Associations of Prestroke Physical Activity With Stroke Severity and Mortality After Intracerebral Hemorrhage Compared to Ischemic Stroke

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Abstract

Background and Objectives: Pre-stroke physical activity may protect the brain from severe consequences of stroke. However, prior studies on this subject included mainly ischemic stroke cases, and the association between pre-stroke physical activity and outcomes after intracerebral hemorrhage is uncertain. Therefore, we sought to examine the associations between pre-stroke physical activity, stroke severity, and all-cause mortality after intracerebral hemorrhage in comparison to ischemic stroke.

Methods: This was a longitudinal, register-based, cohort study. All adult patients with intracerebral hemorrhage or ischemic stroke admitted to three stroke units in Gothenburg, Sweden between 1 November 2014 and 30 June 2019 were screened for inclusion. Physical activity was defined as light physical activity ≥4 h/week, or moderate physical activity ≥2 h/week the year before stroke. Stroke severity was assessed on admission using the National Institutes of Health Stroke Scale. All-cause mortality rates were followed up to 7 years, from the time of incident stroke until death or censoring. Ordinal logit models and Cox proportional-hazards models were used to estimate adjusted associations of pre-stroke physical activity.

Results: We included 763 patients with intracerebral hemorrhage and 4225 with ischemic stroke. Pre-stroke physical activity was associated with less severe strokes by an adjusted odds ratio of 3.57 (99% CI, 2.35-5.47) for intracerebral hemorrhages and 1.92 (99% CI 1.59-2.33) for ischemic strokes. During a median follow-up of 4.7 (IQR 3.5-5.9) years, 48.5% of patients with intracerebral hemorrhage died, compared to 37.5% with ischemic stroke. Pre-stroke physical activity was associated with decreased short-term mortality (0 to 30 days) by an adjusted hazard ratio of 0.30 (99% CI 0.17-0.54) after intracerebral hemorrhage, and 0.22 (99% CI 0.13-0.37) after ischemic stroke. Pre-stroke physical activity was further associated with decreased long-term mortality (30 days to 2 years) by an adjusted hazard ratio of 0.40 (99% CI 0.21-0.77) after intracerebral hemorrhage, and 0.49 (99% CI 0.38-0.62) after ischemic stroke.

Discussion: Pre-stroke physical activity was associated with decreased stroke severity and all-cause mortality after intracerebral hemorrhage and ischemic stroke, independent of other risk factors. Based on current knowledge, health care professionals should promote physical activity as part of primary stroke prevention.
Introduction

The health benefits of physical activity are significant, and there is a dose-response relationship between the volume of physical activity and risk of cardiovascular morbidity and mortality. Regular physical activity serves as an important component in the primary and secondary prevention of stroke, and counteracts several cerebrovascular risk factors. However, the association between pre-stroke physical activity and outcomes after stroke is not well established. Pre-stroke physical activity has been associated with reduced stroke severity, in-hospital mortality, cardiovascular mortality, and all-cause mortality. Contrarily, some prior studies found no association between pre-stroke physical activity and stroke severity or post-stroke mortality, after covariate adjustment. Moreover, the relationship between pre-stroke physical activity and post-stroke outcomes has been studied only in samples with a majority of ischemic stroke cases. No prior study has investigated the association between pre-stroke physical activity and stroke severity or risk of mortality for intracerebral hemorrhage.

Non-traumatic intracerebral hemorrhage is a spontaneous bleeding within the brain parenchyma and usually a long-term consequence of arterial hypertension or cerebral amyloid angiopathy. It is the most lethal type of stroke, with early mortality rates above 40%, and no trend towards improvement in recent decades. The global socioeconomic consequences of intracerebral hemorrhages are significant, and the incidence is particularly high in low-income populations. Modifiable predictors of outcomes following intracerebral hemorrhage are scarce and there is no largely applicable intervention that can improve the outcome for those affected. Regular physical activity decreases the risk of intracerebral hemorrhage, prevents small vessel disease through decreased arterial blood pressure, and could potentially lower levels of circulating beta-amyloid. Recent preclinical data also suggest that preconditioning physical activity reduces hematoma volume, and facilitate recovery after induced intracerebral hemorrhage in mice.

The Physical Activity Pre-Stroke in GOTHenbug (PAPSIGOT) is a register-based project that investigates the association between physical activity and outcomes after stroke (Swedish registry of trials number: 246671). In this study, we investigated the associations between pre-stroke physical
activity, stroke severity, and all-cause mortality in patients with intracerebral hemorrhage compared to patients with ischemic stroke.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Regional Ethical Board of Gothenburg on 4 May 2016 (registration number: 346-16) and by the Swedish Ethical Review Authority in 2021 (registration number: 2021-03324). Research using quality registers (Väststroke and Riksstroke) are exempt from the general rule of patient consent according to the Swedish Personal Data Act (Swedish law No. SFS 1998:204), but patients are informed about the possibility to opt-out from the registers. The Swedish Personal Data Act also allows data from medical records to be collected for quality control, without receiving written informed consent.

Data collection

In this longitudinal, register-based cohort study, we collected data on all adult patients with intracerebral hemorrhage admitted to three stroke units between 1 November 2014 and 30 June 2019. We also included all adult patients with ischemic stroke treated during this period, with complete data on corresponding variables to patients with intracerebral hemorrhage. Stroke cases were identified in the Väststroke register, which includes data from routine clinical work on all patients treated for stroke within the Sahlgrenska University Hospital, in Gothenburg, Sweden. Identified stroke cases were cross-referenced with inpatient medical records to ensure reliability and reduce missing data. We reviewed and included assessments of stroke characteristics, physical activity, smoking status, and comorbidities diagnosed on hospital arrival. Additional stroke characteristics were collected from the National Swedish Stroke Register (Riksstroke). Socioeconomic variables were collected from the Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA). Pre-stroke comorbidities were collected from the National Patient Registry (NPR). Survival rates were collected from the Swedish Cause of the Death Register. Data merging with national registries was performed by the National Board of Health and Welfare using the personal identity numbers that are provided to all residents in Sweden at birth or shortly after immigration. Patients with a non-specified
stroke (i.e. no radiology), unavailable medical records, or lacking a Swedish personal identity number were excluded. Follow-up of post-stroke survival continued until 19 October 2021. The study adheres to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.29

Outcomes

Admission stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).30 Higher NIHSS scores indicate greater stroke severity, with a maximum score of 42. The NIHSS scores were categorized as severe (>14), moderate (5-14), or mild (0-4). NIHSS scores were assessed using medical records for cases with missing data, based on the first neurological examination at the hospital, prior to any documented intervention.31 Patients in a comatose state, for which a complete neurological examination was not possible, were categorized as having a severe stroke. All-cause mortality and cerebrovascular disease (CVD) as underlying causes of death were recorded for all included patients. CVD was defined according to the International Statistical Classification of Diseases and Related Health Problems - Tenth Revision (ICD-10) codes (I60-I69). The follow-up time for survival was measured from the time of incident stroke until death or censoring on 19 October 2021, allowing for a minimum follow-up of >2 years. Short-term mortality was defined as 0 to 30 days and long-term mortality as 30 days to 2 years.

Pre-stroke physical activity

Physical activity was defined as light physical activity ≥4 h/week, or moderate physical activity ≥2 h/week during the year before stroke, using the Saltin-Grimby Physical Activity Level Scale (SGPALS).32,33 Light physical activity includes activities such as bicycling, walking, gardening, or bowling, in the SGPALS; whereas moderate physical activity includes activities such as running, swimming, gymnastics or playing tennis. The assessments were performed by physiotherapists working at the included stroke units. A next of kin was asked if the patient had impaired cognition or was unconscious. For cases with missing data on SGPALS in the Väststroke register, assessments were based on available information from medical records. Patients who were unable to move freely indoors before the stroke were always categorized as inactive.
Definition of covariates

All covariates were recorded at the time of incident stroke, and included sex, age, country of birth, education, income, living situation, independence in activities of daily living (ADL), smoking, alcohol disorder, drug abuse, comorbidities, and pre-stroke medical treatments. Income was defined as household income during the year before the stroke and congregated in tertiles. Educational level was defined as the highest completed stage, trichotomized in <10 years (primary school), 10-12 years (secondary school), and >12 years (postsecondary or university education). Smoking was defined as current smoking or absence of smoking for <1 year. If smoking status was not recorded in the registries or medical records, the patient was considered a non-smoker. Pre-stroke comorbidities and medications accounted for are presented in eTables 1 and 2.

Charlson comorbidity index

The Charlson comorbidity index was calculated for each patient at the time of incident stroke. It is a weighted score, validated to predict the risk of 1-year mortality for hospitalized patients, based on specific comorbid conditions. Survival rates were stratified using Charlson comorbidity index scores in groups with no comorbidity (0 points), mild comorbidity (1-2 points), and severe comorbidity (>2 points).

Statistical analysis

A priori power calculation was performed to estimate the required time period for data collection, and has been published previously. The calculation was based on NIHSS scores trichotomized in three groups. We calculated that a sample size of >628 patients with intracerebral hemorrhage would be sufficient for analyses at an alpha level of 0.01 with 0.8 power. Descriptive statistics for patients with missing observations are presented in eTable 3. Missing observations were handled using predictive mean matching, implemented for multiple imputation by chained equations (MICE). Each variable was imputed via an iterative series of predictive models for ordered categorical data. All covariates and outcome variables were included in each model. However, separate imputation models were used for patients with intracerebral and ischemic stroke.
Descriptive data are presented as counts and proportions for categorical variables or median with interquartile range (IQR) for ordinal variables. Multicollinearity was assessed using Spearman's rank correlation for ordinal variables, and Phi coefficient for nominal variables. Adjusted associations between pre-stroke physical activity and admission stroke severity (NIHSS scores 0-4 vs 5-14 or > 14) were evaluated using ordinal logit regression models for intracerebral hemorrhage and ischemic stroke, respectively. Only variables with ≥10 observations in each outcome category were included. Cumulative survival probabilities were calculated with additional Kaplan-Meier curves. Associations between pre-stroke physical activity, short- and long-term all-cause mortality was evaluated using Cox proportional-hazards models. Schoenfeld residuals were used to check the independence between residuals and time.

All statistical tests were interpreted at a two-tailed significance level of 0.01 to account for multiple comparisons. Adjusted odds ratios (aOR) and hazard ratios (aHR) for included covariates were derived from the respective model coefficients, and accompanying 99% confidence intervals (CIs) are presented for each covariate. There was no stepwise selection in the regression models, as all included covariates were considered potential confounders to the association between pre-stroke physical activity and stroke outcomes. All analyses were done using SPSS Statistics (IBM Corp. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY) and R software (R Core Team, Version 4.0.2 for Windows; R Foundation for Statistical Computing, Vienna, Austria).

Data Availability
Anonymized data not published within this article will be made available to any qualified investigator by Professor Katharina Stibrant Sunnerhagen.

Results
Patient characteristics
During the study period, 770 patients were diagnosed with intracerebral hemorrhage. In total, six patients were excluded due to a lack of a Swedish personal identity number and one due to unavailable medical records. The final sample consisted of 763 patients with intracerebral hemorrhage in addition to 4425 patients with ischemic stroke. Baseline characteristics of the study population are presented in Table 1. Among physically active patients with intracerebral hemorrhage, 255 (88.5%) performed light physical activity for ≥4 h/week, and 33 (11.5%) moderate physical activity for ≥2 h/week the year before stroke, compared to 1659 (86.8%), and 252 (13.2%) among patients with ischemic stroke. The localizations of hematomas were similarly distributed in physically active and inactive patients, however only inactive patients presented with primary intraventricular hemorrhages (eTable 4). Following intracerebral hemorrhage, 50 (6.6%) patients underwent neurosurgery, while 7 patients with ischemic stroke were treated with hemicraniectomy, 381 (8.6%) with thrombectomy, and 558 (12.6%) received thrombolysis.

**Stroke severity**

In the group of patients with intracerebral hemorrhage, 265 (34.7%) presented with mild stroke, 236 (30.9%) moderate stroke, and 262 (34.3%) severe stroke, compared to 2889 (65.3%), 1071 (24.2%), and 465 (10.5%) for patients with ischemic stroke. Pre-stroke physical activity was the strongest predictor of less severe stroke symptoms for intracerebral hemorrhages (aOR 3.57, 99% CI 2.35-5.47, p<0.001) and ischemic strokes (aOR 1.92, 99% CI 1.59-2.33, p<0.001) in the ordinal regression models (Figure 1).

**Post-stroke mortality**

During a median follow-up of 4.7 (IQR, 3.5-5.9) years after the incident stroke, 2029 (39.1%) of the patients had died (370 [48.5%] after intracerebral hemorrhage and 1659 [37.5%] after ischemic stroke). Following intracerebral hemorrhage, 183 (24.0%) died within 30 days, compared to 329 (7.4%) after ischemic stroke. CVD was the cause of death in 218 (58.9%) patients with intracerebral hemorrhage and in 804 (48.5%) patients with ischemic stroke. Physically active patients had considerably higher survival compared to inactive patients (Figure 2), and the difference remained stable over the course of 5 years (Table 2). Notably, the group of patients with severe comorbidities who were physically active before intracerebral hemorrhage had a higher survival probability.
compared to inactive patients with no comorbid conditions, and a similar trend was observed for ischemic strokes (Figure 3). The comorbid conditions are presented in eTable 5.

Pre-stroke physical activity was associated with 70% lower short-term mortality after intracerebral hemorrhage (aHR 0.30, 99% CI 0.17-0.54, p<0.001), and 78% after ischemic stroke (aHR 0.22, 99% CI 0.13-0.37, p<0.001) (Table 3). Thereafter was pre-stroke physical activity associated with a 60% lower risk of long-term mortality after intracerebral hemorrhage (aHR 0.40, 99% CI 0.21-0.77, <0.001), and 51% after ischemic stroke (aHR 0.49, 99% CI 0.38-0.62, p<0.001). When additionally adjusted for admission stroke severity (NIHSS), pre-stroke physical activity remained associated with a 52% lower risk of long-term mortality after intracerebral hemorrhage and 48% after ischemic stroke (eTable 6).

Dose-response of physical activity

There was no statistically significant difference in the odds of less severe stroke symptoms between patients who performed light physical activity ≥4 h/week and moderate physical activity ≥2 h/week the year before stroke (Table 4). Moderate pre-stroke physical activity was associated with a lower crude hazard ratio for post-stroke mortality (HR 0.11, 99% CI 0.06-0.19, p<0.001) compared to light physical activity (HR 0.33, 99% CI 0.28-0.39, p<0.001) in patients with ischemic stroke. Although a similar trend was observed for intracerebral hemorrhages, there was no statistically significant difference.

Discussion

In this longitudinal, register-based, cohort study, we observed that pre-stroke physical activity was strongly associated with less severe stroke symptoms at hospital admission in patients with intracerebral hemorrhage and ischemic stroke. Notably, the magnitude of this association was greater for intracerebral hemorrhage than for ischemic stroke, with non-overlapping confidence intervals. Furthermore, we found that pre-stroke physical activity was independently associated with a lower risk of short- and long-term all-cause mortality. We also found a dose-response relationship between a higher intensity of pre-stroke physical activity and reduced mortality hazards after ischemic strokes. However, there were no significant differences between patients with light and moderate physical activity in predictions of stroke severity or post-stroke mortality after intracerebral hemorrhage, which is likely contributed by the small proportion of moderately active patients in this group. Although the
association between pre-stroke physical activity and favorable outcomes after stroke has been reported previously, few studies included patients with intracerebral hemorrhage. To our knowledge, only one prior study has reported separate analyses for intracerebral hemorrhage, in which there was no association between pre-stroke physical activity and modified Rankin Scale scores at discharge in 221 men with intracerebral hemorrhage from the Physicians' Health Study.37

Pre-stroke physical activity emerged as the strongest predictor of milder admission stroke severity in our study. This finding is consistent with previous research within the PAPSIGOT project, in which patients engaging in light physical activity for ≥4 hours/week were more likely to have a mild stroke (NIHSS 0-5) compared to those who were less active.10 In a larger study, pre-stroke physical activity for ≥30 minutes, 3 times/week was associated with less severe strokes (NIHSS 1-20), and in particular, with the lowest quintile of stroke severity (NIHSS 1-5).12 Similarly, a dose-dependent relationship between the duration of weekly pre-stroke physical activity and reduced ischemic stroke severity (NIHSS 0-3) has been reported previously.7,8 In another study, pre-stroke physical activity, defined as >1000 MET minutes/week, predicted lower NIHSS scores in patients with ischemic stroke.11

Independent of admission stroke severity and other risk factors, our findings demonstrate an association between pre-stroke physical activity and a lower risk of all-cause mortality among patients with intracerebral hemorrhage and ischemic stroke. Comparable results were observed in two recent studies with samples including predominantly ischemic stroke cases. Most recently, a higher level of 6-year accumulated pre-stroke physical activity was associated with lower all-cause mortality, and cardiovascular mortality,13 whereas the other study indicated that inactive individuals, with a basal metabolic rate <1.70, had a greater risk of mortality at 1, and 5 years after stroke.15 Earlier, women with no pre-stroke physical activity were found to have a 39% higher risk of post-stroke mortality compared to women with physical activity for >150 minutes/week.14 Pre-stroke physical activity has also been previously associated with reduced in-hospital mortality.12

Although some studies have failed to detect associations between pre-stroke physical activity, stroke severity, and post-stroke mortality, cumulative evidence suggests that pre-stroke physical activity...
improves outcomes after stroke. Exercise and physical activity are thought to induce brain ischemic tolerance via changes in endothelial function and the inflammatory response, induced angiogenesis and neurogenesis, inhibition of apoptotic pathways, and increased cerebral blood flow. For intracerebral hemorrhage, the outcome is strongly determined by the volume, localization, and expansion of the hematoma. The role of ischemic tolerance in intracerebral hemorrhage remains unknown; however, a recent preclinical study reported that treadmill exercise before intracerebral hemorrhage in aging mice can decrease hematoma volume, prevent withstanding neurological deficits, and improve recovery from weight loss. In addition, physically active individuals are likely to have healthier vessels, with less vascular calcification from atherosclerotic changes, mineral deposition, and cerebral amyloid angiopathy, which may decrease the possibility of hematoma expansion. Predictors of the outcome after intracerebral hemorrhage may also differ significantly between deep and lobar hematomas. Although hematoma volumes were not analyzed in the current study, the location of hematomas were similar between physically active and inactive patients.

The key contribution of this study is the finding of a relationship between pre-stroke physical activity and favorable outcomes after intracerebral hemorrhage, which has not been previously reported, and is strengthened by the size of the data. This study also draws strength from Sweden’s large, comprehensive, and validated inpatient registry data, where underreporting is generally low. In addition, all persons in Sweden have equal access to tax-funded healthcare services, and very few with stroke can be expected to not receive hospital care, which increases the generalizability of our results. However, we acknowledge that the limitations of this study make causal inferences impossible. First, the internal validity is limited, due to the observational research design, which is sensitive to several types of bias. It is apparent that the group with pre-stroke physical activity differs from those with no physical activity in many aspects. Although several potential confounders were adjusted for in the multivariate regression models, there are factors unobserved in the present study. In particular, we were not able to adjust for body mass index, which may confound the relationship between pre-stroke physical activity and stroke outcomes. Second, there is an uncertainty associated with assessments collected from medical records. Third, the use of self-reported retrospective assessments for pre-stroke physical activity introduces a risk of misclassification and recall bias. The neurological consequences of stroke may hinder patients from correctly estimating their pre-stroke
activity. However, there is evidence supporting that self-reported physical activity assessments may be reliable and reproducible in stroke populations, and the SGPALS is a widely used instrument, which has been validated as an indicator of sedentary behavior and cardiovascular risk profile. Also, as the data were collected from routine clinical work, all patients and clinicians recording the variables were unaware of our research hypotheses.

Despite the well-known health benefits of physical activity, almost 30% of adults in the world are insufficiently active. Based on all current knowledge, public health strategies and health care professionals should promote physical activity to decrease the consequences of stroke. Physical activity is considered a safe intervention and can serve as a counterpart to polypharmacy in elderly and cerebrovascular at-risk populations. The results of this study strengthen the notion that a pre-stroke habit of physical activity may protect the brain in cases of intracerebral hemorrhage, and provide new incentives to explore related mechanisms. Future research, with prospectively collected data on physical activity is needed to confirm the results of the current study.
Figure 1. Associations between covariates and lower stroke severity.

Multivariate ordinal logit models predicting less severe stroke symptoms (NIHSS scores 0-4 vs 5-14 or > 14) for patients with intracerebral hemorrhage and ischemic stroke. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale. a=adjusted associations from models including pre-stroke physical activity, sex, age, country of birth, education, income, living situation, dependency, hyperlipidemia, prior stroke/TIA, atrial fibrillation, diabetes, coronary heart disease, heart failure, cancer, smoking, lipid-lowering drugs, antiplatelet drugs, anticoagulant drugs, and antihypertensive drugs.

|                           | Intracerebral hemorrhage | Ischemic stroke |
|---------------------------|--------------------------|-----------------|
|                           | aOR (99% CI) p           | aOR (99% CI) p  |
| Physical activity         | 3.57 (2.35-5.47) <0.001 | 1.92 (1.59-2.33) <0.001 |
| Sex, female               | 0.84 (0.57-1.24) 0.255  | 0.85 (0.71-1.01) 0.018  |
| Age <80 years             | 1.00 (Reference)        | 1.00 (Reference) |
| Age 70-80 years           | 0.93 (0.57-1.50) 0.689  | 1.02 (0.80-1.29) 0.869  |
| Age >80 years             | 0.80 (0.47-1.37) 0.294  | 0.77 (0.59-0.99) 0.007  |
| Born in Sweden            | 1.00 (Reference)        | 1.00 (Reference) |
| Born in Europe            | 0.71 (0.41-1.23) 0.113  | 0.92 (0.73-1.17) 0.381  |
| Born outside of Europe    | 0.92 (0.45-1.87) 0.760  | 0.71 (0.49-1.04) 0.020  |
| Education <10 years       | 1.00 (Reference)        | 1.00 (Reference) |
| Education 10-12 years     | 1.07 (0.70-1.64) 0.675  | 1.12 (0.92-1.36) 0.143  |
| Education ≥12 years       | 1.21 (0.72-2.04) 0.340  | 1.22 (0.96-1.55) 0.031  |
| Low income                | 1.00 (Reference)        | 1.00 (Reference) |
| Medium income             | 0.83 (0.53-1.32) 0.312  | 1.10 (0.89-1.35) 0.263  |
| High income               | 0.72 (0.43-1.20) 0.100  | 1.01 (0.79-1.20) 0.972  |
| Living alone              | 1.43 (0.96-2.13) 0.022  | 0.96 (0.79-1.15) 0.539  |
| Independent in ADL        | 1.43 (0.90-2.27) 0.044  | 1.64 (1.33-2.03) <0.001  |
| Hypertension              | 0.92 (0.48-1.75) 0.728  | 1.07 (0.84-1.38) 0.712  |
| Prior stroke/TIA          | 0.94 (0.59-1.49) 0.722  | 1.38 (1.08-1.76) <0.001  |
| Atrial fibrillation       | 0.67 (0.36-1.23) 0.092  | 0.44 (0.35-0.54) <0.001  |
| Diabetes                  | 1.04 (0.61-1.77) 0.842  | 1.07 (0.86-1.33) 0.420  |
| Coronary heart disease    | 0.88 (0.43-1.82) 0.657  | 0.73 (0.55-0.96) 0.003  |
| Heart failure             | 1.34 (0.69-2.61) 0.253  | 0.94 (0.72-1.24) 0.579  |
| Cancer                    | 0.98 (0.53-1.82) 0.930  | 0.95 (0.73-1.23) 0.581  |
| Smoking                   | 0.87 (0.51-1.50) 0.519  | 1.31 (1.00-1.72) 0.012  |
| Lipid-lowering drugs      | 1.42 (0.88-2.32) 0.061  | 0.96 (0.77-1.20) 0.639  |
| Antiplatelet drugs        | 1.08 (0.62-1.89) 0.705  | 1.06 (0.85-1.32) 0.512  |
| Anticoagulant drugs       | 1.47 (0.75-2.89) 0.138  | 1.48 (1.10-2.00) <0.001  |
| Antihypertensive drugs    | 1.33 (0.86-2.06) 0.092  | 1.05 (0.86-1.29) 0.493  |

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Figure 2. Kaplan-Meier curves for post-stroke survival stratified by physical activity.
Cumulative survival with 99% confidence intervals for (A) patients with intracerebral hemorrhage, and (B) patients with ischemic stroke.

Figure 3. Kaplan-Meier curves for post-stroke survival stratified by comorbidity.
Cumulative survival stratified by the weighted Charlson Comorbidity index as no comorbidity (0 points), mild comorbidity (1-2 points), and severe comorbidity (>2 points) for (A) inactive patients with intracerebral hemorrhage, (B) physically active patients with intracerebral hemorrhage, (C) inactive patients with ischemic stroke, and (D) physically active patients with ischemic stroke. Abbreviations: CCI, Charlson comorbidity index.
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### Table 1. Pre-stroke characteristics stratified by physical activity.

| Pre-stroke physical activity | Intracerebral hemorrhage | Ischemic stroke |
|-----------------------------|--------------------------|-----------------|
|                             | No physical activity     | Physical activity | No physical activity | Physical activity |
|                             | (n=475)                  | (n=288)         | (n=2514)             | (n=1911)          |
| Sex, Female                 |                          |                 |                      |                   |
| Female                      | 254 (53.5)               | 111 (38.5)      | 1353 (53.8)          | 745 (39.0)        |
| Age <70 years               | 129 (27.2)               | 131 (45.5)      | 618 (24.6)           | 791 (41.4)        |
| Age 70-80 years             | 134 (28.2)               | 93 (32.3)       | 716 (28.5)           | 693 (36.3)        |
| Age >80 years               | 212 (44.6)               | 64 (22.2)       | 1180 (46.9)          | 427 (22.3)        |
| Born in Sweden              | 368 (77.5)               | 234 (81.3)      | 1988 (79.1)          | 1544 (80.8)       |
| Born in Europe              | 68 (14.3)                | 30 (10.4)       | 396 (15.8)           | 252 (13.2)        |
| Born outside of Europe      | 39 (8.2)                 | 24 (8.3)        | 130 (5.2)            | 115 (6.0)         |
| Education <10 years         | 201 (42.3)               | 80 (27.8)       | 1037 (41.2)          | 532 (27.8)        |
| Education 10-12 years       | 184 (38.7)               | 132 (45.8)      | 984 (39.1)           | 762 (39.9)        |
| Education >12 years         | 90 (18.9)                | 76 (26.4)       | 493 (19.6)           | 617 (32.3)        |
| Low income                  | 179 (37.7)               | 71 (24.7)       | 1004 (39.9)          | 475 (24.9)        |
| Medium income               | 171 (36.0)               | 100 (34.7)      | 875 (34.8)           | 583 (30.5)        |
| High income                 | 125 (26.3)               | 117 (40.6)      | 635 (25.3)           | 853 (44.6)        |
| Living alone                | 246 (51.8)               | 105 (36.5)      | 1494 (59.4)          | 734 (38.4)        |
| Independent in ADL          | 296 (62.3)               | 265 (92.0)      | 1641 (65.3)          | 1820 (95.2)       |
| Hyperlipidemia              | 58 (12.2)                | 23 (8.0)        | 425 (16.9)           | 303 (15.9)        |
| Obesity (BMI > 30)          | 13 (2.7)                 | 0 (0)           | 95 (3.8)             | 48 (2.5)          |
| Prior stroke/TIA            | 127 (26.7)               | 47 (16.3)       | 467 (18.6)           | 271 (14.2)        |
| Atrial fibrillation         | 140 (29.5)               | 44 (15.3)       | 812 (32.3)           | 378 (19.8)        |
| Diabetes                    | 90 (18.9)                | 26 (9.0)        | 665 (26.5)           | 318 (16.6)        |
| Coronary heart disease      | 42 (8.8)                 | 16 (5.6)        | 353 (14.0)           | 176 (9.2)         |
| Heart failure               | 57 (12.0)                | 14 (4.9)        | 353 (14.0)           | 144 (7.5)         |
| Dementia                    | 25 (5.3)                 | 5 (1.7)         | 152 (6.0)            | 33 (1.7)          |
| Cancer                      | 48 (10.1)                | 21 (7.3)        | 325 (12.9)           | 191 (10.0)        |
| Depression                  | 29 (6.1)                 | 9 (3.1)         | 185 (7.4)            | 55 (2.9)          |
| Psychotic disorder          | 6 (1.3)                  | 1 (0.3)         | 36 (1.4)             | 6 (0.3)           |
| Alcohol disorder            | 19 (4.0)                 | 10 (3.5)        | 78 (3.1)             | 36 (1.9)          |
| Drug abuse                  | 10 (2.1)                 | 3 (1.0)         | 18 (0.7)             | 18 (0.9)          |
| Smoking                     | 75 (15.8)                | 34 (11.8)       | 346 (13.8)           | 219 (11.5)        |
| Lipid-lowering drugs        | 125 (26.3)               | 73 (25.3)       | 683 (27.2)           | 466 (24.4)        |
| Antiplatelet drugs          | 88 (18.5)                | 44 (15.3)       | 694 (27.6)           | 432 (22.6)        |
| Anticoagulant drugs         | 111 (23.4)               | 38 (13.2)       | 335 (13.3)           | 161 (8.4)         |
| Antihypertensive drugs      | 340 (71.6)               | 134 (46.5)      | 1783 (70.9)          | 1106 (57.9)       |

Abbreviations: ADL, Activities in Daily Living; TIA, transient ischemic attack; BMI, Body mass index. Variables in table with imputed data due to missing observations: Saltin-Grimby Physical Activity Level Scale (SGPALS), education, income, living situation, dependency, lipid-lowering drugs, antiplatelet drugs, anticoagulant drugs, antihypertensive drugs.
Table 2. Survival probabilities stratified by physical activity. Cumulative survival probabilities with 99% confidence intervals at 30 days, one year, three years, and five years after intracerebral hemorrhage, and ischemic stroke

|                     | 30-day survival | 1-year survival | 3-year survival | 5-year survival |
|---------------------|-----------------|-----------------|-----------------|-----------------|
| **Intracerebral hemorrhage** |                 |                 |                 |                 |
| No physical activity | 0.67 (0.62-0.73) | 0.55 (0.49-0.61) | 0.44 (0.39-0.50) | 0.33 (0.27-0.40) |
| Physical activity   | 0.91 (0.87-0.95) | 0.86 (0.81-0.91) | 0.80 (0.74-0.86) | 0.73 (0.66-0.81) |
| **Ischemic stroke**  |                 |                 |                 |                 |
| No physical activity | 0.88 (0.8-0.90)  | 0.73 (0.71-0.75) | 0.57 (0.55-0.60) | 0.44 (0.41-0.48) |
| Physical activity   | 0.98 (0.97-0.99) | 0.94 (0.92-0.95) | 0.86 (0.84-0.88) | 0.77 (0.75-0.80) |
|                                      | Short-term mortality (0 - 30 days) |                           | Long-term mortality (30 days - 2 years)* |                           |
|--------------------------------------|-------------------------------------|---------------------------|------------------------------------------|---------------------------|
|                                      | Intracerebral hemorrhage             | Ischemic stroke           | Intracerebral hemorrhage                 | Ischemic stroke           |
|                                      | aHR (99% CI)                        | p                         | aHR (99% CI)                             | p                         |
| Physical activity                    | 0.30 (0.17-0.54)                    | <0.001                    | 0.40 (0.21-0.77)                         | <0.001                    |
| Sex, Female                          | 0.98 (0.64-1.49)                    | 0.888                     | 0.95 (0.69-1.30)                         | 0.675                     |
| Age <80 years                         | 1.00 [Reference]                    |                            | 1.00 [Reference]                         | 1.00 [Reference]          |
| Age 70-80 years                       | 2.89 (1.44-5.82)                    | <0.001                    | 1.37 (0.78-2.41)                         | 0.144                     |
| Age >80 years                         | 4.16 (2.02-8.56)                    | <0.001                    | 1.91 (1.10-3.31)                         | 0.002                     |
| Born in Sweden                        | 1.00 [Reference]                    |                            | 1.00 [Reference]                         | 1.00 [Reference]          |
| Born in Europe                        | 1.05 (0.59-1.87)                    | 0.813                     | 0.99 (0.67-1.48)                         | 0.965                     |
| Born outside of Europe                | 0.99 (0.40-2.43)                    | 0.966                     | 0.50 (0.18-1.36)                         | 0.074                     |
| Education <10 years                   | 1.00 [Reference]                    |                            | 1.00 [Reference]                         | 1.00 [Reference]          |
| Education 10-12 years                 | 0.90 (0.57-1.42)                    | 0.538                     | 0.88 (0.63-1.23)                         | 0.328                     |
| Education >12 years                   | 0.80 (0.45-1.45)                    | 0.338                     | 1.13 (0.73-1.75)                         | 0.464                     |
| Low income                            | 1.00 [Reference]                    |                            | 1.00 [Reference]                         | 1.00 [Reference]          |
| Medium income                         | 1.37 (0.84-2.24)                    | 0.101                     | 0.87 (0.62-1.23)                         | 0.307                     |
| High income                           | 1.21 (0.67-2.17)                    | 0.401                     | 0.85 (0.54-1.34)                         | 0.360                     |
| Living alone                          | 0.75 (0.48-1.16)                    | 0.090                     | 0.95 (0.68-1.33)                         | 0.690                     |
| Independent in ADL                    | 0.92 (0.59-1.43)                    | 0.625                     | 0.49 (0.35-0.69)                         | <0.001                    |
| Hyperlipidemia                        | 1.24 (0.64-2.40)                    | 0.411                     | 0.59 (0.36-0.96)                         | 0.005                     |
| Prior stroke/TIA                      | 1.71 (1.09-2.69)                    | 0.002                     | 0.53 (0.34-0.82)                         | <0.001                    |
| Atrial fibrillation                   | 1.45 (0.82-2.57)                    | 0.094                     | 1.99 (1.43-2.76)                         | <0.001                    |
| Diabetes                              | 1.32 (0.77-2.26)                    | 0.177                     | 1.07 (0.76-1.52)                         | 0.605                     |
| Coronary heart disease                | 0.78 (0.36-1.71)                    | 0.422                     | 1.37 (0.91-2.05)                         | 0.048                     |
| Heart failure                         | 1.05 (0.53-2.07)                    | 0.855                     | 1.26 (0.85-1.87)                         | 0.129                     |
| Cancer                                | 1.08 (0.55-2.12)                    | 0.756                     | 1.16 (0.78-1.74)                         | 0.336                     |
| Smoking                               | 0.96 (0.48-1.94)                    | 0.882                     | 0.54 (0.28-1.04)                         | 0.015                     |
| Lipid-lowering drugs                  | 0.66 (0.39-1.18)                    | 0.047                     | 0.93 (0.64-1.34)                         | 0.603                     |
| Antiplatelet drugs                    | 1.25 (0.73-2.16)                    | 0.283                     | 1.40 (0.99-1.96)                         | 0.011                     |
| Anticoagulant drugs                   | 0.80 (0.42-1.51)                    | 0.371                     | 0.92 (0.60-1.42)                         | 0.621                     |
| Antihypertensive drugs                | 0.87 (0.53-1.42)                    | 0.467                     | 1.03 (0.71-1.50)                         | 0.844                     |
Multivariate Cox proportional-hazards models predicting short- and long-term mortality for patients with intracerebral hemorrhage and ischemic stroke. * Only patients who survived the first 30 days are included in analyses of long-term mortality: n=580 patients with intracerebral haemorrhage, and n=4096 patients with ischemic stroke. Abbreviations: aHR, adjusted hazard ratio; CI, Confidence interval; ADL, Activities in Daily Living; TIA, transient ischemic attack. a=adjusted associations from models including pre-stroke physical activity, sex, age, country of birth, education, income, living situation, dependency, hyperlipidemia, prior stroke/TIA, atrial fibrillation, diabetes, coronary heart disease, heart failure, cancer, smoking, lipid-lowering drugs, antiplatelet drugs, anticoagulant drugs, and antihypertensive drugs.
Table 4. Associations between physical activity levels, stroke severity, and all-cause mortality.

| Admission stroke severity | Intracerebral hemorrhage | Ischemic stroke |
|---------------------------|--------------------------|-----------------|
|                           | OR (99% CI) | p | OR (99% CI) | p |
| Light physical activity   | 3.61 (2.45-5.33) | 0.899 | 2.59 (2.17-3.11) | 0.332 |
| Moderate physical activity | 3.45 (1.45-8.61) | 3.05 (2.04-4.70) |
| Post-stroke mortality     | HR (99% CI) | p | HR (99% CI) | p |
| Light physical activity   | 0.29 (0.21-0.42) | 0.136 | 0.33 (0.28-0.39) | <0.001 |
| Moderate physical activity | 0.14 (0.04-0.49) | 0.11 (0.06-0.19) |

Crude associations of light physical activity ≥4 h/week or moderate physical activity ≥2 h/week from univariate ordinal logit regression models and Cox proportional-hazards models. p values show the significance for comparisons between light and moderate physical activity. Abbreviations: HR, Hazard ratio; OR, Odds ratio; CI, Confidence interval.
Associations of Prestroke Physical Activity With Stroke Severity and Mortality After Intracerebral Hemorrhage Compared to Ischemic Stroke
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