of haematoma volume for ICH are scarce and may differ much depending on the underlying pathology and haematoma location.[6]

Physical activity (PA) reduces the risk of stroke[7] and may induce brain ischaemic tolerance with neuroprotective properties in stroke recovery.[8] We previously reported that prestroke PA is associated with decreased admission stroke severity and a lower poststroke mortality hazard in patients with ICH.[9] Possibly, these associations were mediated by smaller haemorrhages among physically active patients, although the association

between prestroke PA and ICH volume in humans has not been investigated. Exercise preconditioning has, however, demonstrated reduced haematoma volumes and improved recovery following ICH in mice.[10] Several studies have also suggested that sedentary behaviour is associated with an increased risk of microvascular and macrovascular changes in the brain, which in turn predispose the expansion of intracerebral haematomas.[11 12]

The present study aims to investigate associations of prestroke PA with admission haematoma volume in deep, lobar and infratentorial ICH. We also explore associations of prestroke PA with stroke severity on admission, 1-week functional status and 90-day survival in relation to haematoma volumes.

METHODS

Data collection

This was a longitudinal, register-based study using routinely collected health data.[13] We reviewed medical records and initial CT or MRI scans of all adult patients with a non-traumatic ICH treated at the stroke units of three large hospitals and one regional neurosurgical ward at the Sahlgrenska University Hospital in Gothenburg, Sweden. The inclusion period was between 1 November 2014 and 30 June 2019. The catchment area for neurosurgery covers approximately 2 million people. We identified all patients through the quality-control stroke register Väststroke.

Stroke characteristics and information on prestroke medical treatments were obtained from the national Stroke Register in Sweden (Riksstroke). Socioeconomic data were obtained from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies held by Statistics Sweden. Prestroke comorbid conditions were obtained from the National Patient Registry in Sweden. Information on all-cause mortality was collected from the Swedish Cause of Death Register. The National Board of Health and Welfare merged and pseudonymised the data using the personal identification numbers in Sweden. Exclusion criteria were unavailable medical records, lack of a personal identification number and secondary aetiologies of ICH: traumatic haemorrhage, multifocal haemorrhages, primary intraventricular haemorrhage (IVH), vascular malformations, cerebral venous thrombosis, vasculitis, haemorrhagic infarction, primary or metastatic tumours, infections, Moyamoya disease, bleeding disorders, cerebral hyperperfusion syndrome and reversible cerebral vasoconstriction syndrome.

Physical activity

Prestroke PA was assessed from interviews using the four-level Saltin-Grimby Physical Activity Level Scale.[14] Level 1: mostly sedentary leisure time. Level 2: light PA including walking, cycling, skiing for ≥4 hour/week. Level 3: moderate PA including running and playing tennis for ≥2–3 hour/week. Level 4: vigorous PA including training for competitive sports several times/week. Patients performing light PAs for ≥4 hour/week were considered physically active. Physiotherapists employed at the included stroke units conducted the PA assessments, which refer to the average activity level during the year before ICH. For patients with missing observations, medical records were screened to retrieve this information.

Prestroke characteristics

Educational level was dichotomised as having a postsecondary education (>12 years) or not. Income refers to the annual household income in the year prior to ICH, and low income was defined as the lowest tertile. Independence in activities of daily living (ADL) was defined as taking care of personal hygiene, dressing, toileting and household activities independently. Living situation was defined as living alone or with others such as roommates, family members, or multiresident dwelling. Active smoking was defined as the use of cigarettes or any tobacco product within the past year. Alcohol use disorder was defined based on an International Classification of Diseases, 10th Revision (ICD-10) diagnosis of such or information on alcohol overconsumption from medical records. Other comorbidities were defined according to relevant ICD-10 codes for each condition. Prestroke use of lipid-lowering drugs, antihypertensive drugs, antiplatelet drugs, warfarin and non-vitamin k oral anticoagulants (NOACs) was registered if currently prescribed or reported by the patient or a next of kin.

Admission evaluations

Systolic and diastolic blood pressures (BP) were recorded at hospital admittance. Blood values of sodium and potassium were collected if analysed within 24 hours of admission. The degree of anticoagulation from Warfarin was measured using International Normalised Ratio (INR) if analysed within 24 hours of admission and before medical reversal. Patients not using Warfarin with missing INR values were given a value of 1 (normal coagulation). Reversal of anticoagulants using prothrombin complex concentrates, vitamin K or idarucizumab was recorded. Any neurosurgical intervention was registered, including invasive monitoring of intracranial pressure, cerebrospinal fluid drainage, minimal invasive haematoma evacuation and craniotomy.

Brain imagining

All patients admitted to the included hospitals with a suspected or clinically verified stroke undergo routine brain imaging. We analysed the first available CT or MRI scan after admission. For patients transferred from other hospitals, any prior radiological examination was imported and evaluated. The intraparenchymal haematoma volume was evaluated using the ABC/2 method. The ICH volume in millilitres is calculated as the greatest haematoma diameter (A) multiplied with the perpendicular diameter (B) and the number of slices multiplied by the slice thickness (C).[15] IVH was noted, but

intraventricular blood was excluded from the volumetric assessment. The location of haematomas was classified as deep, lobar or infratentorial. Haematomas located in the thalamus, basal ganglia, internal capsule or surrounding the lateral ventricles were defined as deep. Haematomas located in the cerebellum or brain stem were defined as infratentorial. Midline shift was defined as a perpendicular distance greater than 3 mm from the septum pellucidum to a straight line drawn between the attachments of the falx cerebri. All additional MRI or CT angiography examinations during the hospital stay were reviewed to find patients with a secondary cause of ICH. Two reviewers assessed all the radiological variables independently with excellent inter-rater reliability for haematoma volume assessments (Cohen's kappa coefficient of 0.97 for 20 patients). Any difficulties in the interpretation of radiological variables were noted and resolved in the group of researchers by discussion until a consensus was reached.

ICH outcomes

Three clinical ICH outcome measures were assessed: admission stroke severity, 1-week functional status and 90-day survival. Stroke severity on admission was evaluated using the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is widely used to measure the extent of impairment resulting from a stroke across 11 domains, with a maximum attainable score of 42.[16] Mild stroke severity was defined as a total NIHSS score of 0–4 at the time of admission. Functional status was assessed from medical records 1 week after the incident stroke using the modified Rankin Scale (mRS). The mRS is a measure of disability, commonly used in stroke research.[17] The mRS comprises six ordinal levels, ranging from (0) indicating no stroke symptoms to (1) representing no significant disability, (2) slight disability, (3) signifying moderate disability but with the ability to walk without assistance, (4) moderately severe disability and the inability to walk without assistance, (5) severe disability and being confined to bed and (6) death. A good 1-week functional status was defined as an mRS score of 0–3. For patients discharged within the first week, mRS was assessed on the day of discharge. Survival was evaluated 90 days after the incident ICH for each patient using data from the Swedish Cause of Death Register.

Statistical analysis

All statistical analyses were conducted using R software V.4.0.2 for Windows. Descriptive data are presented as numbers and percentage, medians and IQR, or means and SD. Group comparisons were performed using the χ^2 for categorical variables and the Mann-Whitney U test for quantitative variables. Haematoma volumes were log transformed for statistical analyses due to a highly right-skewed distribution. We constructed a multivariate ordinary least squares model predicting haematoma volume, including all covariates, adjusted for haematoma location. The explained variance (R^2) was computed for each covariate in this model as a measure of relative importance using the *rms* package for R.[18] The R^2 is bounded between 0 and 1, and a value approaching 1 indicates that more of the variance is explained by the covariate. Separate linear models were constructed for each haematoma location. As subgroup analyses did not allow for extensive covariate adjustment, propensity score weights were used to avoid overfitting. The propensity scores were calculated in a generalised boosted logistic regression model adjusting for the imbalance between physically active and inactive patients using the *twang* package for R.[19] The evaluation of propensity scores revealed satisfactory covariate balance (online supplemental figure 1).

Multivariate logistic regression models were constructed to predict associations of prestroke PA with midline shift, IVH, stroke severity on admission (NIHSS score 0–4), 1-week functional status (mRS score 0–3) and 90-day survival. Admission haematoma volume was explored as a mediator in the logistic regression models. Bootstrapped mediation analyses were conducted to determine causal paths between prestroke PA and admission stroke severity, 1-week functional status and 90-day survival. Mediation was interpreted based on the estimated average direct effect (ADE), average causal mediation effect (ACME) and average total effect (ATE). The ADE represents the effect of the independent variable (PA) on the outcome measure, and the ACME represents the effect of the independent variable on the outcome through the mediator variable (haematoma volume). The ATE is a summarisation of ADE and ACME. We tested the significance of estimates using a non-parametric bootstrapping procedure, and unstandardised effects were computed for each 1000 bootstrapped sample with 95% CIs using the *mediation* package for R.[20]

In the regression analyses, multiple imputation by chained equations was applied to handle variables with missing observations using the *mice* package for R.[21] Imputation of missing values was performed using an iterative sequence of predictive models for each variable with incomplete observations, based on all other variables in the data set and under the assumption that data are missing at random. Predictive mean matching was applied as imputation method and at least 80% useful data were set as a threshold for each covariate. Finally, sensitivity analyses on cases with complete assessments of PA were conducted. The level of significance was $p<0.05$.

Data availability statement

Due to regulations in Sweden, the data cannot be made publicly available. Researchers may apply to access anonymised data from Professor Katharina Stibrant Sunnerhagen after obtaining necessary approvals.

RESULTS

There were 770 patients diagnosed with ICH during the study period, of which 763 had available data (figure 1). We restricted analyses to primary cases of ICH, excluding rare aetiologies (n=47), multifocal haematomas (n=19)

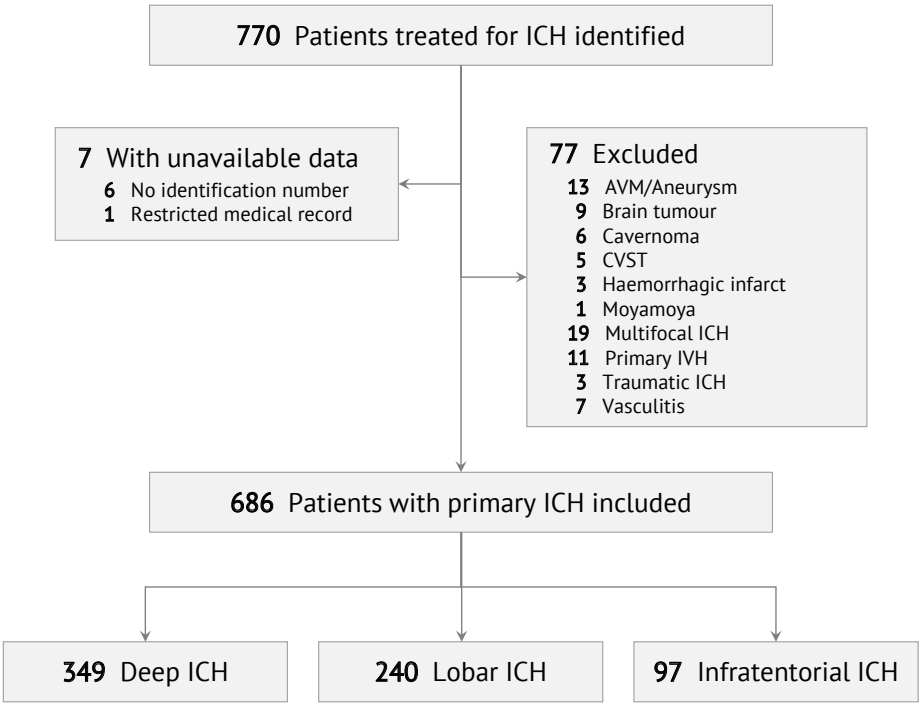

Figure 1 Flowchart of inclusion process. AVM, ateriovenosus malformation; CVST, cerebral venous sinus thrombosis; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage.

and primary IVH (n=11). There were 349 (51%) cases of deep ICH, 240 (35%) of lobar ICH and 97 (14%) of infratentorial ICH. Among infratentorial cases, 65 (67%) were cerebellar and 32 (33%) brainstem ICH. The mean age was 73 years (SD±14), 320 (47%) were women and 235 (38%) were physically active (table 1). Only one patient performed vigorous PA, and 31 patients performed moderate PA before ICH. Notably, inactive patients were older, predominately women, had lower education and income, were more often dependent in ADL, lived alone and had more comorbid conditions with a higher frequency of antihypertensive treatment and anticoagulation measured by INR.

Prediction of haematoma volumes

The most influential predictors of haematoma volume were time to scan, PA ≥4 hour/week, potassium blood value, education, diastolic BP and INR (figure 2). In the fully adjusted model, smaller haematoma volumes were associated with longer time to scan (β=−0.046; SE=0.02; p=0.002), PA≥4 hour/week (β=−0.313; SE=0.06; p<0.001), and high education (β=−0.175; SE=0.07; p=0.008), whereas larger haematoma volumes were associated with increasing INR (β=0.117; SE=0.06; p=0.048).

Prestroke PA ≥4 hour/week was associated with 36% smaller haematoma volumes in deep ICH (β=−0.36; SE=0.09; p<0.001) and 23% smaller haematoma volumes in lobar ICH (β=−0.23; SE=0.09; p=0.016) (table 2). There was, however, no significant association between PA and infratentorial haematoma volume after adjustment for covariate imbalance (β=−0.29; SE=0.19; p=0.114). Associations of prestroke PA with deep and lobar ICH volume remained significant in sensitivity analyses (online supplemental table 1).

Prediction of ICH outcomes

Seen in table 3, midline shift and IVH occurred more often among inactive patients compared with physically active patients (38% and 41% vs 23% and 28%, respectively). Prestroke PA ≥4 hour/week was associated with an adjusted OR of 0.67 (95% CI 0.44 to 0.99; p=0.049) for midline shift and 0.65 (95% CI 0.42 to 0.98; p=0.044) for IVH. The associations of PA with radiological characteristics did, however, not remain significant in sensitivity analyses (online supplemental table 2). Physically active patients more often presented with mild stroke severity on admission (57% vs 26%), had a good functional status after 1 week (54% vs 19%) and survived 90 days (92% vs 66%) compared with inactive patients. Prestroke PA ≥4 hour/week was associated with an adjusted OR of 2.53 (95% CI 1.59 to 4.01; p<0.001) for mild stroke, 2.12 (95% CI 1.37 to 3.30; p<0.001) for a good 1-week functional status and 3.48 (95% CI 2.06 to 5.91; p<0.001) for 90-day survival. Sensitivity analyses revealed significant associations between prestroke PA and clinical outcome measures (online supplemental table 2).

Mediation analyses

After adjustment for admission haematoma volumes, prestroke PA remained associated with mild stroke severity, a good 1-week functional status, and 90-day survival, but not with midline shift and IVH (tables 2 and

Table 1 Characteristics of patients with primary ICH

	Overall (n=686)	Physical activity <4 hour/week (n=387)	Physical activity ≥4 hour/week (n=235)	P value	Missing
Age, mean (SD)	73 (14)	77 (13)	69 (14)	<0.001	0
Female, n (%)	320 (47)	208 (54)	86 (37)	<0.001	0
Born in Sweden, n (%)	542 (79)	302 (78)	191 (81)	0.334	0
Education>12 years, n (%)	141 (21)	62 (16)	65 (29)	<0.001	13
Low income, n (%)	222 (32)	148 (38)	54 (23)	<0.001	3
ADL independent, n (%)	482 (76)	216 (61)	215 (95)	<0.001	55
Living alone, n (%)	311 (47)	212 (57)	88 (38)	<0.001	30
Smoking, n (%)	97 (14)	61 (16)	27 (12)	0.138	0
Alcohol use disorder, n (%)	85 (12)	57 (15)	26 (11)	0.193	0
Comorbidities, n (%)					
Hypertension	497 (72)	293 (76)	163 (69)	0.083	0
Hyperlipidaemia	73 (11)	48 (12)	21 (9)	0.182	0
Prior stroke or TIA	155 (23)	106 (27)	37 (16)	<0.001	0
Atrial fibrillation	165 (24)	122 (32)	36 (15)	<0.001	0
Diabetes mellitus	106 (16)	80 (21)	23 (10)	<0.001	0
Cardiac disease	52 (8)	37 (10)	15 (6)	0.165	0
Heart failure	61 (9)	48 (12)	13 (6)	0.005	0
Dementia	29 (4)	23 (6)	5 (2)	0.026	0
Cancer	60 (9)	38 (10)	19 (8)	0.467	0
Prestroke medications, n (%)					
Lipid-lowering drugs	173 (25)	102 (26)	55 (23)	0.411	0
Antiplatelet drugs	128 (19)	81 (21)	37 (16)	0.110	0
Antihypertensive drugs	431 (63)	288 (74)	112 (48)	<0.001	0
NOACs	63 (9)	44 (11)	15 (6)	0.040	0
Warfarin	88 (13)	65 (17)	19 (8)	0.002	0
Admission evaluations, mean (SD)					
Sodium (mEq/L)	140 (5)	140 (6)	139 (3)	0.106	29
Potassium (mEq/L)	4.1 (0.5)	4.1 (0.5)	4.1 (0.5)	0.372	32
INR	1.3 (0.7)	1.3 (0.8)	1.2 (0.5)	<0.001	1
Systolic BP (mm Hg)	167 (29)	169 (30)	165 (28)	0.156	36
Diastolic BP (mm Hg)	90 (17)	92 (18)	89 (16)	0.085	43
Interventions, n (%)					
Reversal of anticoagulation	119 (17)	84 (22)	28 (12)	0.002	0
Neurosurgery	39 (6)	19 (5)	18 (7)	0.229	0

Percent (%) reported from valid numbers.
ADL, activities of daily living; BP, blood pressure; ICH, intracerebral haemorrhage; INR, International Normalised Ratio; NOAC, non-vitamin k oral anticoagulants; TIA, transient ischaemic attack.

3). The volume of ICH mediated the relationship between prestroke PA and that of admission stroke severity, 1-week functional status and 90-day survival (table 4). However, direct effect estimates were also significant, indicating that smaller haematoma volumes only partly explain why physically active patients had higher probabilities of favourable clinical outcomes. Figure 3 visualises predicted probabilities of ICH outcomes in relation to haematoma volume, stratified by prestroke PA. Physically active patients had a higher probability of improved outcomes at haematoma volumes up to 35 mL for admission stroke severity, 45 mL for 1-week functional status, and 125 mL for 90-day survival.

DISCUSSION

In 686 patients with primary ICH, we found that light prestroke PA of ≥4 hour/week was associated with smaller

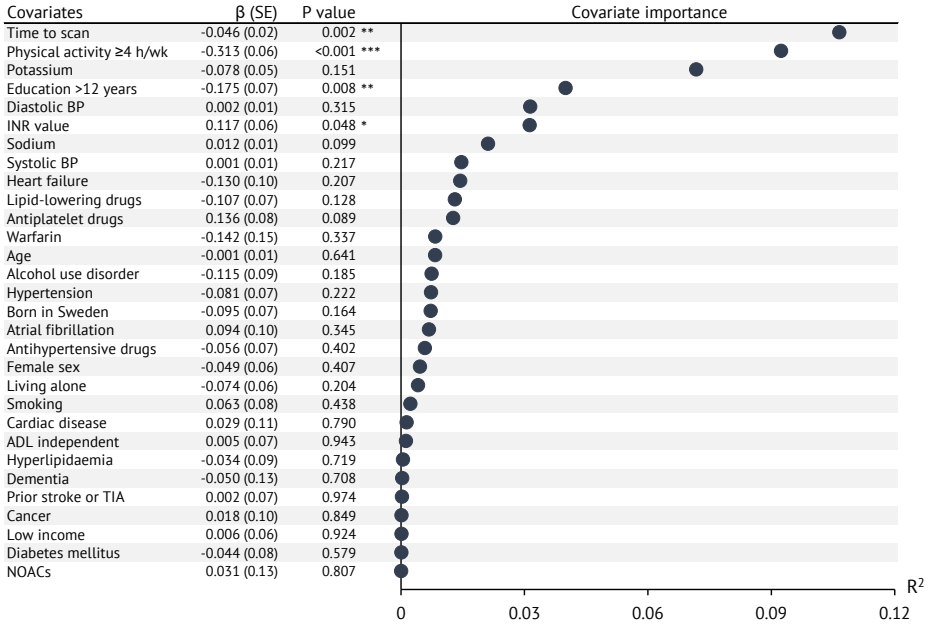

Figure 2 Relative importance among predictors of haematoma volume. Associations of covariates with haematoma volume were calculated in a multivariate ordinary least-squares model including all covariates, adjusted for haematoma location. The explained variance (R^2) was computed for each covariate in this model as a measure of relative importance. The R^2 takes values between 0 and 1, and a value closer to 1 indicates that more of the variance is explained by the covariate (ie, higher importance). Covariates are arranged in descending order according to their importance. The estimated beta coefficients and R^2 values are indicated on the same line for each covariate. Results were obtained from imputed data. ADL, activities of daily living; BP, blood pressure; ICH, intracerebral haemorrhage; INR, International Normalised Ratio; NOACs, non-vitamin k oral anticoagulants; SE, standard error; TIA, transient ischaemic attack.

haematoma volumes in deep and lobar locations. Being physically active prior to ICH was also associated with mild stroke severity, a good 1-week functional status and 90-day survival. Associations between prestroke PA and ICH outcomes were partly mediated by smaller haematoma volumes, although the direct effects of PA were also significant. Hence, our results indicate that prestroke PA may independently decrease admission haematoma volume, improve recovery and prevent mortality in primary ICH.

Despite several neurosurgical and pharmaceutical trials in recent years, ICH remains a devastating disease with no broadly applicable treatment regime.[22] We have previously reported that prestroke PA was associated with lower NIHSS scores on admission and decreased short-term and long-term morality hazards for patients with ischaemic stroke and ICH.[9] In another recent study, prestroke PA was the only significant predictor of case fatality in 203 patients with haemorrhagic stroke (including ICH

Table 2 Associations of physical activity with ICH volume

	Physical activity <4 hour/week	Physical activity ≥4 hour/week	β (SE)	P value
Deep ICH, median volume (IQR)	11.7 (4.3–28.3)	5.9 (1.8–13.1)	−0.35 (0.08)*	<0.001
			−0.36 (0.09)†	<0.001
Lobar ICH, median volume (IQR)	30.3 (7.6–71.7)	15.1 (4.8–39.0)	−0.24 (0.10)*	0.018
			−0.23 (00)†	0.016
Infratentorial ICH, median volume (IQR)	8.0 (2.1–17.9)	3.9 (0.8–10.5)	−0.35 (0.14)*	0.017
			−0.29 (0.18)†	0.114

Associations of prestroke physical activity with haematoma volume in deep, lobar and infratentorial ICH were calculated in multivariate linear regression models. Results were obtained from imputed data.
*Adjusted for age, sex, education, time to scan and International Normalised Ratio (INR).
†Adjusted for propensity scores based on age, sex, birthland, education, income, activities of daily living, living situation, smoking, alcohol, hypertension, hyperlipidaemia, prior stroke or TIA, atrial fibrillation, diabetes mellitus, cardiac disease, heart failure, dementia, cancer, lipid-lowering drugs, antiplatelet drugs, antihypertensive drugs, non-vitamin k oral anticoagulants, warfarin and INR.
ICH, intracerebral haemorrhage; TIA, transient ischaemic attack.

Table 3 Associations of physical activity with radiological and clinical ICH outcomes

	Physical activity <4 hour/week	Physical activity ≥4 hour/week	OR (95% CI)	P value
Midline shift, Number/total number (%)	160/387 (41.3)	65/235 (27.7)	0.67 (0.44 to 0.99)*	0.049
			1.09 (0.64 to 1.87)†	0.740
IVH, Number/total number (%)	148/387 (38.2)	55/235 (23.4)	0.65 (0.42 to 0.98)*	0.044
			0.88 (0.55 to 1.39)†	0.573
Admission NIHSS 0–4, Number/total number (%)	102/387 (26.4)	133/235 (56.6)	2.53 (1.59 to 4.01)*	<0.001
			1.99 (1.18 to 3.35)†	0.010
One-week mRS 0–3, Number/total number (%)	75/387 (19.4)	127/235 (54.0)	2.12 (1.37 to 3.30)*	<0.001
			1.64 (1.01 to 2.66)†	0.048
90-day survival, Number/total number (%)	254/387 (65.6)	217/235 (92.3)	3.48 (2.06 to 5.91)*	<0.001
			2.91 (1.58 to 5.37)†	<0.001

Associations of prestroke physical activity with midline shift, IVH, NIHSS 0–4, mRS 0–3 and 90-day survival were calculated in binary logistic regression models. Results were obtained from imputed data.
*Adjusted for haematoma location and propensity scores based on age, sex, birthland, education, income, activities of daily living, living situation, smoking, alcohol, hypertension, hyperlipidemia, prior stroke or TIA, atrial fibrillation, diabetes mellitus, cardiac disease, heart failure, dementia, cancer, lipid-lowering drugs, antiplatelet drugs, antihypertensive drugs, non-vitamin k oral anticoagulants, warfarin and International Normalised Ratio.
†Adjusted for haematoma location, propensity scores and haematoma volume.
ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

and subarachnoid haemorrhages).[23] Studies on ischaemic strokes have found associations between regular PA and improved short-term and long-term clinical outcome, increased levels of endothelial growth factor and insulin-like growth factor I as well as smaller infarct volumes.[24] Although related mechanism for ICH remain unknown, PA may to promote cerebral ischaemic tolerance via beneficial effects on the autonomic regulation,

Table 4 Mediation analyses

Associations of physical activity ≥4 hour/week	Estimate (95% CI)	P value
Admission NIHSS 0–4		
Average causal mediation effect	0.10 (0.05 to 0.16)	<0.001
Average direct effect	0.08 (0.02 to 0.15)	0.004
Average total effect	0.18 (0.10 to 0.27)	<0.001
Proportion mediated by haematoma volume	0.57 (0.31 to 0.87)	<0.001
One-week mRS 0–3		
Average causal mediation effect	0.10 (0.05 to 0.15)	<0.001
Average direct effect	0.07 (0.01 to 0.15)	0.032
Average total effect	0.17 (0.09 to 0.25)	<0.001
Proportion mediated by haematoma volume	0.58 (0.29 to 0.96)	<0.001
90-day survival		
Average causal mediation effect	0.05 (0.02 to 0.09)	<0.001
Average direct effect	0.14 (0.06 to 0.22)	<0.001
Average total effect	0.19 (0.10 to 0.28)	<0.001
Proportion mediated by haematoma volume	0.28 (0.14 to 0.48)	<0.001

Associations of prestroke physical activity with NIHSS 0–4, mRS 0–3 and 90-day survival were calculated in bootstrapped binary logistic regression analyses with ICH volume as mediator. Proportion (%) denotes the magnitude of the mediation effect (average causal mediation effect divided by the total effect). The models were adjusted for age, sex, birthland, education, income, activities of daily living, living situation, smoking, alcohol, hypertension, hyperlipidaemia, prior stroke or TIA, atrial fibrillation, diabetes mellitus, cardiac disease, heart failure, dementia, cancer, lipid-lowering drugs, antiplatelet drugs, antihypertensive drugs, non-vitamin k oral anticoagulants, warfarin and International Normalised Ratio (INR). Results were obtained from imputed data.
ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

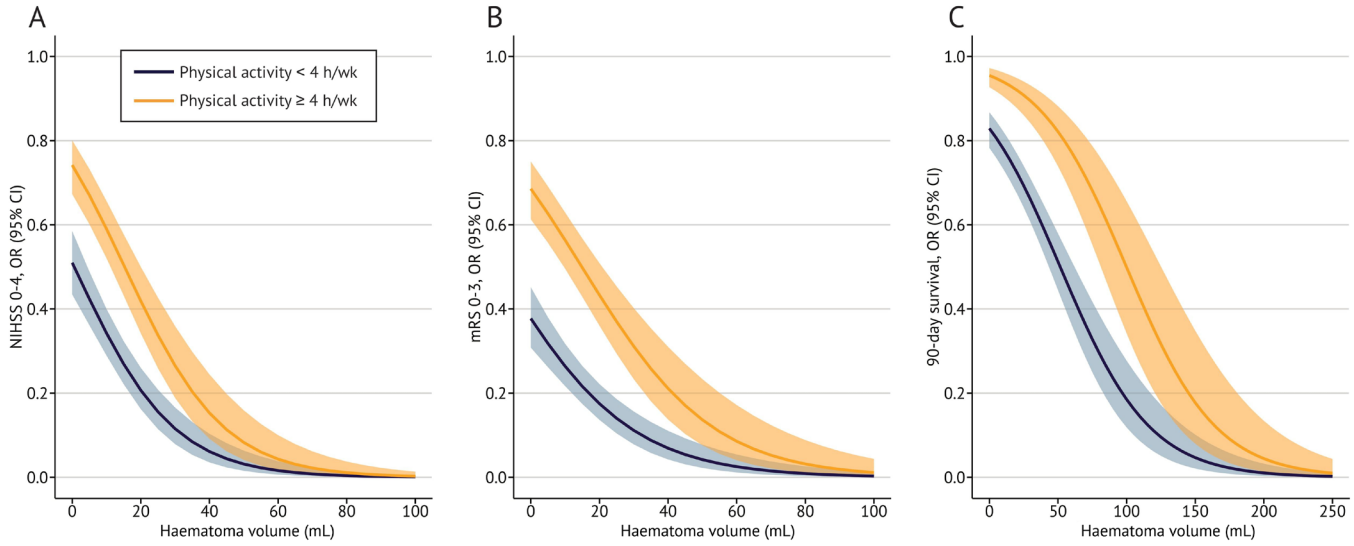

Figure 3 Relationship between physical activity, haematoma volume and ICH outcomes. Probability of (A) mild admission stroke severity (NIHSS 0–4), (B) a good 1 week functional status (mRS 0–3) and (C) 90-day survival with 95% CIs were calculated using multivariable logistic regressions, adjusted for prestroke physical activity and haematoma volume. ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

with improved cardiac function, and increased cerebral blood flow.[25] Additionally, regular PA is thought to promote angiogenesis, neurogenesis and maintenance of the blood-brain barrier, while reducing apoptosis and decreasing inflammation.[8]

Exercise preconditioning has been studied in relation to haematoma volume in one prior experimental study on mice, in which the authors found smaller haematoma volumes after 5 weeks of treadmill exercise for 60 min/day when compared with mice those were kept sedentary.[10] Physically active individuals have lower BP,[26] and potentially lesser beta-amyloid depositions,[27 28] with overall healthier vessels and may thereby be less prone to haematoma expansion compared with their physically inactive counterparts. Furthermore, radiological markers such as white-matter injury,[29] and asymptomatic microbleeds,[30] have previously been linked to the volume of ICH. In turn, higher levels of PA have been linked to fewer white matter lesions, upheld cerebral microstructural integrity and less microbleeds.[31–33] These associations may potentially explain the biological pathways for how prestroke PA could affect the volume of ICH. Nevertheless, our results indicate that associations of prestroke PA with ICH outcomes diminish as the haematoma volumes increase. For patients with large haematomas, surgical interventions are likely needed to improve the outcome. We could, however, not test the effect modification of neurosurgery in the regression models, as only 6% of included patients received such interventions.

Few among previously identified predictors of haematoma volume are modifiable. A dose–response relationship has been reported between higher INR values and haematoma volume.[6 34] In the present study, increasing INR values were also associated with larger ICH volumes. High education emerged as an important predictor of decreased ICH volume in our study. Education may indirectly influence haematoma volume through its impact on lifestyle factors and health literacy. Individuals with higher education often demonstrate better abilities to obtain, understand and use health-related information, enabling them to make informed decisions and adhere to medical recommendations and treatments. However, no prior study has confirmed a protective association between education and haemorrhagic strokes.[35] Statin treatment,[36] antihypertensive treatment[37] and antiplatelet treatment[6] have been associated with larger ICHs previously. Conversely, we found no associations between prestroke medications and ICH volume. As in previous studies, time to scan was inversely associated with haematoma volume.[6 34]

Strengths and limitations

To our knowledge, no prior study has explored the relationship between PA and ICH volume. We identify novel, location-specific associations between prestroke PA and the volume of deep and lobar ICH. This study provides a mechanistic explanation to the association between prestroke PA and favourable poststroke outcomes for patients with ICH. The results are supported by the large cohort of included patients, detailed ascertainment of ICH and the use of data from validated in-patient registries. The high coverage in Sweden's quality-of care stroke registries (>90%),[38] in combination with the tax-financed healthcare in Sweden which is accessible to everyone, minimises selection bias.

Our study also has several limitations. First, there were only 97 patients with infratentorial ICH included. The association between PA and infratentorial haematoma

volume did not remain significant when adjusted for the covariate imbalance. Although, the pathophysiological mechanisms of infratentorial ICH may be less susceptible to PA, it is possible that the analysis was underpowered to detect a true difference and, therefore, merits further evaluation. The self-reported and retrospective assessments of prestroke PA are another limitation of the study, which introduce the risk of recall and misclassification bias. No automated software for quantification of ICH volume was available at the included hospitals at the time of this study. Volumetric assessments were instead performed using the ABC/2 method with limited accuracy in comparison to computerised techniques, particularly in larger irregular or non-ellipsoid-shaped haematomas. However, as our analyses aimed to explore the relative difference in haematoma volume between physically active and inactive patients, the ABC/2 method provides adequate precision.[39] Another limitation is the nonrandomised design, with a risk of unobserved confounders. Owning to the use of clinical routine data and in-patient registries, there were a limited number of covariates available. Importantly, we were unable to study the relationship between prestroke PA and haematoma expansion, as patients did not routinely undergo repeated brain imaging, nor were we able to assess the long-term functional outcomes of ICH. Additionally, pain, fatigue and emotional distress are common factors following ICH that were not observed in this study but may have influenced clinical outcomes and confounded reported associations.[40] Consequently, our results need to be confirmed by future prospective, population-based studies.

CONCLUSIONS

In this register-based cohort study of 686 patients with primary ICH, we found significant associations between light prestroke PA of ≥4 hour/week in the year prior to stroke and smaller haematoma volumes in deep and lobar locations. We also observed higher likelihoods of mild admission stroke severity, a good 1-week functional status and 90-day survival in physically active patients, which were in partly mediated by smaller haematoma volumes.

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Contributors AV, DB, TS and KSS designed the study. AV, AD and KSS performed the literature search and review of evidence before the study. AV and DB collected the data under supervision of TS. AV and DB analysed the data. AV created the figures. All authors contributed to the interpretation of the results. All authors reviewed and approved the final version of the manuscript. The study was guaranteed by KSS, who had access to the data and made the final decision to publish

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Approval for data collection was obtained from the Regional Ethics Board of Gothenburg in 2016 (Number 346–16) and from the Swedish Ethics Review Authority in 2021 (Number 2021–03324).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data cannot be made publicly available because of Swedish regulations. Researchers may apply to access anonymised data from Professor Katharina Stibrant Sunnerhagen after obtaining necessary approvals.

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Supplemental Content

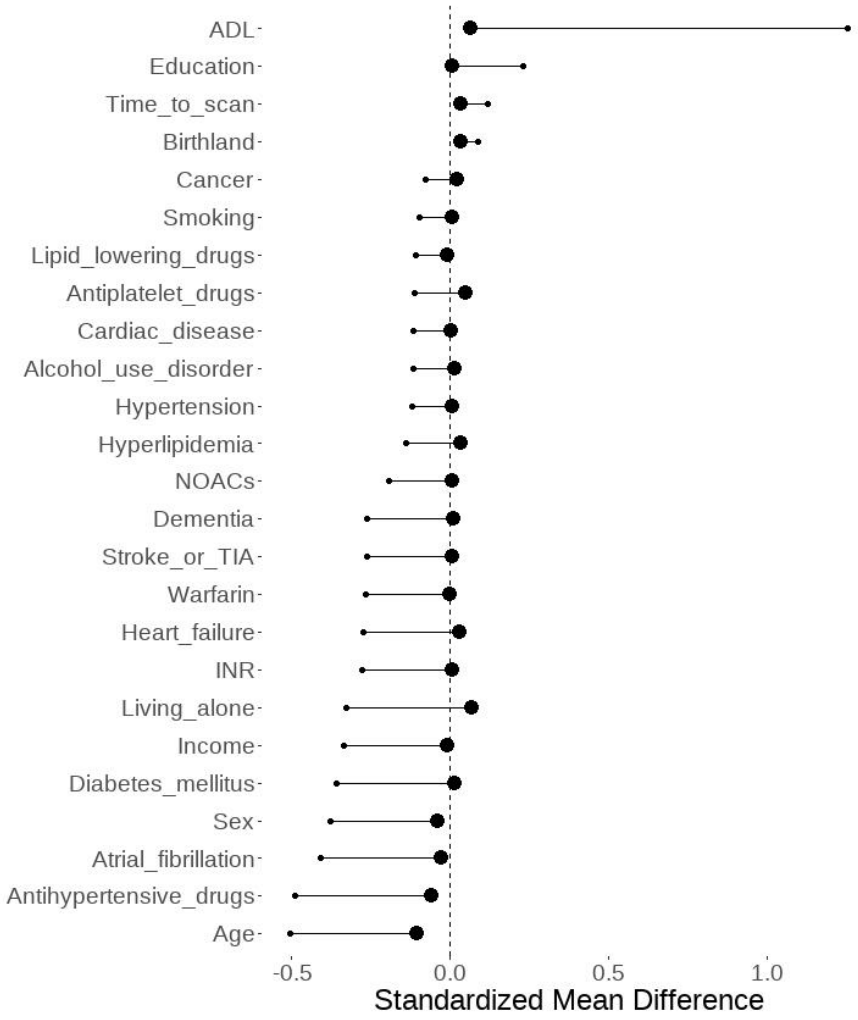
Viktorisson A, Buvarp D, Danielsson A, Skoglund T, S Sunnerhagen K. Prestroke Physical Activity is Associated with Admission Hematoma Volume and the Clinical Outcome of Intracerebral Hemorrhage

Supplementary Figure 1. Distribution of covariates before and after propensity score adjustment

Supplementary Table 1. Sensitivity analyses for associations of physical activity with ICH volume

Supplementary Table 2. Sensitivity analyses for associations of physical activity with radiological and clinical ICH outcomes

Viktorisson A, *et al. Stroke Vasc Neurol* 2023;0:1–10. doi: 10.1136/svn-2023-002316



Supplementary Figure 1. Distribution of covariates before and after propensity score adjustment

Standardized mean differences in distribution of covariates between physically active and inactive patients before and after propensity score adjustment. A standardized mean difference of > 0.1 is commonly considered a sign of important covariate imbalance. Small dots represent unadjusted differences, and large dots represent adjusted differences. The propensity scores were computed using a generalized boosted logistic regression model including all covariates displayed. Abbreviations: ADL indicates Activities of daily living; NOAC, Non-vitamin k oral anticoagulants; and TIA, Transient ischemic attack.

Supplementary Table 1. Sensitivity analyses of associations between pre-stroke physical activity and hematoma volume

	Deep ICH volume		Lobar ICH volume		Infratentorial ICH volume	
	β (SE)	**P value**	**β (SE)**	**P value**	**β (SE)**	**P value**
Physical activity ≥4 h/wk	-0.35 (0.08) †	< 0.001	-0.26 (0.10) †	0.011	-0.32 (0.15) †	0.039
	-0.39 (0.09) ‡	< 0.001	-0.22 (0.10) ‡	0.024	-0.18 (0.18) ‡	0.317

Associations of pre-stroke physical activity with hematoma volume in deep, lobar and infratentorial ICH were calculated in multivariate linear regression models for cases with complete data on physical activity (n=622). Abbreviations: ICH indicates Intracerebral hemorrhage; and SE, Standard error.

† Adjusted for age, sex, education, time to scan and International Normalized Ratio (INR). ‘

‡ Adjusted for propensity scores based on age, sex, birthland, education, income, activities of daily living, living situation, smoking, alcohol, hypertension, hyperlipidemia, prior stroke or TIA, atrial fibrillation, diabetes mellitus, cardiac disease, heart failure, dementia, cancer, lipid-lowering drugs, antiplatelet drugs, antihypertensive drugs, and non-vitamin k oral anticoagulants, warfarin, time to scan, and INR.

Supplementary Table 2. Sensitivity analyses for associations of physical activity with radiological and clinical ICH outcomes

	Midline shift		IVH		Admission NIHSS 0-4		One-week mRS 0-3		90-day survival	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Physical activity ≥4 h/wk	0.69 (0.44-1.08) †	0.107	0.68 (0.43-1.06) †	0.092	2.22 (1.38-3.58) †	< 0.001	2.13 (1.34-3.39) †	0.002	3.38 (1.84-6.23) †	< 0.001
	1.09 (0.61.1.93) ‡	0.780	0.92 (0.57-1.49) ‡	0.744	1.77 (1.04-3.01) ‡	0.037	1.71 (1.03-2.84) ‡	0.039	2.43 (1.22-4.84) ‡	0.012

Associations of pre-stroke physical activity with midline shift, intraventricular hemorrhage, NIHSS 0-4, mRS 0-3, and 90-day survival were calculated in multivariate binary logistic regression models for cases with complete data on physical activity (n=622). Abbreviations: OR indicates Odds ratio; CI, Confidence interval; IVH, Intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale; and mRS, modified Rankin Scale.

† Adjusted for hematoma location propensity scores based on age, sex, birthland, education, income, activities of daily living, living situation, smoking, alcohol, hypertension, hyperlipidemia, prior stroke or TIA, atrial fibrillation, diabetes mellitus, cardiac disease, heart failure, dementia, cancer, lipid-lowering drugs, antiplatelet drugs, antihypertensive drugs, and non-vitamin k oral anticoagulants, warfarin, time to scan, and INR

‡ Adjusted for hematoma location, propensity scores, and hematoma volume.