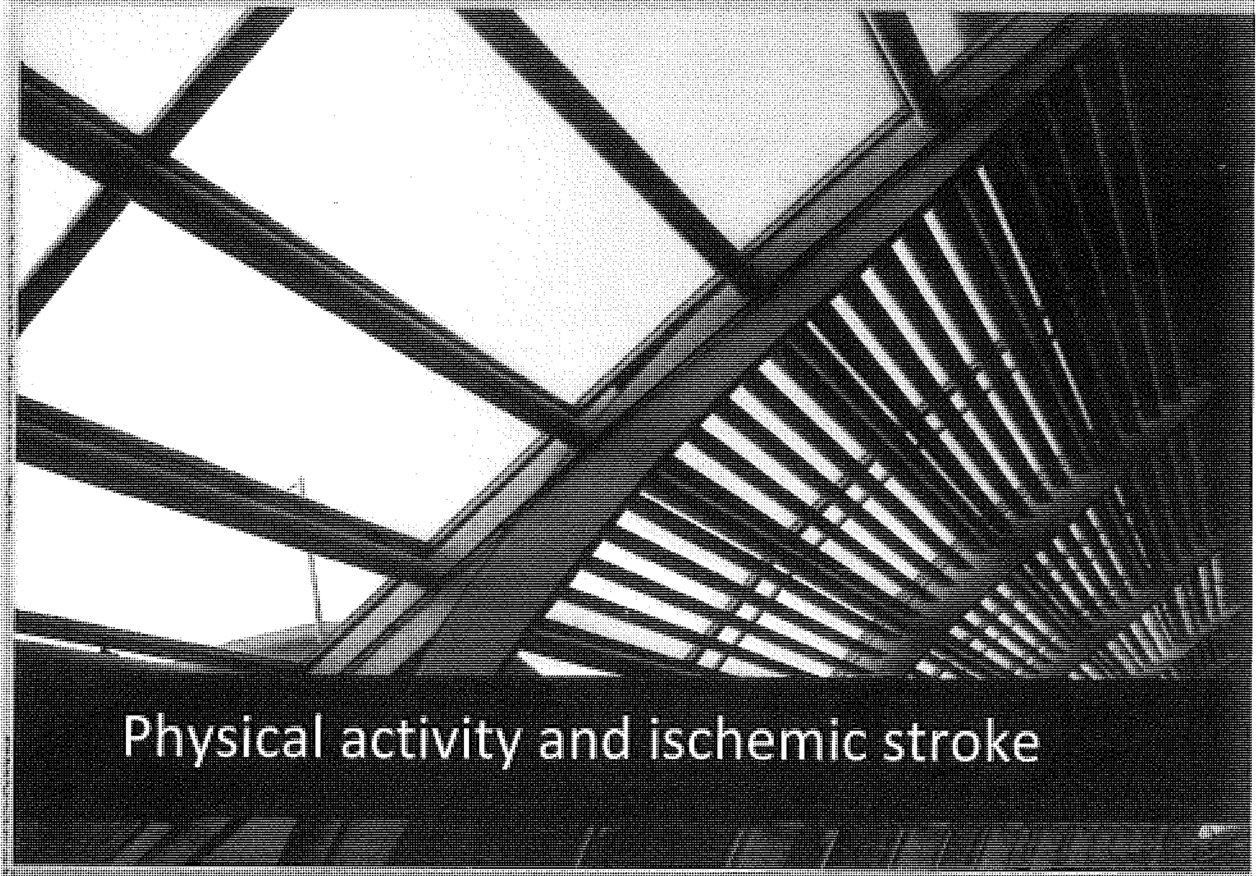

Physical activity and ischemic stroke

A Ph.d. thesis

by

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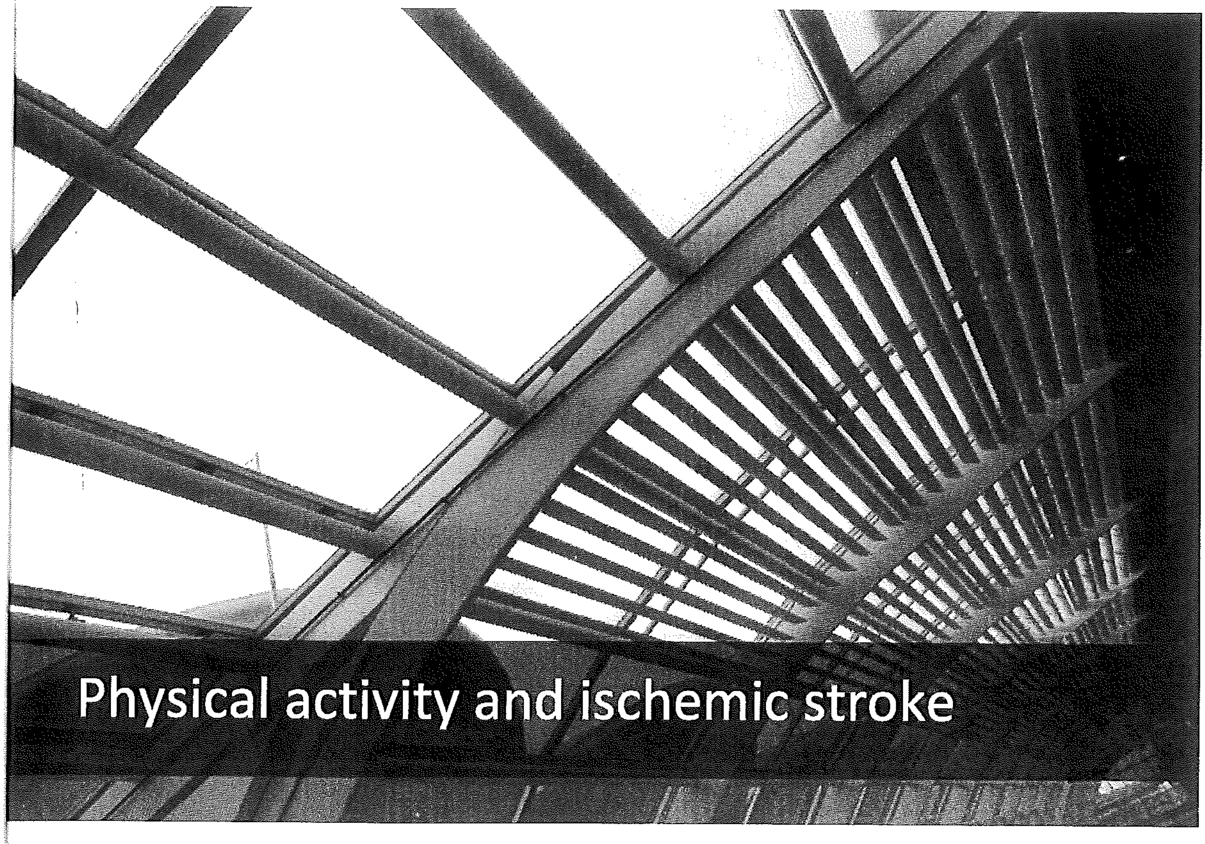

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Preface

This Ph.D. thesis was done during my period as a research fellow at the department of neurology, Bispebjerg Hospital, Copenhagen Denmark. I would like to thank my two advisors, Professor Gudrun Boysen and Dr. Thomas Truelsen, for excellent collaboration and thorough guidance. Gudrun Boysen has an endless amount of knowledge, which she has willingly passed on at any given opportunity.

Thomas Truelsen has an outstanding analytic ability and can always see alternatives when problems occur. Gudrun and Thomas have supplemented each other in the best possible way and have patiently read my drafts.

I would also like to thank our secretary Inger Hedegaard, our study nurse Anders Pedersen, our two physiotherapists Marianne Lindahl and Lotte Hansen, our partners from CTU with Christian Gluud in the lead, and all members of the ExStroke Pilot Trial study group. Further thanks are given to the laboratory at Bispebjerg Hospital, Ruth Rousing from Center of Inflammation and Metabolism, Dr. med. Lene Werdelin, and all the people who have helped during the last three years.

In memory of Grethe Kur,

September 2008

Lars-Henrik Krarup

Summary

Physical inactivity is a major health problem for the individual as well as for the society. The World Health Organization has estimated, that 60% of the population do not meet the minimum requirement of 30 minutes of daily moderate physical activity, and that physical inactivity results in 2 million deaths worldwide annually. Medical costs due to physical inactivity is estimated to be 75 billion$ in the US. Physical inactivity is a major risk factor for cardiovascular diseases and persons who do not meet the minimum recommendations of physical activity have a 1.5 times increased risk of cardiovascular disease including stroke.

Stroke is a common disease with 12,000 new events every year in Denmark, of which 20-30% die during the first year and half of the survivors will have lasting disabilities. A number of studies have shown, that a low level of physical activity in the years preceding stroke is associated with increased risk of stroke. Estimates from meta-analyses suggest, that persons who have a high level of physical activity have a 25% lower risk of stroke compared to their low active counterparts. Less is known about how physical activity after stroke affects the prognosis and whether it is possible to increase stroke patients' level of physical activity. In the ExStroke Pilot Trial we examined if it was possible to increase stroke patients level of physical activity through an intervention consisting of repeated encouragement and verbal instructions in being physically active. Patients of 40 years or older with ischemic stroke were randomized to intervention group or control group. Six follow-up visits were planned during the intervention period, which lasted for 2 years. We planned to test the following null hypotheses:

Stroke patients' level of physical activity at the time of stroke does not differ from that of community controls.

We did a matched case-control study in which we assessed the level of physical activity in the week preceding the ischemic stroke and compared it with participants of the Copenhagen City Heart Study. Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) questionnaire. The results showed that

stroke patients had a significant lower level of physical activity in the week preceding an ischemic stroke compared to community controls.

The level of physical activity prior to stroke is not associated with severity and long-term outcome from first-ever stroke.

Data from 265 patients with first-ever stroke were included in the analyses, which showed that patients who reported a high level of physical activity prior to stroke had less severe stroke and a better long-term outcome compared to patients who reported a low level of physical activity.

Randomization to repeated encouragement and verbal instruction on being physically active does not increase physical activity.

The results from the ExStroke Pilot trial showed that we were not able to increase stroke patient's level of physical activity. Patients randomized to 6 intervention visits did not obtain a higher level of physical activity compared to patients in the control group. Repeated encouragement and verbal instructions on being physically active was not sufficient to increase the level of physical activity. Other methods are needed in order to increase physical activity in stroke patients.

Randomization to repeated encouragement and verbal instruction on being physically active does not affect insulin sensitivity.

Impaired insulin sensitivity is a known stroke risk factor and is prevalent in 38-62 % of patients following stroke or TIA. A subset of the study population had blood samples taken at the end of follow-up and insulin sensitivity was assessed using the homeostasis model assessment based on fasting glucose and insulin measurements. The results showed that insulin sensitivity was significantly better in patients randomized to the intervention group.

Dansk Resumé

Fysisk inaktivitet er blevet et stort sundheds problem ikke bare for det enkelte individ, men for samfundet generelt. Verdens Sundheds Organisationen (WHO) har estimeret at 60% af befolkningen ikke udfører de anbefalede daglige 30 minutters moderat fysisk aktivitet, og at fysisk inaktivitet på verdensbasis er associeret med 2 millioner dødsfald årligt. Omkostningerne forbundet med fysisk inaktivitet er estimeret til 75 milliarder dollars i USA. Fysisk inaktivitet er en risikofaktor for kardiovaskulær sygdom, og personer der ikke dyrker de anbefalede 30 minutters fysisk aktivitet dagligt har en 1.5 gange øget risiko for kardiovaskulær sygdom, inklusiv slagtilfælde.

Slagtilfælde er en hyppig sygdom med 12.000 nye tilfælde hvert år i Danmark hvoraf 20-30% dør indenfor det første år. Flere prospektive epidemiologiske undersøgelser har vist, at et lavt fysisk aktivitetsniveau er associeret med en øget risiko for apopleksi. Meta-analyser har vist, at personer med et højt aktivitetsniveau har en 25% mindre risiko for slagtilfælde sammenlignet med inaktive personer. Man ved mindre om hvordan fysisk aktivitet efter slagtilfælde påvirker prognosen, og om patienter med slagtilfælde kan øge deres fysiske aktivitetsniveau. I ExStroke Pilot studiet undersøgte vi, om det var muligt at øge det fysiske aktivitetsniveau hos patienter med slagtilfælde ved hjælp af gentagne opfordringer og mundtlig instruktion i at være fysisk aktiv. Patienter, der var 40 år eller ældre med iskæmisk slagtilfælde, blev randomiseret til interventionsgruppe eller kontrolgruppe. Seks kontrolbesøg blev planlagt i interventionsperioden, der varede i 2 år. I forbindelse med undersøgelsen testede vi følgende nulhypoteser.

Det fysiske aktivitetsniveau ved tidspunktet for slagtilfældet er ikke forskelligt fra den generelle befolkning.

Vi lavede et matchet case-kontrol studie, hvor vi undersøgte det fysiske aktivitetsniveau i ugen op til slagtilfældet og sammenlignede det med en kontrolgruppe fra Østerbroundersøgelsen. Fysisk aktivitet blev målt ved hjælp af et spørgeskema: the Physical Activity Scale for the Elderly (PASE). Resultaterne viste, at

patienter med slagtilfælde havde et signifikant lavere fysisk aktivitetsniveau i ugen op til slagtilfældet sammenlignet med kontrolgruppen.

Det fysiske aktivitetsniveau før slagtilfældet er ikke associeret til slagtilfældets sværhedsgrad og langtids prognosen.

Data fra 265 patienter med førstegangs slagtilfælde blev inkluderet i analyserne, der viste, at patienter, der havde rapporteret et højt fysisk aktivitetsniveau havde et mindre alvorligt slagtilfælde og en bedre prognose efter 2 år.

Randomisering til gentagne opfordringer og instruktion i at være fysisk aktiv øger ikke det fysiske aktivitetsniveau.

Resultaterne fra ExStroke Pilot studiet viste, at vi ikke var i stand til at øge det fysiske aktivitetsniveau hos patienter med slagtilfælde. Patienter randomiseret til 6 interventionsbesøg havde ikke et højere fysisk aktivitetsniveau sammenlignet med patienterne i kontrolgruppen. Information og mundtlig opfordring til at være fysisk aktiv er ikke tilstrækkeligt. Der er behov for andre metoder til at fremme det fysiske aktivitetsniveau hos patienter med slagtilfælde.

Randomisering til gentagne opfordringer og instruktion i at være fysisk aktiv øger ikke insulinfølsomheden.

Nedsat insulinfølsomhed er en risikofaktor for apopleksi og forekommer efter slagtilfælde eller TCI hos 32-68% af patienterne. En subgruppe af studiepopulationen gav tilladelse til at få taget blodprøver ved det sidste kontrolbesøg. Resultaterne viste, at insulinfølsomheden var signifikant bedre hos patienter randomiseret til interventionsgruppen.

List of abbreviations

CTU: Copenhagen Trial Unit

CVD: Cardiovascular Disease

CCHS: Copenhagen City Heart Study

DLW: Doubly Labeled Water Method

eNOS: endothelial nitric oxide syntethase

HOMA: HOmeostasis Model Assessment

HRT: Hormone Replacement Therapy

MET: Metabolic Equivalent

mRS: modified Rankin Scale

NIHSS: The National Institue of Health Stroke Scale

PASE: Physical Activity Scale for the Elderly

RMR: Resting Metabolic Rate

rt-PA: recombinant tissue plasminogen activator

SSS: Scandinavian Stroke Scale

TEE: Total Energy Expenditure

Definitions

Physical activity is defined as any body movement, which increases energy expenditure [1]. Physical activity can further be subdivided into leisure time physical activity, occupational physical activity and commuting physical activity. A subset of physical activity is physical exercise. In **physical exercise** all exercises are planned and structured with the purpose of increasing body strength or cardio respiratory fitness. Physical fitness is a set of attributes, which people have or achieve, that relate to the ability to perform physical activity [1].

Impaired insulin sensitivity and insulin resistance are used throughout the litterature to describe a condition where normal amount of insulin is insufficient to obtain normal blood glucose levels. This results in increasing secreted levels of insulin to keep the glucose level within normal range. Insulin resistance is a condition in which the person has impaired insulin sensitivity. Throughout the text I will consistently use insulin sensitivity to describe the effect of insulin on glucose levels, as the study population have not been diagnosed to have insulin resistance.

Background and introduction

Stroke is a disease with few options for acute treatment. Thrombolysis is now an accepted treatment for acute ischemic stroke[2,3], however, the majority of stroke patients will not be eligible for thrombolysis due to contra indications or delay in reaching appropriate treatment within the 180-minute time-window[4].
Secondary prevention after stroke consist of lowering of blood pressure[5], antithrombotic treatment[6-9], and to reduce cholesterol[10]. Despite treatment approximately 10-15% of patients with a first-ever stroke will experience a recurrent stroke within the first year[11]. In routine clinical setting stroke patients are often advised to change lifestyles in order to modify stroke risk factors as smoking, alcohol abuse, obesity, and physical inactivity. Currently, we do not know if patients can change their lifestyle or how it would affect risk factors.

Association between physical activity and stroke.

A number of studies since the late 70's have examined the association between physical activity and the risk of ischemic stroke. All of these studies are observational studies with the majority being cohort studies[12-36] and some being case-control studies[37-44]. Some studies found an association between increased level of physical activity and reduced risk of stroke[12, 19, 20, 25, 26, 28, 32-34, 36-38, 40, 41, 44] while others found a U-shape or no association[13-15, 17, 18, 21-24, 27, 29-31, 35, 39, 42, 43]. So far no study has shown that a higher level of physical activity increases the risk of stroke. There were small differences in which variables the different studies stratified for. Some focused on gender while others focused on stroke subtypes. Physical activity was measured using a variety of questionnaires, which makes individual comparison difficult.
In the Nord-Trøndelag Health Survey Ellekjaer and co-workers investigated 14,101 women, age ≥ 50 years, and free of stroke[34]. In a multivariable logistic regression model the results showed that increasing levels of physical activity was associated with a decreased risk of stroke, $P_{trend} = 0.0027$. The association was consistent across all age groups. Data from the Copenhagen City Heart Study on 7,060 women showed a small protective effect of physical activity on the avoidance of stroke, $P = 0.04$[26]. Wannamethee G et al. [25] followed 7,735 men between 40-59

years for 9.5 years. Physical activity was at baseline categorized into three groups (inactivity, moderate activity, and vigorous activity). The results showed linear association between increased levels of physical activity and decreased risk of stroke, $P_{trend} = 0.008$. The association between physical activity and myocardial infarctions was U-shaped. The authors concluded, that moderate physical activity was sufficient to produce a beneficial effect on cardiovascular risk, while more vigorous activity did not seem to confer any further protection.

The different results published on the association between physical activity and stroke and the heterogeneity in assessment of physical activity was addressed in two meta-analyses[45, 46]. The two studies were published a year apart and included many of the same studies, and except from small differences in stratification the results were similar. Increased level of physical activity was associated with decreased risk of stroke both for ischemic and hemorrhagic stroke. Further, there was a dose-response relationship suggesting that patients with a high level of physical activity had a greater risk reduction compared to patients with a moderate level of physical activity.

Since the publication of the two meta analyses a Finnish study on the association between physical activity and risk of stroke analysed leisure time-, occupational-, and commuting physical activity separately[47]. A total of 22,481 men and 24,880 women were included into the analyses. The results showed that increasing levels of leisure time-, occupational-, or commuting physical activity were independently associated with a decreased risk of stroke, $P_{trend} < 0.0001$, 0.007, and 0.002, respectively. When the results were further adjusted for the other types of physical activity leisure time physical activity showed the strongest association with the risk of stroke. The impact physical activity has on the risk of stroke subtypes was also tested in this study. Leisure time physical activity decreased the risk of subarachnoid hemorrhagic stroke ($P_{trend} = 0.011$), intracerebral hemorrhagic stroke ($P_{trend} = 0.024$) and ischemic stroke ($P_{trend} = 0.001$) while occupational- and commuting physical activity only decreased the risk of ischemic stroke.

There are not many studies that have focused on the association between cardio respiratory fitness and the risk of stroke. In the Aerobic Center Longitudinal Study 20,728 men and 5,909 women free of cardiovascular disease completed a maximal treadmill exercise test in order to assess cardio respiratory fitness[48]. Based on the test results the cohort was grouped into three groups of cardio respiratory fitness (low, moderate or high). The cohort was followed for an average of 10 years. The results showed that patients with a high or moderate cardiorespiratory fitness had a decreased risk of cardiovascular disease including stroke, $P_{trend} = 0.001$. Taken the risk of stroke alone the trend was, $P_{trend} = 0.04$.

All in all there is quite a lot of evidence supporting the beneficial effects of physical activity in the prevention of first ever stroke. However, it has to be mentioned that the hypothesis has never been tested in a randomized setting. To draw a parallel, hormone replacement therapy was long considered to protect against cardiovascular disease when taken by post-menopausal women based on results from observational studies[49]. When the hypothesis was tested in a randomized setting the results were surprising and showed that the use of hormone replacement therapy increased the risk of cardiovascular disease[50]. The difference in results between the observational studies and the randomized trial was explained by "a healthy user effect". The women taking hormone replacement therapy had a lifestyle, which protected them from cardiovascular disease and confounded the results. Could the same kind of mechanism underlie the results seen in observational studies regarding physical activity and the prevention of stroke? At the moment the answer must be that until a randomized trial is conducted we do not know. There is evidence from observational studies, which shows the protective effect of physical activity. Further, there is evidence showing the beneficial effects of physical activity in the modification of stroke risk factors, which in theory could explain why physical activity decreases the risk of stroke.

Physical activity and ischemic stroke risk factors.

For a characteristic to be an ischemic stroke risk factor it implies that an individual with the specific characteristic has an increased risk of ischemic stroke compared to an individual without that characteristic. It does not imply that the risk factor causes ischemic stroke, as it may simply be a marker of a causal risk factor (e.g. having a cigarette lighter is a risk factor for stroke but only as a marker of current smoking)[51]. The causal risk factors include hypertension, hypercholesterolemia, carotid stenosis, and atrial fibrillation. These ischemic stroke risk factors are causal as there is evidence not only from observational studies but also from randomized controlled trials that treating these risk factors reduces the incidence of ischemic stroke. Other risk factors as diabetes mellitus, ischemic heart disease, and cigarette smoking are probably also causal risk factors, however no studies have shown that treating these risk factors reduces the incidence of ischemic stroke[51].

Physical activity has been shown to positively modify almost all known risk factors including the most prominent ones such as high blood pressure, diabetes mellitus/ impaired glucose metabolism, and high cholesterol levels. Most studies of the beneficial effects of physical activity on risk factors have been done in the general population, patients with hypertension, and coronary heart disease, but not in stroke patients.

Physical activity and blood pressure

Hypertension is a recognised risk factor for cardiovascular diseases including stroke[52]. The association between physical exercise and blood pressure has been studied extensively in both observational studies and randomized clinical trials and in addition several meta-analyses and review articles have been published. In 1986 a smaller trial was published in the Lancet showing, that physical exercise reduced blood pressure and noradrenalin levels in persons with essential hypertension[53]. A meta-analysis including 71 studies assessed the effect of physical exercise on blood pressure[54]. The blood pressure (sys/dia) was reduced by an average of 3.3/3.5 mmHg in normotensive participants and 6.9/4.9 mmHg in hypertensive participants. Baseline blood pressure was an important determinant of blood pressure reduction. In PROGRESS[5], a blood pressure lowering trial using perindopril and indapamid, the mean reduction in blood pressure (sys/dia) was 12/5 mmHg. Consequently, in stroke patients physical exercise could be an important supplement to medication to achieve a blood pressure reduction.

Physical activity and lipids

The association between high cholesterol and myocardial infarction has been well documented[55] whereas epidemiological studies on cholesterol and stroke have not found a clear association[56-58]. In studies patients with myocardial infarction treated with statins have shown to reduce the risk of recurrent myocardial infarction and to reduce the risk of stroke[59]. Treating stroke patients with statins have shown to reduce the risk of recurrent stroke[10]. The effect of physical exercise on cholesterol levels was tested in the HERITAGE family study[60]. Six hundred and seventy five sedentary normolipidemic persons were included in this non-randomized study of 20 weeks exercise training on cycle ergometers. The results showed an increase in mean HDL-cholesterol from baseline to end of study of 3.6% ($P<0.001$), while there was no effect on LDL-cholesterol or total-cholesterol. A review article of 51 exercise trials reported that exercise could increase HDL-cholesterol levels both in randomized and non-randomized studies while a reduction in triglycerides and T- and LDL-cholesterol was a less consistent finding[61].

Physical activity and glucose metabolism

In stroke survivors decreased insulin sensitivity and abnormal glucose metabolism is highly prevalent[62, 63]. Decreased insulin sensitivity is linked to changes in the vascular system, including thickening of the carotid media intima[64] and to induce hypercoagulability[65]. These changes might explain the association between impaired insulin sensitivity and the risk of stroke[66, 67]. Physical exercise using treadmill training has in one randomized trial shown to be able to increase glucose tolerance through 6 months training[68]. In this trial, n=46, patients randomized to the intervention group had a significantly better glucose tolerance compared with the patients in the control group, $P<0.05$.

In patients with type 2 diabetes mellitus studies have shown, that exercise training could reduce Hgb A1C with 0.5-1.0%[69]. Another study has shown, that exercise can reduce the onset of type 2 diabetes mellitus in high-risk persons[70].

Physical activity and eNOS

In 2003 an article was published showing that physical activity influenced the regulation of the endothelial nitric oxide synthetase (eNOS)[71]. The authors showed on mice the effect of up regulating the eNOS enzyme. Mice randomized to exercise had smaller lesion size after experimental middle cerebral arterial occlusion for one hour compared to sedentary control animals. The effect of physical exercise was lost when the mice in the running group had the gene for eNOS removed. The eNOS system is one of the main sources of NO in the brain. NO plays a major role as a messenger molecule and influence resistance vessel tone[72], increases cerebral blood flow[73], inhibits vasospasm[74, 75], and inhibits cerebral vascular growth[76]. The impact the eNOS system might have on stroke patients is less well elucidated. In patients with stable coronary artery disease (CAD) exercise training increased the eNOS mRNA expression in the left internal mammary artery (LIMA) by 96% compared to the control group and LIMA endothelial function was improved[77].

Physical activity and other ischemic stroke risk factors

The association between the risk of stroke and body mass index, waist circumference, and waist-to-hip ratio was investigated in a Finnish study[78]. A total of 49,996 participants, age 25 to 74, and free of coronary heart disease or stroke at baseline were followed for 19.5 years. The results showed that a BMI > 25 was associated with increased risk of all strokes and ischemic stroke in both men and women. Increased abdominal adiposity measured as waist circumference and waist-to-hip ratio was more strongly associated with risk of total stroke and ischemic stroke than BMI but only in men. Physical activity and exercise seems to be an important adjunct to diet for achieving and maintaining weight loss[79] and it seems, as physical fit obese persons do not have the increased risk of early mortality as otherwise seen for obese persons[80]. However, it has never been shown that weight reduction reduces the risk of stroke.

The trainability of stroke patients

Following stroke sequelae such as hemiparesis and ataxia may limit the trainability of stroke patients and lead to decreasing levels of physical activity and physical performance. A Cochrane review from 2004 reviewed the literature until 2002 and aimed to evaluate the effect of exercise on a number of outcomes (mortality, recurrent stroke, muscle strength, physical fitness, mobility, and physical function)[81]. In total 12 randomized trials including 289 stroke patients were identified. All studies were small randomized studies and none of them assessed the effect of exercise on recurrent stroke or mortality. Two studies investigated the effect of physical exercise on cardiorespiratory fitness[82, 83]. In both studies it was concluded, that cardiorespiratory fitness could be increased. In a meta-analysis of the two studies a significant effect of physical exercise on cardiorespiratory fitness measured as peak VO2 after exercise could not be shown[81]. Mobility measured as walking speed was assessed in 5 studies[84-88]. A meta-analysis of those five studies showed a significant effect of physical exercise on walking speed. Walking speed could be improved by 0.42 m/sec, 95% CI 0.04-0.79[81]. The effect of isokinetic strength training on muscle strength was investigated in a randomized study of 22 stroke patients[89]. No significant effect of strength training on muscle strength was shown. Since 2002 not many studies have been published, which further could clarify the effect of physical training on cardiorespiratory fitness and muscle strength. In a non-randomized study walking speed was increased using an outpatient exercise protocol through 2 months[90]. Patients randomized to mixed training (resistance and endurance training) through 12 weeks obtained a significantly better timed-up-and-go (time to raise from chair and walk 6 meters) and walking economy (O^2 mL/kg/meter) compared to the control group[91]. However, the effect was lost after 7 months. In 222 stroke patients with a paretic upper extremity the effect of 2-weeks constraint-induced movement therapy (ipsilesional limb restraint while training of paretic arm is conducted) was evaluated[92]. The function of the paretic arm was significantly better in the group randomized to constraint-induced movement therapy compared to the control group 12 months from baseline.

Methods

Study population

The study population throughout this thesis except for paper 2 are patients included in the ExStroke Pilot Trial. The design of the ExStroke Pilot Trial is described in detail in paper 1.

The ExStroke Pilot Trial was a randomized, multi-centre, multi-national intervention trial investigating if repeated encouragement and instruction in being physically active could improve stroke patients' level of physical activity.

The ExStroke Pilot Trial started to randomize patients in 2003 and included a total of 314 patients from 2003 to 2005. Six Danish centres (Bispebjerg, Frederiksberg, Rigshospitalet, Hvidovre, Amager, and Aarhus) and 1 centre in Estonia, Poland, and China included patients.

Patients were considered for inclusion if they had an ischemic stroke diagnosis and could be included within 90 days after stroke symptom onset. The specified inclusion and exclusion criteria were as follows:

Inclusion criteria:

1) An ischemic stroke diagnosis.
2) Age ≥ 40 years.
3) CT/MRI scan without cerebral pathology not suggesting ischemic stroke.
4) Ability to walk. Canes and walkers were allowed.
    i. Not for patients included in paper 2
5) Able to understand the trial and willing to give informed consent.

Exclusion criteria:

1) Patients who were unable to understand the purpose of the trial
2) A modified Rankin Score ≥ 4
    i. Not for patients included in paper 2
3) CT/MRI showing intracerebral haemorrhage or focal pathology other than infarction.
4) Serious medical disease such as AIDS, metastatic cancer, or abnormalities that the investigator feels may compromise the patient's successful participation in the trial.
5) Earlier randomization in this trial.

Randomization

Patients were randomized centrally in coorperation with the Copenhagen Trial Unit (CTU). Investigators wishing to randomize a patient phoned or faxed to CTU, which then randomized the patients according to gender, age (40-70 or > 70) and stroke severity (SSS 20-39 or 40-58) strata in blocks of 10. Stratified randomization was chosen in order to keep the two groups well balanced with regards to age, gender, and stroke severity as these factors were presumed to influence outcome.

Intervention

Patients randomized to the intervention group were scheduled to meet with a physiotherapist (physician in the Chinese centre) soon after randomization. Together with the physiotherapist a detailed training program was made taking the patients resources and prior training status into account. The physiotherapist and the patient signed the training program.

Study population for paper 2-4

In paper 2 patients who could not walk and patients with a modified Rankin score higher than 3 were allowed to participate. Also in some cases patients who did not want to participate in the ExStroke Pilot Trial accepted to be included in paper 2. This means that when we started recruiting patients for the ExStroke Pilot Trial patients who fulfilled all inclusion criteria and none of the exclusion criteria were included in both the ExStroke Pilot Trial and paper 2. Patients who were unable to walk or had a modified Rankin score above 3 were included into paper 2, but did not continue in the ExStroke Pilot Trial.

Patients included in paper 4 were all patients who completed the ExStroke Pilot Trial and gave oral and written permission to have blood samples taken at the final follow-up visit.

Physical Activity for the Elderly - questionnaire

Physical activity was assessed throughout the study using the Physical Activity Scale for the Elderly (PASE). The PASE questionnaire was developed by Washburn R and colleagues[93, 94] in order to obtain an instrument, that assessed physical activity in the elderly. Age-neutral activity questionnaire tends to underestimate the amount of physical activity and time spent on physical activities done by the elderly population[95]. The PASE questionnaire scores the average amount of hours/day spent on each category over a seven-day period. Each item has an activity weight, which was computed based on movements count, activity diaries, and global self-report of physical activity. The component scores were then regressed on responses to the PASE questionnaire to derive the optimal item weight.

The PASE questionnaire consists of the following 12 items (activity weight):

Walk outside home (20)

Light sport/ recreational activities (21)

Moderate sport /recreational activities (23)

Strenuous sport / recreational activities (23)

Muscle strength / endurance exercises (30)

Light housework (25)

Heavy housework or chores (25)

Home repairs (30)

Lawn work or yard care (36)

Outdoor gardening (20)

Caring for another person (35)

Work for pay or as a volunteer (21)

Validity of the PASE questionnaire.

The validity of the PASE questionnaire is tested in a number of studies[94, 96-98]. The initial validation was done by the developers[93]. Two hundred and twenty two participants completed the PASE questionnaire and additional physical tests and questions (activity dairy, global self-reported activity, grip strength, movement counts, static balance, leg strength). The results showed, that the PASE questionnaire was positively associated with grip strength ($r=0.37$, $P<0.01$), static balance ($r=0.33$, $P<0.01$), and leg strength ($r=0.25$, $P<0.01$) and negatively associated with heart rate ($r=-0.13$, $P<0.05$), perceived health status ($r=-0.34$, $P<0.01$), and Sick Impact profile ($r=-0.42$, $P<0.01$). Washburn et al.[94] revalidated the PASE questionnaire in sedentary adults as part of a randomized trial. The PASE questionnaire was positively associated with peak oxygen uptake ($r=0.20$, $P<0.01$), balance ($r=0.20$, $P<0.01$) and negatively associated with systolic blood pressure ($r=-0.18$, $p<0.05$). Other groups have validated the PASE questionnaire. Schuit et al.[96] validated the PASE questionnaire against the doubly labeled water method. The doubly labeled water method is considered to be gold standard when measuring energy expenditure. The PASE questionnaire was validated against the physical activity ratio, which is the ratio of total energy expenditure (TEE) and resting metabolic rate (RMR). TEE was measured over a 14-day period using the doubly labeled water method. Participants drank $H_2{}^{18}O$ and ^2H_2O labeled water and urine was collected and stored at -20° Celsius on day 1, 7, and day 14. The urine was analyzed for ^2H and ^{18}O in order to calculate the TEE measured in megaJ/day. RMR was measured using a ventilated hood. The PASE score was positively and significantly correlated with the physical activity ratio (r=0.68, CI = 0.35-0.86). Martin KA et al. validated the PASE questionnaire in patients with chronic knee pain and disability[97]. In a sample size of 471 the PASE questionnaire was positively and significantly associated with perceived difficulty with physical function (r=0.35, P<0.001), 6-min walk performance (r=0.35, P<0.001), and knee strength (r=0.41, P<0.001). Overall the PASE questionnaire has been validated in a variety of population groups, both healthy and persons with disability, and found to be valid. The PASE questionnaire was used in the ExStroke Pilot Trial as listed in the appendix together with an example on how to calculate the PASE score.

Bias

The PASE questionnaire was developed in the United States of America, which is reflected in one of the scoring items. Bicycling is scored under the category strenuous sports. In Denmark and China, which are the two main countries that have included patients in the ExStroke Pilot trial, bicycling is a normal way of transportation. Transporting oneself on a bicycle does not constitute a strenuous sports activity. Therefore it may be that people who use their bicycle for transportation gets a higher PASE score than they should. However, this potential bias would be equally distributed in the two groups and furthermore the percentages of PASE point obtained from strenuous sports were overall 3.1%. The level of physical activity varies across seasons[99] but as all participants were followed for 24 months this potential bias will not affect the results. In Paper 2 cases and controls were matched according to season to handle this bias.

Scandinavian Stroke Scale

The Scandinavian Stroke Scale (SSS)[100] is one of the two most widely used stroke scales the other one being the National Institute of Health Stroke Scale (NIHSS). At inclusion into the ExStroke Pilot Trial stroke severity was assessed using the Scandinavian Stroke Scale. The SSS is a simple stroke scale and consists of the following 9 items: consciousness, orientation, eye movement, facial palsy, arm motor power, hand motor power, leg motor power, gait, and speech. The SSS score may range from 0-58 where full score means no deficits in these items. Research has shown, that there is good correlation between the SSS and NIHSS and the score from one scale can be translated into a score on the other scale with reasonably good results[101]. However, in the SSS "ability to walk" is tested which is not the case in the NIHSS.

Modified Rankin Scale

Outcome after stroke was assessed using the modified Rankin Scale (mRS)[102]. The modified Rankin scale is an inventory, which is used to report global disability. The scale ranges from 0-6 where a score of zero corresponds to no symptoms and six corresponds to the patient being dead. The mRS is widely used to assess outcome in randomized clinical trials and is reliable and validated[103].

The Charlson Comorbidity Index

General comorbidity may be a confounder in outcome studies and in studies of physical activity. In paper 2 the results were adjusted for prior diseases that could influence the amount of physical activity done. In paper 3 the same confounders were used as in paper 2, however, by request of reviewers the results were adjusted for the Charlsons Comorbidity Index. The Charlson Comorbidity Index is a comorbidity scoring system that includes weighting factors based on disease severity[104]. The Charlson Comorbidity Index has been modified to the use in ischemic stroke patients and validated for the use in ischemic stroke outcome studies[105]. In paper 3 the modified version of the Charlson Comorbidity Index was used.

Homeostasis Model Assessement

Insulin sensitivity was measured the HOmeostasis Model Assessment index (HOMA) index for insulin sensitivity. The HOMA index is calculated based on fasting glucose and fasting insulin measurements. The use of the HOMA index as a measure for insulin sensitivity was introduced by Mathews and co-workers in 1985[106]. The background was to develop a method to estimate insulin sensitivity, which would be more suitable for larger studies[106]. The first HOMA index was based on a series of linear equations, developed to approximate the non-linear relationship between glucose and insulin concentrations in steady state. The equations were simplified to:

$$HOMA1\text{-}IR = (FPI * FPG)/22.5$$

where IR is insulin resistance, FPI is fasting plasma insulin, and FPG is fasting plasma glucose. In 1996 the HOMA2 model was introduced[107]. This HOMA2 model solves the non-linear association between insulin and glucose concentration using a computer program[108]. The computer model can be used to determine insulin sensitivity (HOMA2-S%) from plasma insulin in the range of 20-400 pmol/l and glucose from 3.5-25 mmol/l. One should judge the results of the glucose and insulin assays before calculating the HOMA2-S%[109]. For example glucose levels of 2.5 mmol/l reflects either hypoglycemia, which is not steady state or problems with the glucose assay.

Validation of the HOMA model

The hyperinsulinemic-euglycemic clamp is often referred to as the "gold standard" for measuring insulin sensitivity although comparing a model that tested insulin sensitivity outside steady state conditions with the HOMA model which tests insulin sensitivity in steady state is problematic[109]. In the hyperinsulinemic-euglycemic clamp persons are given intravenously high levels of insulin at a fixed rate and in order to compensate for the high insulin levels IV glucose is administrated. The amount of glucose needed to be administrated over a period of time reflects the person's insulin sensitivity. The HOMA model correlates well with the hyperinsulinemic-euglycemic clamp in both diabetic[106, 110] and non-diabetic persons[106, 111, 112] with correlation coefficients from 0.73-0.88.

Blood samples

Venous blood samples were collected from all patients who completed the ExStroke Pilot Trial and gave oral and written informed consent to have blood samples taken. The blood samples were taken by venous puncture in main cubital vein and then centrifuged within one hour at 5° C at 3500 rpm for 15 minutes. Plasma and serum were stores at -80° C until all samples were collected. Fasting glucose was analyzed immediately.

Glucose

Fasting glucose was analyzed at the Bispebjerg Hospital laboratory. It is a common assay, based on the ability of the two enzymes hexokinase and G-6-Phosphate-dehydrogenase to catalyse the main reactions. Buffer, ATP, and NADP are added to the sample together with the catalysts.

Hexokinase catalysis the first step:

$$\text{glucose} + \text{ATP} \Leftrightarrow \text{G-6-P} + \text{ADP}.$$

G-6-P-DH catalysis the second step:

$$\text{G-6-P} + \text{NADP}^{+} \Leftrightarrow \text{gluconate-6-P} + \text{NADPH} + \text{H}^{+}.$$

The concentration of NADPH can be measured spectrophotometrically and is directly proportional with the glucose concentration. All results are in mmol/l.

Insulin

Fasting insulin was analyzed in cooperation with the Centre for Inflammation and Metabolism at Rigshospitalet. The assay used was developed by DakoCytomation and is an enzyme linked immunosorbent assay (ELISA) for the quantitative measurement of insulin in human plasma. Two antibodies were incubated with the sample in a microplate microwell coated with a specific anti-insulin antibody, which then forms a complex. The bound conjugate is detected spectrophotometrically and compared with a calibration curve to give the result. The results are given in pmol/l.

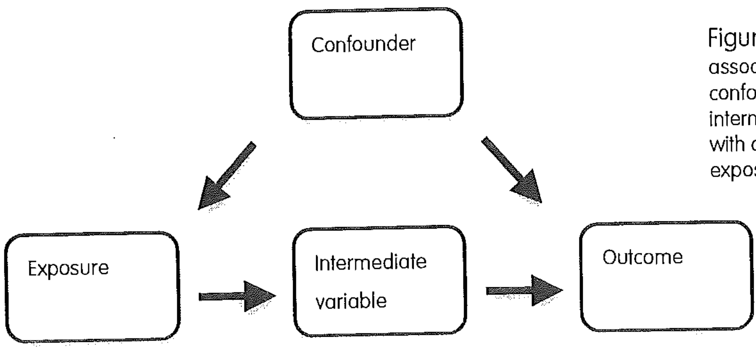

Figure 1. Shows the association between confounders and intermediate variables with outcome and exposure

Confounders and intermediate variables

The interaction between different variables, outcome, and exposure can have a marked impact on results. For a variable to be a confounder it has to be associated with exposure and outcome, but not be in the causal way between exposure and outcome. If a variable is considered to be in the causal way between exposure and outcome then the variable is an intermediate variable[113].

Confounding variable	Intermediate variable
Smoking	History of stroke
Years of education	History of myocardial infarction
Alcohol consumption	Diabetes mellitus
Atrial fibrillation	Blood pressure
BMI	BMI

Table 1. The table shows the list of confounding and intermediary variables used in paper 2. The results were adjusted for all variables by request of reviewers, however the estimates did not differ if the intermediary variables were excluded.

In paper 2 the results were adjusted for history of stroke, myocardial infarction, diabetes mellitus, atrial fibrillation, blood pressure, smoking, alcohol consumption, years of education and body mass index, table 1. One could argue, that it is only smoking, years of education, and alcohol consumption that are confounders. History of former cardiovascular diseases, diabetes mellitus, and blood pressure are all risk factors for ischemic stroke and modifiable by physical activity. Therefore they are in the causal pathway between physical activity and ischemic stroke and by definition intermediate variables. BMI is a variable that could be considered both an intermediate and a confounding variable. BMI is associated with increased risk of stroke, and patients with a large BMI are less physically active. Therefore BMI is a confounder. Or, patients who are physically active affect their BMI and thereby lower the risk of stroke.

To examine whether other factors have a marked impact on the association of physical activity and ischemic stroke results in univariate analyses were compared with those in multivariable analyses. As can be seen from the results in paper 2 there were no marked difference between the univariate analyses and the multivariable analyses[44]. Reanalyzing our results from paper 2 by including only the confounding variables did not alter the results (data not shown). Upon request of reviewers all variables listed in table 1 were included in the multivariable analysis. The association between physical activity and stroke severity in paper 3 was adjusted for age, gender, Charlson Comorbidity Index, educational level, fasting glucose level, and history of diabetes mellitus. All of these variables are

confounders except for fasting glucose levels and history of diabetes mellitus, which again could be considered intermediate variables. Redoing the multivariable analyses without these two variables did not change the results (data not shown).
In paper 5 participants were randomized to intervention group or control group. Randomization diminishes the differences between two groups as all patients are randomly assigned. If the randomization is optimal demographic variables and potential confounders are equally distributed between the two groups and the results do not have to be adjusted. In paper 5 that goal was not achieved as the pre-stroke level of physical activity differed between the two groups. The results were therefore adjusted by including this variable. The association between physical activity and insulin sensitivity was adjusted for age, sex, smoking, educational level, and anti hypertensive medication (thiazide, betablockers). All of these variables are confounders as they are associated with both exposure and outcome, but not in the causal way between the two.

Statistical considerations

The data used throughout this thesis are of quantitative (discrete and continuous) and qualitative (categorical, ordinal) nature. All continuous variables were tested for normal distribution before used in statistical analyses. Normal distribution was tested visually by a histogram and tested using a combined chi^2 test based on a test for skewness. The statistical test of normal distribution was only used as a guideline as it is well recognized that if a variable has many observations the statistical test will often show that the variable differs significantly from the normal distribution even though the differences is of no practical importance. Data were transformed for most variables using log-transformation. PASE-score and fasting insulin were transformed using the square root. Statistical analyses of data were done using a variety of statistical tools. Two-sample mean comparison of normal- and transformed variables was done using the two-sample t-test, which assumes variance homogeneity and equal standard deviations. For non-normal distributed data the Wilcoxons ranksum test was used. Categorical variables were analyzed using the chi^2 test.
In paper 2 the main results were analyzed using conditional logistic regression as cases were matched with controls according to gender and age.

In paper 3 the dependent variables were Scandinavian Stroke Scale and modified

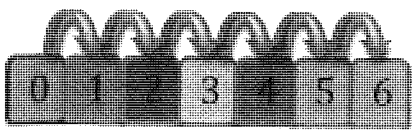

Figure 2. The figure shows the ordinal logistic regression approach to analysis of the modified Rankin scale. All possible cut-offs are used to give one cumulative odds ratio. Adapted from Saver JL[114].

Rankin scale, which are ordinal scales. Traditionally, researchers have chosen to dichotomize ordinal scales and analyze the outcome using binary logistic regression. In order not to lose information by dichotomization ordinal logistic regression was applied for the main analyses instead. Ordinal logistic regression takes all possible cut-off points into account and gives cumulative odds ratio based on all the cut-offs, figure 2. Ordinal logistic regression assumes proportional odds, which means that the odds ratio between each cut-off point does not vary significantly. The assumption of proportional odds was tested using the Brant test of the statistical software.

An external statistician analyzed the results of paper 4 due to the complicated nature of these analyses. The method used was linear mixed model, which is optimal for analysis of longitudinal data with missing values, as all observations can be used. In mixed model analysis a random effect is modelled in addition to the fixed effect.

In paper 5 the mean HOMA2-S% in the two groups was compared using two-sample t-test. As a play of change the pre-stroke level of physical activity was not equally distributed in the groups. Therefore the results were adjusted for differences in pre-stroke level of physical activity using linear regression. Linear regression assumes variance homogeneity, which was tested visually by plotting the residuals against the fitted values. Further, it was assumed that the residuals were normally distributed, which was tested visually by a probability plot of the residuals. In the last analysis of paper 5 the association between HOMA2-S% and physical activity was tested. As both variables were skewed, a log-log transformation of the dependent variable and the main independent variable was performed. The result from the regression model was used to estimate the association between HOMA2-

S% and physical activity. From the regression model the association between the two variables can be described as:

$$\text{Log (HOMA2-S\%)} = \beta_0 + \beta_1 * \log(\text{PASE-AUC})$$

β_0 and β_1 represent the regression coefficients where β_0 is the slope and β_1 describes the association between PASE-AUC and HOMA2-S% adjusted for potential confounders. The fold change in HOMA2-S% (θ) relative to the fold change in PASE-AUC (θ_1) can through mathematical reorganising be described as:

$$\theta = \text{antilog}[\beta_1 * \log(\theta_1)]$$

The fold change in HOMA2-S% was estimated based upon a 50% (1.5 fold) increase in PASE-AUC. Insertion of the regression coefficient for the PASE-AUC(β_1) gives the result:

$$\theta = \text{antilog}[\beta_1 * \log(1.5)]$$

Sample-size calculation

The sample-size calculation for the ExStroke Pilot Trial was based on mean difference of 20 points on the primary endpoint (PASE score), a standard deviation of 50, an alpha of 0.05, and a beta of 0.1. Based on the sample size calculation 99 patients were to be included in each group. A total of 300 patients were planned to allow for dropouts to occur.

The sample-size calculation for paper 4 was based on the results from an article, which showed that physically inactive obese participants could increase insulin sensitivity[115]. Based on these results including 102 patients would give 90% power at the 0.05 level to detect a mean HOMA-IR difference of 0.9 with a standard deviation 1.1.

Paper 1: The ExStroke Pilot Trial: Rationale, design, and baseline data of a randomized multicenter trial comparing physical training versus usual care after an ischemic stroke

Krarup, LH, Gluud C, Truelsen, Pedersen A, Lindahl M, Hansen L, Michelsen S, Andersen G, Zeng X, Kõrv J, Oskedra A, Boysen G, and the ExStroke Pilot Trial Group.

Abstract

Introduction: A high level of physical activity is associated with a decreased risk of first stroke and physical activity modifies recognized stroke risk factors and is recommended for stroke survivors. Available research shows that stroke patients can increase their level of physical performance over a short period. When the intervention period is over, physical performance often declines towards baseline level. Currently, there is no evidence on the association between physical activity and the risk of recurrent stroke. The ExStroke Pilot Trial is a randomized clinical trial with the aim of increasing stroke patients' level of physical activity and secondarily to associate the level of physical activity to the risk of recurrent stroke, myocardial infarction, and all-cause mortality in the two groups. We describe the rationale, design, and baseline data of the ExStroke Pilot Trial.

Methods: Patients with ischemic stroke above 39 years were randomized to intervention or control group. The intervention group will, over a 2-year period, receive information on and verbal instruction to exercise by a physiotherapist or a physician. The control group will receive the department's usual care. Physical activity is assessed in both groups seven times during follow-up using the Physical Activity Scale for the Elderly (PASE) questionnaire, which quantifies the amount of physical activity done in the last seven days prior to interview. The PASE score constitutes the primary outcome measure. The secondary outcome is the time from randomization to recurrent stroke, myocardial infarction, or all-cause mortality. Further outcome measures include: time from randomization to recurrent stroke,

myocardial infarction, and vascular death; recurrent stroke; modified Rankin Scale; quality of life; occurrence of falls and fractures. Trial status: From 9 centers in 4 countries, 314 patients were included and follow-up is ongoing. Mean age and standard deviation (SD) of the study participants was 68.4 (11.9) years and 56.4% were male. Mean (SD) PASE score was 84.1 (55.9) and median (interquartile range) Scandinavian Stroke Scale score was 54 (51–58).

Paper 2: The level of physical activity in the week preceding an ischemic stroke

Krarup LH, Truelsen T, Pedersen A, Lerke H, Lindahl M, Hansen L, Schnohr P, Boysen G

Hypotheses

- H_0 = the level of physical activity in the week preceding stroke does not differ from that of community control an ischemic stroke.
- H_0 = low level of physical activity is not associated with increased risk of ischemic stroke

Abstract

Background: Most observational studies investigating physical activity as a risk factor for stroke have concentrated on the years preceding a stroke event. In the present case control study we compared the reported level of physical activity performed during the week preceding an ischemic stroke with that of community controls. Furthermore we calculated the odds ratio for stroke based on the level of physical activity.

Subjects and methods: Patients with an ischemic stroke were recruited consecutively from hospitals covering Copenhagen city. Community controls were recruited among participants of The Copenhagen City Heart Study and matched according to age and gender. The level of physical activity was assessed using The Physical Activity Scale for the Elderly (PASE), which quantifies the amount of physical activity done in the last seven days.

Results: A total of 127 cases and 301 control subjects were included in the study. Mean (SD) PASE scores for cases were 76.0 (46.2) and 119.7 (69.4) for controls, $p<0.001$. For each 1-point increase in PASE score the odds ratio for ischemic stroke was 0.98 (0.98-0.99), equivalent to an odds ratio of 0.86 (95% CI: 0.82-0.90) for each 10-point increase.

Conclusion: Stroke patients are less physically active in the week preceding an ischemic stroke when compared to age and sex matched controls. Increasing PASE score was inversely, log-linearly and significantly associated with odds ratio for ischemic stroke.

Paper 3: Pre-stroke physical activity affects severity and long-term outcome after stroke.

Krarup LH, Truelsen T, Gluud C, Andersen G, Zeng X, Kõrv J, Oskedra A, Boysen G and the ExSTroke Pilot Trial Group

Hypotheses

- H_0 = pre-stroke level of physical activity is not associated with initial stroke severity in first-ever stroke.
- H_0 = pre-stroke level of physical activity is not associated with long-term outcome following first-ever stroke.

Abstract

Objective: The objectives were to determine if pre-stroke level of physical activity influenced stroke severity and long-term outcome.

Methods: Patients included into the present analyses represent a subset of patients with first-ever stroke enrolled into the ExStroke Pilot Trial. Ischemic stroke patients were randomized in the ExStroke Pilot Trial to an intervention of repeated instructions and encouragement to increase the level of physical activity or to a control group. Pre-stroke level of physical activity was assessed by interview using the Physical Activity Scale for the Elderly (PASE) questionnaire. The PASE questionnaire quantifies the amount of physical activity done during a seven-day period. Initial stroke severity was measured using the Scandinavian Stroke Scale (SSS). Long-term outcome was assessed after two years using the modified Rankin Scale. Statistical analyses were done using ordinal logistic regression.

Results: Data from 265 patients were included with a mean (SD) age of 68.2 (12.2) years. Confirming univariable analyses, multivariable analyses showed that patients with physical activity in the top quartile more likely presented with a less severe stroke, odds ratio 2.54 (95% confidence limits 1.30-4.95), and had a decreased likelihood of poor outcome odds ratio 0.46 (95% confidence limits 0.22-0.96), compared to patients in the lowest quartile.

Conclusions

In the present study physical activity prior to stroke was associated with a less severe stroke and better long-term outcome.

Paper 4: Failure of repeated instructions to improve physical activity after ischaemic stroke. The ExStroke Pilot Trial: a randomised, multicentre, multinational clinical trial with masked outcome assessment

Boysen G, Krarup LH, Zeng X, Oskedra A, Kõrv J, Andersen G, Gluud C, Pedersen A, Lindahl M, Hansen L, Truelsen T, and the ExStroke Pilot Trial Group

Hypotheses

- H_0 = patients randomized to an intervention of repeated encouragement and instruction in being physically active do not increase their level of physical activity.
- H_0 = patients randomized to an intervention of repeated encouragement and instruction in being physically active do not obtain better modified Rankin score after the end of the intervention period.

Abstract

Objectives

To investigate if repeated verbal instructions about physical activity to patients with ischaemic stroke could increase long-term physical activity.

Design.

A randomised, multicentre, multinational clinical trial with masked outcome assessment.

Setting

Stroke units in Denmark, China, Poland, and Estonia.

Participants

Patients with ischaemic stroke aged 40 years or more, who were able to walk, were enrolled after informed consent.

Interventions

314 patients were enrolled, 157, mean age 69.7 years, were randomised to the intervention group and instructed in a detailed training program before discharge, and at 6 follow-up visits during 24 months. 157 patients, mean age 69.4 years, in the control group had follow-up visits with the same frequency without instructions in physical activity.

Outcome measures

The primary outcome was physical activity assessed using the Physical Activity Scale for the Elderly (PASE) at each visit. Secondary outcomes were clinical events.

Results

The estimated mean PASE scores were 69.1 in the intervention group and 64.0 in the control group. The difference was 5.0 (95% confidence interval -5.8 to +15.9), p= 0.36. There was no significant effect of the intervention on mortality, recurrent stroke, myocardial infarction, or on falls and fractures.

Conclusion

Repeated encouragement and verbal instruction in being physically active did not lead to a statistically significant increase in physical activity measured by the PASE-score. More intensive strategies seem to be needed to promote physical activity after ischaemic stroke.

Paper 5: Physical activity after ischemic stroke improves insulin sensitivity

Krarup LH, Truelsen T, Gluud C, and Boysen G

Hypotheses

- H_0 = patients randomized to the intervention group do not obtain better glucose control measured by the HOMA method compared to patients in the control group.
- H_0 = increased level of physical activity is not associated with better glucose control adjusted for confounding factors.

Abstract

Objective: To examine if stroke patients randomized to repeated encouragement to be physically active through a 2-year period could improve insulin sensitivity compared with control patients receiving usual care.

Methods: Patients included in the ExStroke Pilot Trial in the Copenhagen area were eligible. Participants had fasting blood samples taken at the end-of-trial visit. Blood samples were analyzed for glucose and insulin. Insulin sensitivity was calculated according to the homeostasis model assessment for insulin sensitivity (HOMA2-S%). Two-sample t-test was used to compare HOMA2-S% in the two groups and multivariable linear regression was used to adjust for differences in pre-stroke physical activity level.

Results: A total of 107 (59%) of 180 eligible patients were included. Median (IQR) age was 69 years (58-76), and 54 (51%) were female. Geometric mean (SD) HOMA2-S% was 128.2 (1.6) in the intervention group vs. 100.9 (1.8) in the control group, P=0.049. Adjusting for pre-stroke level of physical activity did not alter the result, P=0.043.

Conclusion: Insulin sensitivity was significantly better in the group encouraged to be physically active than in the control group.

Discussion

The design of the ExStroke Pilot Trial (described in full detail in paper 1[116]) was developed to examine the hypothesis, that physical activity in stroke patients could be increased through repeated encouragement and instruction in being physically active. In paper 2[44] data suggest that the level of physical activity in stroke patients is low in the week preceding stroke symptom onset. Considering the large annual number of stroke patients and limited resources a low budget intervention was expected to be the most relevant in standard clinical settings. Quarterly visits with a physiotherapist (in China a stroke physician) were planned for the first year and two visits were scheduled for the second year of the intervention period. Each participant randomized to the intervention group had a personal physiotherapist with whom they met throughout the trial. The physiotherapists helped to plan what seemed to be a realistic activity program taken into account the patients' resources and comorbidities. An investigator masked to randomization, scored physical activity and outcome events and an independent adjudication committee adjudicated all events to increase the validity of the results. The main strengths of the design are the multicentre design, central and stratified randomization, and study length. The inclusion of multiple centres increases the generalisability of the results[117-119]. In the present study the results showed, that there was no interaction between the centre and the intervention. A two-year study period was considered to be sufficient time for the intervention to be effectual, nevertheless, it cannot be excluded that a longer follow-up or study period would alter the results.

Stratified randomization was used in order to obtain an equal distribution of important prognostic factors. Central randomisation stratifying for SSS score, age, and gender, reduced allocation bias[120].

The main limitation of the design is that the study population is not representative of all stroke patients, but rather of hospitalised stroke patients with mild stroke. The number of patients enrolled in the trial was assessed in the Danish centre during a 3-month period and showed that a total of 12% of patients diagnosed with ischemic stroke were included, whereas the remaining 88% of the patients either had more severe stroke or declined to participate.

Paper 2[44] was conducted in order to assess the level of physical activity in a stroke population in the week preceding stroke compared with community controls. It is known, that a low level of physical activity is a risk factor for ischemic stroke. Many of these results are based on several years of follow-up without considering, that level of physical activity diminishes with age. Furthermore age neutral questionnaires are used which may not be adequate for measuring physical activity in the elderly. We did a case-control study matched according to age, gender, and season in the preceding week both in case and control subjects. The results showed that the stroke population had a lower level of physical activity (PASE score) compared to the control group (76±46.2 vs. 119.7±69.4, P<0.001). Further, we were able to show that there was a trend between the level of physical activity (PASE score) and the risk of stroke, table 2.

PASE score	Univariate	Multivariate[1]
0–49	reference group	reference group
50–99	0.51 (0.28–0.95)	0.53 (0.26–1.08)
100–149	0.27 (0.14–0.54)	0.27 (0.12–0.59)
150+	0.08 (0.03–0.20)	0.09 (0.03–0.25)

[1] Multivariate analyses adjusted for systolic blood pressure, history of stroke, history of myocardial infarction, atrial fibrillation, diabetes mellitus, alcohol consumption, years of education, body mass index and tobacco smoking.

Table 2.
The table shows that with increasing levels of physical activity (PASE score) the risk of stroke diminish both in uni- and multivariable models.

Control subjects were randomly selected from the Copenhagen City Heart Study cohort. The Copenhagen City Heart Study initially included 19,698 randomly selected people living in the "Nørrebro" and "Østerbro" areas of Copenhagen who were invited to four health examinations. As the level of physical activity varies according to season controls were selected for every 50 cases enrolled. It cannot be excluded that some selection bias was introduced. The response rate was 66% and it is possible that responders could be healthier than non-responders. Recall bias can be a problem in retrospective studies. In the present study recall bias is likely to have increased the PASE score. In a recent study from Sweden on physical activity and recall bias in patients with coronary heart disease there was no marked difference in recall bias between cases and controls[121].

The association between increased levels of physical activity and reduced risk of stroke has been shown in multiple observational studies, however, only one study has examined the association between physical activity and stroke severity[122]. In that study stroke severity was assessed using NIHSS and a score of 0-5 was considered a mild stroke. The results showed that a high level of physical activity was related to mild stroke severity and better short-term outcome (day 8) measured using the mRS.

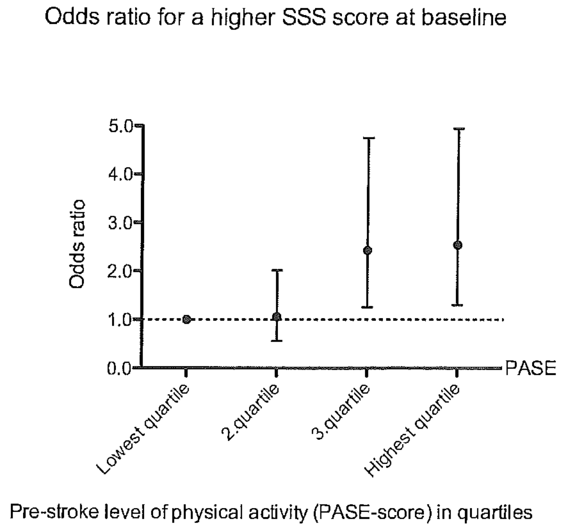

Figure 3. The figure shows the cumulative odds ratio for a higher Scandinavian Stroke Scale score according to the level of pre-stroke physical activity. The association could be considered linear with increasing odds ratio for a higher Scandinavian Stroke Scale score with increasing level of physical activity (OR 1.43 CI: 1.16-1.78). The results are adjusted for age, gender, Charlson score, educational level, fasting glucose level, history of diabetes mellitus.

Using the ExStroke cohort it was possible to investigate the association between pre-stroke level of physical activity and stroke severity and between physical activity and long-term outcome (2 years). Only patients with a first-ever stroke were included, as results should reflect an opportunity for primary prevention.

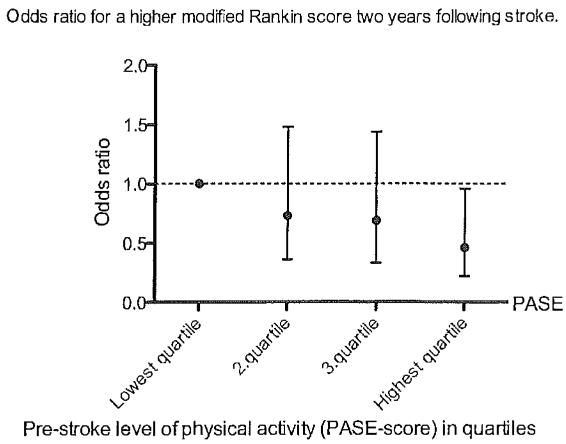

Figure 4. The figure shows the cumulative odds ratio for a higher modified Rankin score according to the level of pre-stroke physical activity. The association could be considered linear with decreasing odds ratio for a higher modified Rankin score with increasing level of physical activity (OR 0.79 CI: 0.62-0.99). The results are adjusted for fasting glucose level, age, educational level, history of atrial fibrillation, diabetes mellitus, depression,Charlson comorbidity index, availability of caretaker, stroke diagnosis (TOAST), randomization group, and Scandinavian Stroke Scale score.

The results showed that pre-stroke level of physical activity was a predictor of stroke severity. Patients in the upper quartile had an OR = 2.54 (95% CI: 1.30-4.95) of a less severe stroke and an OR = 0.46 (95% CI: 0.22-0.96) higher modified Rankin scale, figure 3 and 4. The results of paper 3[123] could have an impact on prevention programs as an additional argument of the beneficial effects of physical activity can be added to the list. Not only does physical activity reduce the risk of first ever stroke, but physically active persons will have a less severe stroke and a better prognosis should they get a stroke.

Pre-stroke inactivity measured using the Frenchay Activities Index, which is based on the frequency of which a person has performed 15 separate activities within (e.g. cooking housework) and outside (e.g. shopping and driving) the house, is in one study associated with increased risk of institutionalisation 5 years following stroke[124] but not with disability measured using the Barthel Index.

The results from the ExStroke Pilot trial, paper 4, showed that it was not possible to increase the level of physical activity in stroke patients.

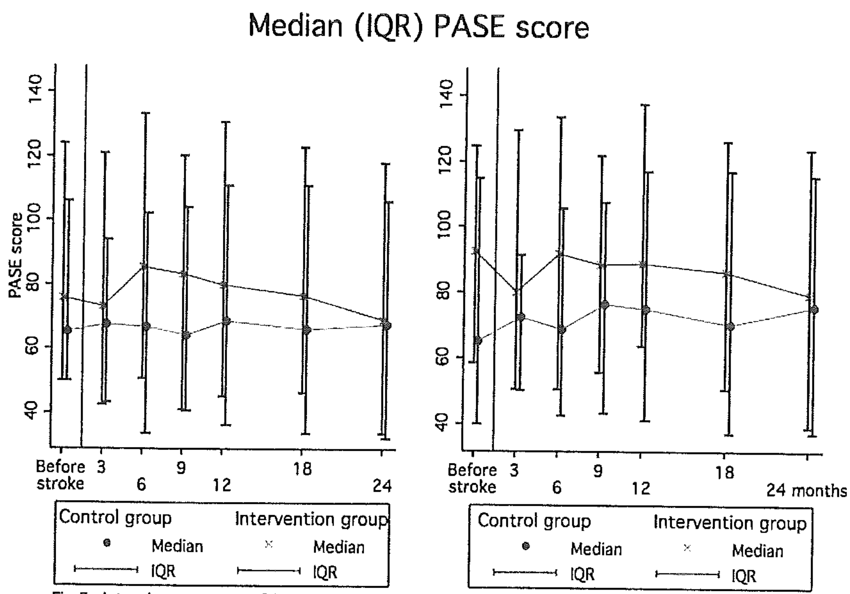

Fig.5a Intention-to-treat n=314

Fig.5b Per-protocol n=161

Figure 5a and figure 5b shows the median (IQR) PASE score in the two groups from baseline until the end of follow-up. The statistical analyses showed that the slopes of the curves did not differ at any time point.

The ExStroke Pilot trial was designed to show a minimal relevant mean difference of 20 PASE point expecting a standard deviation of 50. One explanation for the failure of the trial could be low power. The standard deviation in the trial was 55 and redoing the power calculation with the observed standard deviation suggested that 119 persons were necessary in each group; in the ExStroke Pilot trial 157 persons were included in each group, therefore low power is an unlikely explanation for the results. Another possibility is that the expected increase in physical activity was too high. An increase in PASE score of 20 points roughly corresponds to one hour walking four times a week. Smaller changes would necessitate more patients in the trial, probably longer follow-up, and its clinical relevance is questionable. An additional reason for the results could be the lack of adherence to the study protocol. Half of the study participants complied with all visits, 15% missed one visit, and 35% missed 2 or more visits. For the intervention to work and for the patients to change their sedentary lifestyle it is possible that more frequent visits with the physiotherapist would improve compliance. A per-protocol analysis showed the same results as the intention-to-treat analysis, that there were no significant differences between the groups.

It seems reasonable to conclude that the method used in the ExStroke Pilot trial to increase physical activity in a stroke population was insufficient and that other methods are warranted.

The difference in insulin sensitivity between the intervention group and the control group was reported in paper 5. In this study the PASE score was used as a predictor of insulin sensitivity, and an estimate of the amount of physical activity done in intervention period was calcualted by integrating the PASE scores and obtaining an area-under-curve (PASE-AUC) value for each person. In univariate analysis there was a significant difference in PASE score between the two groups. The baseline characteristics in paper 5 showed that pre-stroke PASE score was not equally distributed in the two groups. The intervention group had a significantly higher pre-stroke PASE score compared to the control group. Reanalysing the PASE-AUC score by adjusting for the difference in pre-stroke PASE score showed that there was no significant difference in PASE-AUC, P=0.14. As seen from paper 4 the intervention did not result in an overall increase in physical activity. In paper 5 a subgroup of patients was used and therefore it is possible that selection bias could have been introduced.

In univariate analysis there was a significant difference in insulin sensitivity between the two groups. As the higher level of pre-stroke physical activity in the intervention group could explain the difference in insulin sensitivity data were reanalysed. Nevertheless, adjusting the results for the difference in baseline PASE score did not alter the results. One explanation for the results could be that the intervention worked in this selected subgroup of patients. Redoing the linear mixed model on this subgroup of patients showed, that there was no effect of the intervention. Another explanation for the conflicting results could be that there was a difference in insulin sensitivity from baseline. HOMA values were not obtained at baseline and therefore it is possible that the difference was present at baseline. In one other study investigating the effect of physical activity on insulin sensitivity in stroke patients the results showed, that at baseline there was no difference in fasting glucose and fasting insulin between the intervention group and control group [68]. After the end of the intervention period there was still no difference in fasting glucose, but there was a significant difference in fasting insulin and glucose tolerance. These results correspond to those seen in paper 5 with no differences in pre- and post intervention fasting glucose, but a significant difference in fasting insulin after the intervention.

Perspectives

As seen from the presented studies physical activity is low in stroke patients compared to community controls. Physical activity is associated with better insulin sensitivity following stroke and is associated with less severe stroke and better long-term outcome. The applied method was insufficient to increase physical activity in stroke patients.

The indication of a potential beneficial effect of physical activity is present, but one question remains to be answered: " How do we get stroke patients to exercise?" In most stroke centres patients are advised at discharge to increase their levels of physical activity. In the ExStroke Pilot Trial we did far more than that without any measurable effect. Consequently, if a higher level of physical activity is warranted in stroke patients the current clinical standard seems insufficient.

Researchers in cardiology have succeeded in showing that exercise based cardiac rehabilitation can reduce mortality in patients with coronary heart disease[125]. A meta-analysis of 48 randomized trials including 8,940 patients showed that exercise cardiac rehabilitation was associated with reduced total mortality OR = 0.80)95% CI: 0.68-0.93) but not with recurrent myocardial infarctions OR = 0.79 (95% CI: 0.57-1.09) [125].

Combining the results from cardiovascular research with the results from the ExStroke Pilot Trial suggests that in order to increase stroke patients' level of physical activity and possibly decrease the risk of mortality or recurrent stroke, supervised training may be necessary. The initial stroke rehabilitation could be gradually moved into exercises that focus more on cardiorespiratory fitness and general strength training. The use of treadmill training with weight support could be a way to facilitate this step as it is feasible in hemiparetic stroke patients[68] and has a larger impact on cardiovascular fitness than regular rehabilitation[126].

In the design of new intervention trials a supervised training approach should be considered. Patients could be given a boost of at least six months of active training thereafter counselling alone may be sufficient[127].

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Appendix

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The ExStroke Pilot Trial: Rationale, design, and baseline data of a randomized multicenter trial comparing physical training versus usual care after an ischemic stroke

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Abstract

Introduction: A high level of physical activity is associated with a decreased risk of first stroke and physical activity modifies recognized stroke risk factors and is recommended for stroke survivors. Available research shows that stroke patients can increase their level of physical performance over a short period. When the intervention period is over, physical performance often declines towards baseline level. Currently, there is no evidence on the association between physical activity and the risk of recurrent stroke. The ExStroke Pilot Trial is a randomized clinical trial with the aim of increasing stroke patients' level of physical activity and secondarily to associate the level of physical activity to the risk of recurrent stroke, myocardial infarction, and all-cause mortality in the two groups. We describe the rationale, design, and baseline data of the ExStroke Pilot Trial.
Methods: Patients with ischemic stroke above 39 years were randomized to intervention or control group. The intervention group will, over a 2-year period, receive information on and verbal instruction to exercise by a physiotherapist or a physician. The control group will receive the department's usual care. Physical activity is assessed in both groups seven times during follow-up using the Physical Activity Scale for the Elderly (PASE) questionnaire, which quantifies the amount of physical activity done in the last seven days prior to interview. The PASE score constitutes the primary outcome measure. The secondary outcome is the time from randomization to recurrent stroke, myocardial infarction, or all-cause mortality. Further outcome measures include: time from randomization to recurrent stroke, myocardial infarction, and vascular death; recurrent stroke; modified Rankin Scale; quality of life; occurrence of falls and fractures.

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Trial status: From 9 centers in 4 countries, 314 patients were included and follow-up is ongoing. Mean age and standard deviation (SD) of the study participants was 68.4 (11.9) years and 56.4% were male. Mean (SD) PASE score was 84.1 (55.9) and median (interquartile range) Scandinavian Stroke Scale score was 54 (51–58).

Keywords: Ischemic stroke; Physical activity; Secondary prevention; Randomized clinical trial

1. Introduction

The importance of physical activity as a stroke risk factor has been investigated in a number of observational studies [1–6]. A meta-analysis showed that level of physical activity is inversely associated with the risk of stroke [7]. Small randomized trials have shown that training can improve stroke patients' ability to walk [8], maintain balance [9], and do daily chores [10]. Non-randomized studies show that physical exercise can improve hemiparetic stroke patients' peak oxygen uptake and gait performance [11,12]. Exercise based cardiac rehabilitation has been shown to reduce mortality in patients with coronary heart disease [13]. So far no clinical trials have been designed to show if physical activity can reduce mortality and the risk of recurrent stroke in stroke survivors. The main characteristic of trials of physical activity in stroke is that the intervention period is short. The level of physical fitness can be increased during the intervention period, but is usually not maintained after the end of the trial intervention. The ExStroke Pilot Trial is designed to assess how repeated encouragement and verbal instruction affect stroke patients' level of physical activity over a 2-year period.

2. Method

2.1. Study design

The ExStroke Pilot Trial is an ongoing randomized, multicenter, multinational trial with blinded outcome assessment. Patients were centrally randomized to intervention group or control group. The intervention consists of repeated encouragement and verbal instruction on being physically active given by a physiotherapist or a physician. The control group receives usual care, including information on the possible benefits of physical activity. Five centers in Estonia, Poland, China, and Denmark participate in the trial.

2.2. Inclusion criteria

Within 90 days of symptom onset patients with an ischemic stroke over 39 years of age were considered for inclusion. All patients had a computed tomography (CT) or magnetic resonance imaging (MRI) scan compatible with ischemic stroke before inclusion. Patients needed to be able to walk unassisted by another person. Canes and walkers were allowed. All patients had to give informed consent, verbal and written, prior to enrollment.

2.3. Exclusion criteria

Patients who were bedridden, in wheelchair, unable to understand the trial, reluctant to provide informed consent, or had CT/MRI scans suggesting intracerebral hemorrhage or other focal pathology not indicating ischemic stroke were excluded from the trial.

2.4. Scandinavian Stroke Scale

Stroke severity was assessed using the Scandinavian Stroke Scale (SSS) [14]. The SSS is a simple stroke scale and consists of the following 9 items: consciousness, orientation, eye movement, facial palsy, arm motor power, hand motor power, leg motor power, gait, and speech. The SSS score may range from 0–58 where full score means no deficits in these items.

2.5. Randomization

Centralized randomization 1:1 was performed by telephone or e-mail within gender, age (40–70 years or >70 years), and stroke severity (Scandinavian Stroke Scale 20–39 points or 40–58 points) strata in blocks of 10. Stratified randomization was chosen in order to keep the two groups balanced with regard to gender, age, and stroke severity, as we presumed that these factors would influence the PASE score the most.

2.6. Experimental intervention

Patients randomized to the intervention group were scheduled for a meeting with a physiotherapist or a physician soon after randomization. The patients and the physiotherapist or the physician then planned a detailed training program. The training program was individualized taking into account the patients' resources and prior training status as well as the patients' preferences for leisure time physical activities and the feasibility of activities in the local community. A guideline was developed for the physiotherapist/physician to use when planning the training program for the individual patients. Specifically, the symptoms of the patients should be taking into considerations so patients with more severe pareses were instructed differently from patients without pareses. Furthermore the guideline instructed the physiotherapist/physician to contact their patient once in between clinical visits to discuss the training program, training progress, and how the patient complied with the training program. Each patient met with their personal physiotherapist/physician every three months the first year and thereafter every six months until the end of the trial.

2.7. Control intervention

Patients randomized to the control group received treatment as usual without any specific information about physical activity, but were told about the possible benefits of physical exercise and that physical activity is recommended for stroke survivors. Patients in the control group were seen for clinical visits at the same time intervals as the patients in the intervention group, but did not see a physiotherapist and were not contacted by telephone in between clinical visits.

2.8. Co-interventions

Both groups were given the same treatment with regard to hypertension, antiplatelet therapy, hypercholesterolaemia, hyperhomocysteinaemia, and diabetes as well as information on smoking, alcohol, and diet.

2.9. The Physical Activity Scale for the Elderly (PASE)

The PASE questionnaire was developed to assess physical activity in the elderly population using age-neutral questionnaires [15,16]. The PASE is a 12-item scale that measures the average number of hours per day spent on leisure, household, and occupational physical activities over the previous seven days. Each item has an activity weight which is multiplied by the amount of time spent on the item. All items are then added to give the PASE score.

The PASE scoring algorithm was derived from physical activity measured by movement counts from an electronic physical activity monitor, activity diaries, self-assessed activity levels in a general population of non-institutionalized persons [15,16]. The activities included (weight): walk outside home (20); light sport (21); moderate sport (23); strenuous sport (23); muscle strength (30); light housework (25); heavy housework or chores (25); home repairs (30); lawn work or yard care (36); outdoor gardening (20); caring for another person (35); work for pay or as a volunteer (21). The PASE score may range from zero to more than 400. When tested in the general population it ranged from 0–361.

The validity of the PASE questionnaire was tested by Washburn et al. [15]. PASE was positively correlated to grip strength ($r=0.37$, $p<0.01$), static balance ($r=0.33$, $p<0.01$), and leg strength ($r=0.25$, $p<0.01$) and negatively correlated to resting heart rate ($r=-0.13$, $p<0.05$), age ($r=-0.34$, $p<0.01$), perceived health status ($r=-0.34$, $p<0.01$), and overall Sickness Impact Profile score ($r=-0.42$, $p<0.01$). PASE was found to vary with changing seasonal temperatures and was highest during the summer. Furthermore, PASE has been correlated to the doubly labeled water method [17], performance on a six-min walk and knee strength in a population with knee pain [18], peak oxygen uptake, systolic blood pressure and balance [16], average three-day portable accelerometer readings [19] and mean seven-day accelerometer counts/min [20].

PASE has been validated in different populations: Healthy with no cardiac risk factors [17,19], patients with knee pain and cardiac risk factors [18], and sedentary people [16,20]. The mean PASE score ranged from 85 to 131 in six validation studies and the mean age ranged from 67 to 76 years [15–20].

The PASE questionnaire was originally translated by the developers into Chinese (Mandarin) and Danish. In Poland and Estonia the participating investigators translated the PASE questionnaire from English into their native languages.

2.10. Baseline visit

After informed consent patients who fulfilled all inclusion criteria and none of the exclusion criteria were randomized to the intervention group or the control group. A thorough medical history was taken at inclusion focusing on risk factors for stroke and diseases that would compromise physical activities. The focus was on the following risk factors: History of stroke, MI, diabetes mellitus, atrial fibrillation, intermittent claudication, hypertension, hypercholesterolaemia, smoking, and alcohol consumption. Hypertension was defined as a systolic/diastolic blood pressure above 140/90 mmHg at baseline or previously diagnosed by another physician. Hypercholesterolaemia was defined as total cholesterol above 5.0 mmol (195 mg/dl) at baseline or diagnosed by another physician. Alcohol consumption was categorized into 3 groups: Never drinking, moderate drinking (less than 14 units of alcohol per week for women and less than 21 units of alcohol per week for men), and heavy drinking (above moderate levels). Smoking was categorized into the following groups: Never, former, and current smoker. The PASE score obtained at baseline referred to the week preceding the stroke.

2.11. Follow-up

All patients are followed for a maximum of two years. Patients are seen for a clinical visit every three months the first year and thereafter every six months until the end of the trial. At each visit, vital signs, clinical outcome measures, adverse events, concomitant medication, and PASE-score data are collected. To monitor the influence physical exercise may have on quality of life patients are asked to complete the World Health Organizations' Well Being Scale-5 [21] and the European Quality of Life Visual Analogue Scale [22] at each visit. In addition to clinical visits patients in the intervention group will at each clinical visit meet with their personal physiotherapist or physician to discuss their training program and training progression.

2.12. Outcome measures

The primary outcome is the level of physical activity measured with the PASE questionnaire. The secondary outcome is the time from randomization to recurrent stroke, MI, or all-cause mortality. Further outcomes include: time from randomization to recurrent stroke, MI, and vascular death; recurrent stroke; disability measured with modified Rankin Scale [23,24]; quality of life; and falls and fractures. Investigators blinded to randomization will interview all patients about their PASE score and new events.

2.13. Adjudication committee

The outcome event adjudication committee will blindly and independently evaluate and adjudicate all events such as death, causes of death, recurrent stroke, MI and traumatic event or other adverse events.

2.14. Statistics

The difference in PASE score between the two groups will be tested using SAS mixed model for repeated measures. Furthermore differences in PASE score will be tested by calculating the area under the curve for all PASE measurements in the intervention period. The secondary outcomes will be analyzed on an intention-to-treat basis by Cox regression analysis after testing for proportionality, allowing for potential risk factors (baseline variables and covariates). Time to any event will be calculated from the day of randomization. The effect of selected baseline

Table 1
Baseline characteristics of ischemic stroke patients in the ExStroke Pilot Trial

Total number of included patients	314
Age — years	
Mean (SD)	68.4 (11.9)
Range	40 –93
Male — no. (%)	177 (56.4)
Race or ethnic group	
Caucasian	273 (86.9)
Asian	41 (13.1)
Time from stroke to inclusion — days	
Median (IQR)	10 (5–24)
PASE score — Mean (SD)	84.1 (55.9)
Scandinavian Stroke Scale — Median (IQR)	54 (51–58)
Stroke characteristics, TOAST criteria	
Large-artery atherosclerosis — no. (%)	69 (22.0)
Cardioembolism — no. (%)	40 (12.7)
Small-artery disease — no. (%)	102 (32.5)
Stroke of other determined etiology — no. (%)	2 (0.1)
Stroke of undetermined etiology — no. (%)	101 (32.2)
Selected clinical cbaracteristics	
History of stroke — no. (%)	49 (15.6)
History of transient ischemic attack — no. (%)	29 (9.2)
History of atrial fibrillation — no. (%)	41 (13.1)
History of myocardial infarction — no. (%)	26 (8.3)
Diabetes — no. (%)	45 (14.3)
History of intermittent claudication — no. (%)	26 (8.3)
History of hypertension — no. (%)	171 (54.5)
History of coronary-artery bypass grafting — no. (%)	5 (1.6)
History of percutaneous transluminal coronary angioplasty — no. (%)	5 (1.6)
Hypercholesterolaemia — no. (%)[a]	179 (57.0)
Baseline Modified Rankin score[b] — no. (%)	
0	230 (73.2)
1	48 (15.3)
2	31 (9.9)
3	5 (1.6)
Smoking — no. (%)	
Current smoker	115 (36.6)
Former smoker	108 (34.4)
Never smoked	91 (29.0)
Alcohol — no. (%)	
Never drinking	78 (24.8)
<14/21(f/m)[c]	197 (62.7)
>14/21(f/m)	38 (12.1)

SD: standard deviation. IQR: interquartile range. TOAST: classification of subtype of acute ischemic stroke according to Trial of Org 10172 in Acute Stroke [25].
[a] Hypercholesterolaemia defined as total cholesterol>5.0 mmol/l (195 mg/dl).
[b] Before stroke onset. Patients with mRS of 4 and 5 were excluded.
[c] Number of drinks on a weekly hasis according to gender (f/m).

variables and covariates will be assessed by either stepwise or backward regression methods. Two-sided statistical test will be used and p-value < 0.05 will be considered siguificant.

2.15. Independent Data Monitoring and Safety Committee

An Independent Data Monitoring and Safety Committee (IDMSC) will monitor all vascular events, falls, and adverse events. The IDMSC will be blinded to randomization. The Copenhagen Trial Unit will provide all data to the IDMSC. The IDMSC can recommend that the trial should stop early if there is a significant ($p < 0.001$) difference in the secondary outcome between intervention and control group. The IDMSC was scheduled to meet twice during the study.

2.16. Data management

All investigators have to maintain a protocol of included patients and case report forms are to be kept in accordance with Good Clinical Practice (GCP). All case report forms will be handled by the Copenhagen Trial Unit, which will enter data into a database for analyses. All data are double entered to diminish the risk of errors. Two instructional visits per clinical site were scheduled to educate investigators in using the PASE questionnaire, to monitor data, and to instruct physiotherapist and physicians on physical exercise.

2.17. Ethical considerations

It is presumed that physical activity will have favorable effect on the prognosis. All patients included in the ExStroke Pilot Trial were therefore informed of the potential beneficial effects of physical activity. The study was approved by the Danish Ethics Committee (KF 11006/04), the Danish Data Protection Agency, and by the local Ethics Committees in China, Poland, and Estonia. The ExStroke Pilot Trial is registered at www.clinicaltrials.gov (NCT00132483).

2.18. Sample size

The sample size was calculated based on a mean difference of 20 PASE points, a standard deviation of 50, an alpha of 5%, and a beta of 20%. Based on a sample size calculation 99 patients would be needed in each group. A total of 300 patients were planned to be included in the ExStroke Pilot Trial to take into account that dropouts could occur.

2.19. Funding

This project is funded by the Ludvig and Sara Elass Foundation, Hede Nielsen Foundation, Eva and Henry Frænkels Foundation, Søren and Helene Hempels Foundation, and King Christian the 10th Foundation. The funding sources have had no impact on the design of the trial and will have no impact on the data collection, data management, data analysis, and reporting.

2.20. Trial status

Screening and patient enrollment started in August 2003 and was completed in October 2005. A total of 314 patients fulfilled entry criteria and were randomized. Patients were included from the following centers: Estonia (n=9), Poland (n=19), China (n=41), Aarhus, Denmark (n=8), Hvidovre, Denmark (n=31), Frederiksberg, Denmark (n=15), Amager, Denmark (n=40), Rigshospitalet, Denmark (n=2), and Bispebjerg, Denmark (n=149). Baseline characteristics for all patients are shown in Table 1. Patients were randomized at a median of 10 days after their stroke, had a mean PASE score of 84, and presented a variety of stroke subtypes defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) groups [25]. More than half of the patients had hypertension and hypercholesterolaemia and about 15% had previous stroke, atrial fibrillation, and diabetes.

3. Discussion

The potential benefits of physical activity have long been recognized and physical exercise is recommended for stroke survivors [26]. Despite the acceptance of physical activity as a beneficial therapy for stroke survivors there is a lack of randomized trials documenting that stroke patients can maintain a long-term increase in physical activity and benefit clinically from it. The ExStroke Pilot Trial will be the first randomized trial designed to show if stroke patients through verbal instruction and encouragement can increase their level of physical activity over a 2-year period.

The ExStroke Pilot Trial is designed as a multicenter trial, in order to facilitate the leap from pilot trial to a large-scale trial. Should the ExStroke pilot trial show a significant increase in PASE score in the intervention group, it would be sensible to conduct a larger trial with recurrent stroke, AMI, and all-cause mortality as the primary outcome measure. This can be done using the same set-up as the ExStroke pilot trial.

The PASE questionnaire was chosen as the instrument for assessing physical activity because it was designed for elderly people. Activities in which elderly people participates are different from those of younger people. Using age-neutral questionnaire might result in a false low activity score and the sensitivity of an age-neutral questionnaire might not be high enough to register improvements achieved by elderly people.

Our trial has a number of strengths. First, it is multicenter and multinational. This increases its external validity. Second, we conducted centralized randomization in order to minimize allocation bias [27–29]. Third, we employed stratified randomization in order to secure equal distribution of important prognostic factors [30]. Fourth, a trained person blinded to randomization assessed the PASE score to avoid possible assessment bias [27–29]. Fifth, we planned the intervention period to two years, which gives the opportunity to assess how physical activity affects the long-term prognosis after stroke. The intervention period in other trials of physical activity in stroke patients has often lasted from 3 to 6 months. Sixth, the ExStroke Pilot Trial intervention is low cost relative to interventions where regular training sessions are being conducted. This means that if a significant increase in PASE score can be demonstrated, it will be possible to use this method in medical practice if a clinical effect can also be demonstrated.

Our trial also has limitations. First, the ExStroke Pilot Trial is not powered to show any beneficial effect of physical activity on the risk of recurrent stroke, MI, or mortality. Secondly, the PASE questionnaire is validated from age 55 and above. In the ExStroke Pilot Trial we have included patients from the age of 40 years. As PASE is validated in sedentary people and in people with disabilities the PASE questionnaire is assumed sufficiently sensitive to differentiate between the small changes in physical activity, which can be expected in stroke patients.

Third, the ExStroke patients are a selected stroke population. As seen from Table 1 the median baseline SSS score is high, matching a stroke population with mild stroke. In the center that included the majority of patients in ExStroke, all patients with ischemic stroke were assessed over a 3-month period. Only 12 (15%) out of 80 patients were included in the trial. The percentage is likely to have been lower in the other centers. Accordingly, many patients had exclusion criteria or declined to participate, when they were informed about the need of performing physical exercise.

The results of the trial will eventually be applicable to patients with mild ischemic stroke.

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Level of Physical Activity in the Week Preceding an Ischemic Stroke

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Key Words

Ischemic stroke · Physical Activity Scale for the Elderly · Physical activity

Abstract

Background: Most observational studies investigating physical activity as a risk factor for stroke have concentrated on the years preceding a stroke event. In the present case control study we compared the reported level of physical activity performed during the week preceding an ischemic stroke with that of community controls. Furthermore we calculated the odds ratio for stroke based on the level of physical activity. ***Subjects and Methods:*** Patients with an ischemic stroke were recruited consecutively from hospitals covering Copenhagen City. Community controls were recruited among participants of the Copenhagen City Heart Study and matched according to age and gender. The level of physical activity was assessed using The Physical Activity Scale for the Elderly (PASE), which quantifies the amount of physical activity done in the last 7 days. ***Results:*** A total of 127 cases and 301 control subjects were included in the study. Mean (±SD) PASE scores for cases were 76.0 ± 46.2 and 119.7 ± 69.4 for controls ($p < 0.001$). For each 1-point increase in PASE score the odds ratio for ischemic stroke was 0.98 (0.98–0.99), equivalent to an odds ratio of 0.86 (95% CI: 0.82–0.90) for each 10-point increase. ***Conclusion:*** Stroke patients are less physically active in the week preceding an ischemic stroke when compared to age- and sex-matched controls. Increasing PASE score was inversely, log-linearly and significantly associated with odds ratio for ischemic stroke.

Introduction

The beneficial effects of physical activity on major stroke risk factors are well documented. Physical activity reduces hypertension, type 2 diabetes mellitus, improves metabolism, and has been linked to direct beneficial changes of the vascular system [1–6]. The impact on major stroke risk factors may explain why physical activity is associated with a reduced occurrence of stroke and other cardiovascular diseases. Regular exercise has been recommended both for the prevention of cardiovascular disease and in stroke survivors [7, 8]. A newly published meta-analysis showed that physical inactivity is a stroke risk factor [9]. Most studies have concentrated on physical activity in the years preceding an ischemic stroke event. One study examined the level of physical activity 2 weeks prior to an ischemic stroke event and compared to community controls [10]. The results showed that the percentages of stroke patients that were inactive were substantially higher when compared to community controls [10]. The aim of the present study was to evaluate

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the level of physical activity in the week preceding an ischemic stroke and to compare it with age- and sex-matched community controls. In addition we calculated odds ratio for ischemic stroke based on the level of physical activity.

Subjects and Methods

Selection of Cases and Control Subjects

Patients were recruited consecutively when admitted to stroke units at one of the five hospitals covering central Copenhagen, Denmark. These departments receive all subjects admitted with suspected acute stroke living in the catchment area. The inclusion period lasted from August 12th, 2003 to April 1st, 2004.

Inclusion criteria were as follows: ischemic stroke compatible with CT scans in patients aged 40 years or older. Patients with transient ischemic attack in whom the scan showed signs of infarction were not included in the study. Patients were excluded if they had other types of stroke than ischemic, if they could not cooperate with the examinations, or if they had previously been enrolled. Verbal and written informed consent was obtained from the patient. This study was approved by the local ethic committee, (KF) 11-006/04.

Community control subjects were randomly recruited among participants in the Copenhagen City Heart Study, which has been described in detail elsewhere [11]. Briefly, 19,698 people living in the Copenhagen areas 'Østerbro' and 'Nørrebro' were chosen randomly within age and sex strata, and invited by letter to four health examinations held in 1976–1978, 1981–1983, 1991–1994, and 2001–2003. Participants at the fourth examination were age- and sex-matched to cases in the present study. As reported, level of physical activity varies according to season; controls were selected for every 50 cases enrolled. Questionnaires were sent by mail within 1 week from the date of selection. A total of 510 subjects were contacted and a response was received from 335 (65.6%).

Physical Activity Assessment

The subjects' physical activity level was measured using the Physical Activity Scale for the Elderly (PASE) [12, 13]. The PASE questionnaire was developed with the purpose of assessing level of physical activity in middle-aged and elderly individuals. The questionnaire is a 12-item scale that measures the average number of hours per day spent on participating in sports, occupational activity, household activities, and leisure time activities over a 1-week period. The PASE scoring algorithm was derived from physical activity measured by movement counts from an electronic physical activity monitor, activity diaries, and self-assessed activity levels in a general population of noninstitutionalized persons. PASE has been validated in healthy subjects [14, 15], people with disabilities [16] and sedentary subjects [12, 17]. Mean PASE score ranged from 85–131 in the validating studies. The PASE questionnaire has validity in line with other physical activity questionnaires [18]. Physical activity in patients referred to the week before onset of stroke symptoms, whereas in controls it referred to the week before responding to the questionnaire.

Statistics

Due to incomplete questionnaires 34 control subjects and 17 case subjects were excluded from the final analyses. Comparison of categorical variables was done using χ^2 statistics and ordinal variables were analyzed using Kruskal-Wallis statistics corrected for ties. Continuous variables were transformed to presumed normality and compared using the two-sample t test. Subjects were divided into four categories according to their total PASE score: 0–49; 50–99; 100–149 and 150+. Multivariate conditional logistic regression for matched data was used to calculate the odds ratio and 95% confidence intervals for the association between physical activity and ischemic stroke. Interactions and tests for linearity of continuous variables were done using log likelihood ratio tests in the multivariate model. The difference in mean PASE score for assessing interview bias was tested using paired t test. The statistical software program STATA version 9.2 was used for all calculations. The level of 5% was considered statistically significant.

Results

A total of 127 patients and 301 control subjects were included in the final analyses. Women accounted for 48% of cases and 45% of controls. Mean age for cases was 71.8 years and 71.5 years for controls. Mean (±SD) PASE score was 76 ± 46.2 for cases and 119.7 ± 69.4 for controls ($p < 0.001$, table 1). Cases had a significantly higher incidence of history of stroke, history of atrial fibrillation and a higher body mass index but not of history of myocardial infarction or history of diabetes mellitus. Cases had a lower level of education and were more often current smokers than controls. Mean (±SD) PASE score for cases (n = 81) and controls (n = 246) without any of the following risk factors history of stroke, history of myocardial infarction, history of diabetes mellitus and history of atrial fibrillation was 77.8 ± 47.5 and 121.3 ± 69.5 ($p < 0.001$), respectively. Subgroup analyses of men and women separately did not alter results significantly. The association between PASE score and ischemic stroke is presented in table 2. Both in univariate and multivariate analyses increasing PASE score was inversely associated with odds ratio for ischemic stroke. The association was significant in all categories except for PASE scores from 50 to 99 in the multivariate analysis. There was no significant difference between the analyses with PASE score entered either in four categories or as a continuous variable ($\chi^2 = 0.81$, 2 d.f.; $p = 0.67$). When entered as a continuous variable odds ratio for each 1-score increase in PASE was 0.98 (95% confidence interval: 0.98–0.99) equivalent to 0.86 (95% confidence interval: 0.82–0.90) for each 10-point increase. There were only minor differences in the estimates for

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Table 1. Baseline characteristics for patients with ischemic stroke and control subjects

Characteristics	Cases (n = 127)	Controls (n = 301)	p value
Age, years	71.8 ± 11.7	71.5 ± 11.6	NS
Gender			
Men	66 (52.0%)	164 (54.5%)	NS
PASE score	76.0 ± 46.2	119.7 ± 69.4	<0.001
PASE (categorical)			<0.001
0–49	30 (24%)	30 (10%)	
50–99	59 (46%)	103 (34%)	
100–149	30 (24%)	92 (31%)	
150+	8 (6%)	76 (25%)	
Years of education			<0.04
≤8 years	67 (53%)	138 (46%)	
9–12 years	47 (37%)	93 (31%)	
≥13 years	13 (10%)	70 (23%)	
Body mass index			<0.01
<20	10 (8%)	9 (3%)	
20–25	61 (48%)	110 (37%)	
25–30	41 (32%)	133 (44%)	
>30	15 (12%)	49 (16%)	
Smoking			<0.05
Never	30 (24%)	83 (28%)	
Ex-smoker	46 (36%)	137 (46%)	
Current smoker	51 (40%)	81 (27%)	
Diabetes mellitus			0.20
Yes	14 (11%)	19 (6%)	
No	113 (89%)	282 (94%)	
History of stroke			<0.001
Yes	26 (20%)	12 (4%)	
No	101 (80%)	289 (96%)	
History of myocardial infarction			0.60
Yes	9 (7%)	27 (9%)	
No	118 (93%)	274 (91%)	
Atrial fibrillation			<0.01
Yes	12 (9%)	9 (3%)	
No	115 (91%)	292 (97%)	
Intake of alcohol units			0.98
Not drinking	24 (19%)	58 (19%)	
1–14(women)/1–21 (men)	83 (65%)	196 (65%)	
>14 (women)/>21 men	20 (16%)	47 (16%)	
Systolic blood pressure, mm Hg	155.6 ± 24.4	145 ± 20.4	<0.001

Number and percent of subjects are given except for age, PASE score and systolic blood pressure (mean ± SD). p values are calculated for overall data.

men and women and interaction analyses were insignificant ($\chi^2 = 0.45$, 1 d.f.; p = 0.50).

Bias

A previous study has shown that the PASE score is often higher when subjects provide information on physical activity by self-administered questionnaires compared to being interviewed [13]. We therefore examined the possible bias due to differences in interview methods by contacting a subsample of 72 randomly selected controls by telephone and asked them the same physical activity questions. The mean PASE score was 110.0 according to the self-reported data and 102.6 when the same subjects where interviewed by telephone (p = 0.13). As the difference was not significant, and the difference was only 7%, the original data derived from the control subjects were used without further adjustment. Physically active subjects may be more likely to respond to a questionnaire

Table 2. Odds ratio for the risk of ischemic stroke related to physical activity

PASE score	Univariate	Multivariate[1]
0–49	reference group	reference group
50–99	0.51 (0.28–0.95)	0.53 (0.26–1.08)
100–149	0.27 (0.14–0.54)	0.27 (0.12–0.59)
150+	0.08 (0.03–0.20)	0.09 (0.03–0.25)

[1] Multivariate analyses adjusted for systolic blood pressure, history of stroke, history of myocardial infarction, atrial fibrillation, diabetes mellitus, alcohol consumption, years of education, body mass index and tobacco smoking.

about exercise than less physically active subjects. A total of 510 control subjects were contacted and we received a response from 335 (65.6%), although only 301 were included in the final analyses due to missing values.

Discussion

The present study showed that physical activity in the week preceding an ischemic stroke is significantly lower than in community controls and that physical activity was inversely and log-linearly associated with odds ratio for ischemic stroke. Our results may reflect that stroke patients are prone to a sedentary lifestyle or that stroke patients have incapacitating comorbidities prior to stroke. In favor of the former is that subgroup analyses excluding cases and controls with risk factors still showed a significantly higher PASE score in controls. In favor of the latter is the higher rate of history of stroke, atrial fibrillation, smoking, higher body mass index and higher blood pressure observed in cases. A lower level of education might also contribute.

Physical inactivity is a well-established risk factor for cardiovascular disease and stroke. A meta-analysis has shown that physical exercise can reduce mortality in patients with coronary heart disease (odds ratio: 0.80; 95% confidence interval: 0.68–0.96) [19]. After a nondisabling stroke it is common to see fluctuation and sustained decline in physical performance [20]. Physical activity is recommended for stroke survivors but so far it has not been studied if physical activity reduces mortality or the risk of recurrent stroke in stroke survivors. In a review of 38 randomized studies, all with the goal of getting older people to exercise, it was not possible to identify which interventions were most effective [21]. The changes in physical activity were small and short-lived. In order to decrease the risk of recurrent stroke through exercise stroke survivors need to continue to exercise after initial rehabilitation. Therefore specific intervention programs need to be developed and tested in randomized settings in order to demonstrate the presumed beneficial effects of physical activity.

The level of physical activity differs according to season [13]. To account for this possible bias control subjects were interviewed within a few weeks after the case subjects were enrolled in the study. We also assessed the difference in PASE score between self-reported PASE score and PASE score obtained by interview in a subsample of controls. This analysis showed that the score was marginally lower when the person was interviewed as compared to self-reported physical activity. Although the difference was marginal and not significant the interview method is likely to have biased the results towards a higher level of physical activity in control subjects compared with case subjects. However, the difference in mean PASE score far exceeded the difference due to interview method.

There is evidence to suggest that prestroke dementia is present in 15% of a stroke population [22]. In the present study we have not assessed cognitive function. A decline in cognitive performance is likely to reduce the level of physical activity performed by the individual. We cannot exclude that some of the difference in PASE score found in this study might be due to a difference in cognitive function.

Controls were recruited among participants in the fourth examination of the Copenhagen City Heart Study, and two thirds responded. It is possible that some selection bias was introduced, as healthier subjects are more likely to respond than nonhealthy subjects. Recall bias will most likely affect the results towards higher scores but as both cases and controls were asked to remember a week back in time recall bias is thought to play a similar role in the two groups.

In conclusion our findings suggest that patients prior to stroke have a low level of physical activity and that the level of physical activity was inversely and log-linearly associated with odds ratio for ischemic stroke. Subgroup analyses of men and women separately and in cases and controls without any prespecified risk factors did not alter results significantly.

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Prestroke physical activity is associated with severity and long-term outcome from first-ever stroke

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ABSTRACT

Objective: To determine whether prestroke level of physical activity influenced stroke severity and long-term outcome.

Methods: Patients included into the present analyses represent a subset of patients with first-ever stroke enrolled into the ExStroke Pilot Trial. Patients with ischemic stroke were randomized in the ExStroke Pilot Trial to an intervention of repeated instructions and encouragement to increase the level of physical activity or to a control group. Prestroke level of physical activity was assessed retrospectively by interview using the Physical Activity Scale for the Elderly (PASE) questionnaire. The PASE questionnaire quantifies the amount of physical activity done during a 7-day period. In this prospectively collected patient population initial stroke severity was measured using the Scandinavian Stroke Scale and long-term outcome was assessed after 2 years using the modified Rankin Scale. Statistical analyses were done using ordinal logistic regression.

Results: Data from 265 patients were included with a mean (SD) age of 68.2 (12.2) years. Confirming univariable analyses, multivariable analyses showed that patients with physical activity in the top quartile more likely presented with a less severe stroke, OR 2.54 (95% CI 1.30–4.95), and had a decreased likelihood of poor outcome, OR 0.46 (95% CI 0.22–0.96), compared to patients in the lowest quartile.

Conclusions: In the present study physical activity prior to stroke was associated with a less severe stroke and better long-term outcome. *Neurology*® **2008;71:1313–1318**

GLOSSARY

mRS = modified Rankin Scale; **PASE** = Physical Activity Scale for the Elderly; **SSS** = Scandinavian Stroke Scales.

Epidemiologic studies have consistently suggested an association between physical activity and the risk of stroke.[1] Physical activity is recommended to reduce the risk of first ever and possibly the risk of recurrent stroke.[2] Stroke severity has marked implications for the patients and society. More severe strokes result in worse outcomes, including longer rehabilitation, absence from work, and higher mortality.[3] A retrospective cross-sectional study investigation of pharmacologic and clinical factors in relation to stroke severity showed that physical activity prior to stroke was inversely associated with stroke severity and short-term outcome.[4]

In this study we investigate if prestroke level of physical activity influences stroke severity and long-term outcome in patients with first-ever stroke enrolled in the ExStroke Pilot Trial.[5]

METHODS This is a retrospective analysis in a prospectively collected patient population. Patients enrolled in the present study had a first-time ever stroke and were included in the ExStroke Pilot Trial. The design of the ExStroke Pilot Trial has been described elsewhere.[5] Briefly, the ExStroke Pilot Trial is a multicenter, multinational, randomized trial in which patients with ischemic stroke were randomized to an intervention consisting of repeated encouragement and verbal instruction in being physically active. The

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Table 1 Baseline characteristics of the study population	
Characteristics	Values
Age, y, mean (SD)	68.2 (12.2)
Women, n (%)	117 (44.3)
Race, n (%)	
Caucasian	230 (86.8)
Asian	35 (13.2)
Education, y, n (%)	
8 or less	121 (45.7)
9–12	100 (37.7)
13 or more	44 (16.6)
Availability of caretaker, n (%)	131 (49.4)
Smoking, n (%)	
Current smoker	101 (38.1)
Former smoker	88 (33.2)
Never smoked	76 (28.7)
Alcohol, n (%)	
Never drinking	61 (23.0)
<14/21 (F/M)*	169 (63.8)
>14/21 (F/M)	35 (13.2)
Prior diseases, n (%)	
Transient ischemic attack	19 (7.2)
Atrial fibrillation	35 (13.2)
Myocardial infarction	22 (8.3)
Diabetes mellitus	39 (14.7)
Depression	28 (10.6)
Hypertension	141 (53.2)
Charlson comorbidity index, n (%)	
0	107 (40.4)
1	92 (34.7)
2	48 (18.1)
3	13 (4.9)
4	5 (1.9)
PASE score prior to stroke, median (IQR)	70 (50–114.6)
Barthel Index, median (IQR)	100 (95–100)
Scandinavian Stroke Scale, median (IQR)	54 (51–58)
Time from onset, d, median (IQR)	10 (5–23.5)
Body mass index, mean (SD)	25.9 (4.3)
Mean arterial blood pressure, mean (SD)	106.8 (16.0)
Blood samples, mean (SD)	
Total cholesterol†	5.4 (1.3)
Fasting glucose	6.1 (2.0)
Stroke diagnosis, n (%)	
Large-artery disease	60 (22.6)
Cardioembolism	36 (13.6)
Small-vessel disease	84 (31.7)
Other determined cause	2 (0.8)
Undetermined etiology	83 (31.3)
Modified Rankin score at 2 years, n (%)	
0	62 (23.4)
1	82 (30.9)
2	63 (23.8)
3	18 (6.8)
4	10 (3.8)
5	4 (1.5)
6	14 (5.3)
Missing	12 (4.5)

—Continued

Total n = 265.
*Units of alcohol according to sex (female/male).
†Cholesterol and glucose is measured in mmol/L.
PASE = Physical Activity Scale for the Elderly.

control group received standard care and information of the possible benefits of physical activity but no active encouragement. Patients aged 40 years or above were included if they fulfilled the following criteria: ischemic stroke diagnosis, CT scan/MRI excluding hemorrhage or other focal pathology not indicating stroke, ability to walk unassisted, and inclusion within 90 days after stroke. Patients were excluded if they were bedridden, unable to understand the trial, reluctant to provide informed consent, or had a modified Rankin Score ≥4 prior to index stroke. All patients were followed for 2 years with four follow-up visits the first year and two follow-up visits the second year. Patients were included from nine centers in four countries (China, Estonia, Poland, Denmark). At baseline a thorough medical history was obtained focusing on risk for stroke as well as other diseases that would compromise physical activities. Comorbidity was assessed using the Charlson comorbidity index[11] modified to use in patients with stroke.[12] The Charlson index is a comorbidity scoring system that includes weighting factors based on disease severity. The Charlson index is validated for the use in ischemic stroke outcome studies.[12]

Physical Activity Scale for the Elderly. Patients were interviewed about their level of physical activity prior to stroke using the Physical Activity Scale for the Elderly (PASE) questionnaire.[6] The PASE questionnaire is a 12-item questionnaire, which quantifies the amount of physical activity over a 7-day period. The PASE scoring algorithm was derived from the assessment of physical activities using movement counts, an electronic physical activity monitor, activity diaries, and self-assessed activity levels in a general population of non-institutionalized persons.[6,7] The PASE score is calculated by taking the average number of hours spent on an activity per day over a 7-day period multiplied by an activity coefficient. Item scores are added to reveal the PASE score. The PASE score may range from 0 to more than 400. The item categories and coefficients in parenthesis included walk outside home (20); light sport (21); moderate sport (23); strenuous sport (23); muscle strength (30); light housework (25); heavy housework or chores (25); home repairs (30); lawn work or yard care (36); outdoor gardening (20); caring for another person (35); work for pay or as a volunteer (21).

The validity of the PASE questionnaire has been tested in many studies[6-9] and significantly correlates to the doubly labeled water-method,[10] considered the gold standard when measuring energy expenditure.

Outcome measures. Stroke severity was assessed using the Scandinavian Stroke Scale (SSS).[13] The SSS consists of the following nine items: consciousness, orientation, eye movement, facial palsy, arm motor power, hand motor power, leg motor power, gait, and speech. No neurologic deficit in those items equals 58 points. The SSS score was obtained upon inclusion in the ExStroke Pilot trial.

Long-term outcome was assessed using the modified Rankin Scale (mRS).[14] The mRS is an inventory, which is used to report global disability. The scale ranges from 0 to 6 where a score of zero corresponds to no symptoms and six corresponds to the patient being dead. The mRS is widely used to assess outcome in randomized clinical trials and is reliable and validated.[15]

Statistical analyses. Univariate and multivariable analyses of the association between baseline characteristics and stroke severity (SSS) and between baseline characteristics and long-term outcome (mRS) were done using ordinal logistic regression. Ordinal logistic regression holds advantages over binary logistic regression when analyzing data on an ordinal scale as ordinal logistic regression gives a cumulative OR based on all possible cutoff points.[16] The underlying assumption of proportional odds was tested using the Brant test of the statistical software. Covariables for the multivariable model were selected from the univariable models if the association with the outcome variable had a significance level of $p < 0.10$. The PASE score was used as a categorical variable grouped into quartiles. The effect of prestroke physical activity on recurrent stroke and on recurrent stroke, myocardial infarction, or death was estimated adjusted Cox's proportional hazard model. All analyses were done using STATA statistical software version 9.2. The ExStroke Pilot Trial was approved by all local ethics committees and registered at ClinicalTrials.gov (NCT000132483).

RESULTS A total of 314 patients participated in the ExStroke Pilot trial, of which 265 (84%) were included in the present analyses with a first ever stroke (135 from the intervention group and 130 from the control group). Mean (SD) age was 68.2 (12.2) years and 44.3% of the patients were female. The distribution of baseline characteristics is shown in table 1.

Univariable analyses showed that the level of prestroke physical activity (PASE score) was one of the main predictors of stroke severity and long-term outcome with increasing ORs for a less severe stroke and better outcome with increasing level of physical activity (table 2). The OR for a milder stroke severity was 1.53 (95% CI 1.25–1.86) and could be expressed as linear ($\chi^2 = 2.75$, 2 *df*; $p = 0.25$). The OR for a higher modified Rankin score was 0.64 (95% CI 0.52–0.79), and could be expressed as linear ($\chi^2 = 1.64$, 2 *df*; $p = 0.44$).

Concordantly, in multivariable analyses the OR for a higher SSS score increased with the level of physical activity (figure 1). The OR for the difference between each quartile was 1.43 (95% CI 1.16–1.78, $p = 0.001$) and could be expressed as linear ($\chi^2 = 2.29$, 2 *df*; $p = 0.32$).

Similarly, the association between PASE quartiles and long-term outcome (mRS) showed that with increasing levels of physical activity the OR for a higher mRS decreased (figure 2). The OR between each PASE quartile was 0.78 (95% CI 0.62–0.99, $p = 0.04$) and could be expressed as linear ($\chi^2 = 0.32$, 2 *df*; $p = 0.85$). Including and excluding mean arterial blood pressure and fasting glucose levels from the analysis did not alter the results. Excluding the SSS score from the analysis strengthened the association between prestroke level of physical activity and mRS (OR 0.75, CI: 0.59–0.94, $p_{trend} = 0.01$). Of note, using the PASE score as a continuous variable did not alter the results.

A total of 21 strokes, 2 myocardial infarctions, and 14 deaths occurred during follow-up. There was no significant association between prestroke level of physical activity and recurrent stroke (hazard ratio 0.88, 95% CI 0.56–1.37) or recurrent stroke, myocardial infarction, or death (hazard ratio 0.86, 95% CI 0.60–1.24).

DISCUSSION In the present study we observed that a higher prestroke level of physical activity was associated with a less severe stroke, and that higher activity levels were reported in patients with the most favorable outcomes. The results were consistent in uni- and multivariable analyses, and the association could be expressed linearly, suggesting a dose-response association.

It has previously been reported that increased level of physical activity is associated with milder stroke severity.[4] Our results confirm these findings, establishing a firm association between reported level of physical activity and stroke severity. Our results also demonstrate a significant association between reported level of physical activity and long-term outcome of first-ever stroke after adjusting for possible confounding factors.

The prestroke level of physical activity may affect the prognosis after stroke in many ways. Physical activity modifies traditional risk factors for cardiovascular diseases, which could lead to a reduction in the risk of recurrent stroke. In the present study we could not observe an effect of prestroke physical activity on long-term outcome mediated through glucose and blood pressure levels. Animal studies have reported that physical activity may have a neuroprotective effect by enhancing endothelial nitric oxide synthase expression, which results in reduced cerebral infarct size and less severe stroke.[17] We observed that excluding the SSS score from the results strengthened the association between prestroke level of

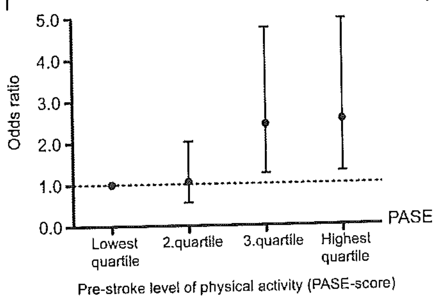
Table 2 Univariate analyses of the association between baseline characteristics and stroke severity (SSS)/long-term outcome (mRS)

	Stroke severity (Scandinavian Stroke Scale): Cumulative OR for a higher SSS score			Long-term outcome (modified Rankin Score): Cumulative OR for a higher modified Rankin score		
	OR	95% CI	p	OR	95% CI	p
Age	0.98	(0.96–0.99)	0.006	1.03	(1.01–1.05)	0.0001
Gender (men/women)	1.31	(0.86–2.00)	0.21	1.01	(0.64–1.57)	0.98
Level of physical activity prior to stroke (PASE score) grouped into quartiles						
1st quartile, n = 64	Reference			Reference		
2nd quartile, n = 68	1.18	(0.64–2.16)	0.60	0.94	(0.49–1.79)	0.86
3rd quartile, n = 64	2.89	(1.56–5.38)	0.001	0.52	(0.27–0.99)	0.05
4th quartile, n = 69	3.05	(1.65–5.64)	0.0001	0.28	(0.15–0.53)	0.0001
Trend	1.53	(1.25–1.86)	0.0001	0.64	(0.52–0.79)	0.0001
Availability of caretaker	1.12	(0.73–1.71)	0.61	0.40	(0.25–0.63)	0.0001
Education	1.40	(1.04–1.87)	0.03	0.72	(0.53–0.98)	0.04
Smoking	0.89	(0.68–1.16)	0.40	1.07	(0.81–1.43)	0.63
Alcohol	0.98	(0.69–1.40)	0.92	1.05	(0.72–1.52)	0.80
History of:						
Transient ischemic attack	0.82	(0.37–1.80)	0.62	0.75	(0.33–1.75)	0.51
Myocardial infarction	0.68	(0.30–1.54)	0.36	1.49	(0.67–3.33)	0.33
Atrial fibrillation	0.80	(0.44–1.46)	0.47	2.05	(1.03–4.06)	0.04
Diabetes mellitus	0.60	(0.31–1.12)	0.11	1.95	(1.05–3.62)	0.04
Depression	0.72	(0.35–1.49)	0.38	2.19	(1.06–4.54)	0.04
Charlson Comorbidity Index						
0	Reference			Reference		
1	0.53	(0.32–0.88)	0.01	2.16	(1.29–3.62)	0.003
2	0.69	(0.39–1.24)	0.22	1.85	(0.96–3.57)	0.07
3	0.80	(0.27–2.35)	0.68	3.67	(1.32–10.13)	0.01
4	0.13	(0.03–0.70)	0.02	9.21	(1.95–43.37)	0.005
Body mass index	0.99	(0.95–1.04)	0.74	1.00	(0.95–1.05)	0.89
Mean arterial blood pressure	1.00	(0.99–1.02)	0.53	1.00	(0.98–1.01)	0.79
Blood samples						
Total cholesterol, mmol/L	0.98	(0.82–1.17)	0.84	0.89	(0.75–1.06)	0.19
Fasting glucose, mmol/L	0.89	(0.79–.01)	0.07	1.10	(0.99–1.23)	0.07
Stroke diagnosis						
Large-artery disease	Reference			Reference		
Small-vessel disease	1.47	(0.81–2.65)	0.21	0.27	(0.14–0.50)	0.0001
Cardioembolism	0.90	(0.45–1.83)	0.78	0.59	(0.28–1.24)	0.17
Other determined cause	0.34	(0.003–42.9)	0.66	0.70	(0.08–6.39)	0.75
Undetermined etiology	1.41	(0.78–2.53)	0.26	0.66	(0.36–1.22)	0.19
Scandinavian Stroke Scale	—	—	—	0.91	(0.88–0.95)	0.0001

physical activity and long-term outcome, suggesting that some of the effect of prestroke physical activity on long-term outcome is mediated though the SSS score.

Guidelines for the primary prevention of ischemic stroke reported that physical inactivity was a modifiable risk factor, which requires greater emphasis in stroke prevention campaigns.[18] The results from the

Figure 1 Cumulative OR for a higher Scandinavian Stroke Scale score according to level of prestroke physical activity

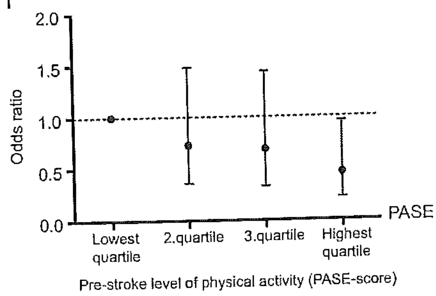


The association could be considered linear with increasing OR for a higher Scandinavian Stroke Scale score with increasing level of physical activity (OR 1.43, CI 1.16–1.78). The results are adjusted for age, gender, Charlson score, educational level, fasting glucose level, and history of diabetes mellitus.

present study suggest that physically active persons may also have milder strokes and a better outcome in the long run.

This study is strengthened by the use of ordinal logistic regression statistics for all analyses. Ordinal scales have often been dichotomized prior to analyses, which leads to loss of statistical power and to controversies as to where the appropriate cutoff point should be. In addition, physical activity was assessed using the PASE, which is a validated questionnaire specifically developed to assess physical activity in the elderly. This will reduce a potential age bias, as age-neutral questionnaires tend to underestimate physical activity in the elderly.[19] The study was conducted as a multicenter study, which adds to the generalizability of the results.

Figure 2 Cumulative OR for a higher modified Rankin score according to level of prestroke physical activity



The association could be considered linear with decreasing OR for a higher modified Rankin score with increasing level of physical activity (OR 0.79 CI: 0.62–0.99). The results are adjusted for fasting glucose level, age, educational level, history of atrial fibrillation, diabetes mellitus, depression, Charlson comorbidity index, availability of caretaker, stroke diagnosis (TOAST), randomization group, and Scandinavian Stroke Scale score.

The main limitation of this study is that prestroke level of physical activity was assessed retrospectively. We cannot exclude that there are confounding factors, e.g., participating in rehabilitation programs and cognitive status, which we have not taken into consideration and which might explain the association between physical activity and long-term outcome reported in this study. The results in this study are based on patients with mild ischemic strokes and of Caucasian and Asian ethnicity. Testing the hypothesis in a broader selection of patients with stroke and in other ethnic groups could add to further clarify the association between physical activity and long-term outcome.

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Failure of repeated instructions to improve physical activity after ischaemic stroke. The ExStroke Pilot Trial: a randomised, multicentre, multinational clinical trial with masked outcome assessment

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Abstract

Objectives

To investigate if repeated verbal instructions about physical activity to patients with ischaemic stroke could increase long-term physical activity.

Design.

A randomised, multicentre, multinational clinical trial with masked outcome assessment.

Setting

Stroke units in Denmark, China, Poland, and Estonia.

Participants

Patients with ischaemic stroke aged 40 years or more, who were able to walk, were enrolled after informed consent.

Interventions

314 patients were enrolled, 157, mean age 69.7 years, were randomised to the intervention group and instructed in a detailed training program before discharge, and at 6 follow-up visits during 24 months. 157 patients, mean age 69.4 years, in the control group had follow-up visits with the same frequency without instructions in physical activity.

Outcome measures

The primary outcome was physical activity assessed using the Physical Activity Scale for the Elderly (PASE) at each visit. Secondary outcomes were clinical events.

Results

The estimated mean PASE scores were 69.1 in the intervention group and 64.0 in the control group. The difference was 5.0 (95% confidence interval -5.8 to +15.9), p= 0.36. There was no significant effect of the intervention on mortality, recurrent stroke, myocardial infarction, or on falls and fractures.

Conclusion

Repeated encouragement and verbal instruction in being physically active did not lead to a statistically significant increase in physical activity measured by the PASE-score. More intensive strategies seem to be needed to promote physical activity after ischaemic stroke.

Trial registration www.ClinicalTrials.gov (NCT00132483)

Competing interest statement

All authors declare that the answer to the questions on your competing interest form are all No and therefore have nothing to declare.

Introduction

In observational studies even a moderate level of physical activity has been associated with a reduction of the risk of cardiovascular disease and of first stroke.[1-7] The influence of physical activity on the risk of recurrent stroke, however, is unknown. Nevertheless, physical exercise is often recommended for stroke survivors, because it is assumed that physical activity may favourably influence the prognosis through its effect on blood pressure, glucose metabolism, and cholesterol level.[8] Counselling on physical activity had shown some effect in elderly sedentary people[9], and in patients with diabetes, hypertension, hypercholesterolaemia, and overweight[10,11]. However, authors of systematic reviews of interventions to promote physical activity found the evidence insufficient to assess effectiveness[12,13]. A number of small randomised trials have shown that supervised physical training can improve stroke patients' balance, walking ability, and physical fitness[14-18]. These trials usually lasted 3 to 6 months.

The ExStroke Pilot Trial was designed to assess if repeated encouragement and verbal instructions regarding how to exercise could result in a sustained increase in stroke patients' physical activity as measured by the Physical Activity Scale for the Elderly (PASE)[19,20]. The rationale and design of the ExStroke Pilot Trial has previously been described[21].

Methods

Trial participants

Patients with ischaemic stroke aged 40 years or more from 6 stroke units in Denmark and from one neurological department in Chengdu, China, Warzaw, Poland, and Tartu, Estonia, were eligible if they were able to walk unassisted. Canes and walkers were allowed. Participants were enrolled within 90 days of symptom onset. A verbal and written informed consent was obtained prior to enrolment. Exclusion criteria were inability to understand the meaning of the trial, unwillingness to participate, medical contraindications to exercise, or a modified Rankin scale[22,23] of 4 or 5 before the qualifying event. The modified Rankin scale for activities of daily living ranges from 0 to 5, where 0 means no limitations, and 5 means confinement to bed requiring constant help.
Stroke severity was assessed using the Scandinavian Stroke Scale (SSS) (24), which ranges from 0-58, the latter meaning no deficits in the measured items.

Patient enrolment started in August 2003 and was completed in October 2005. In the Danish department that included most participants only approximately 15% of stroke patients were recruited into the trial.[21] About 15% expressed non-willingness to participate due to reluctance to engage in physical training. Other reasons for non-eligibility were fatal stroke, severe neurological deficits, dysphasia or cognitive impairment, discharge to nursing homes, transfer to other departments due to comorbidities, enrolment in other trials, or being too young.

Experimental and control interventions

The experimental intervention consisted of repeated encouragement and verbal instruction on being physically active given by a physiotherapist, except for the Chinese centre, where a neurologist gave the instruction. The control group received information on the possible benefits of physical activity, but no specific instruction. Both groups received standard treatment with antithrombotic medication, antihypertensive treatment, and statins as needed after individual assessment. Physiotherapists examined patients during their hospital stay, and rehabilitation was carried out according to the customs of the department.

Patients randomised to the intervention group met with a trial physiotherapist or in China aneurologist for instruction in a detailed training program to start after discharge from the hospital. At the first session the physiotherapist or neurologist spent about ½ to 1 hour getting acquainted with the participant and evaluating the consequences of the stroke. Considerable effort was taken to motivate the participant. The aim was to make the participant choose the most suitable types of physical activity for him or her. The program was individualised according to the patient's resources, former activities, and preferences. The patients were encouraged to use the facilities for physical activity in their local community. They were suggested to use fitness centres, to walk several kilometres per day, possibly as Nordic walking with sticks to improve balance, to go to public swimming pools, and to exercise in their local senior centre. Bicycling using helmets was also encouraged for those, who were used to cycle. At each visit a standard agreement form with various choices of physical activity was to be filled in together with the participant with one copy for the participant to take home, another was kept in the participant's file.

At the follow up visits the physiotherapist or neurologist spent about 20 minutes to half an hour with the participant on repeated instructions and readjustment of the physical activity plan every 3 months during the first year, and thereafter every 6 months until end of the trial. Between visits a telephone call was made to remind the patient in the intervention group about the agreement. They were asked in details about the activities and encouraged to increase efforts and to exercise more, and were told that to become sweaty and short of breath was desirable. No telephone calls were done in the control group. Participants in the control group received standard treatment without detailed information on physical activity. They were seen for clinical visits with the same frequency as the intervention group.

Assessment of physical activity

The PASE[19,20] was obtained at entry concerning the level of physical activity during the week preceding the stroke, and at each follow-up visit concerning the week preceding the visit. The scale has 12 questions each of which has subquestions as to the frequency per week and the time per day spent on the activity. The activities consist of walking outside home, light sport, moderate sport, strenuous sport, exercises to increase muscle strength and endurance, light housework, heavy housework, home repairs, lawn work or yard care, caring for another person, work for pay or as a volunteer. The PASE score can range from 0 to over 400, a higher score means a higher level of physical activity. The validity and reliability of the PASE questionnaire has been tested in a number of studies.[19,20,25-29] The PASE questionnaire is found to be reliable for interview mail and telephone administration[27,28] and valid in a variety of population groups both healthy and persons with disability. The doubly labeled water method is considered to be gold standard when measuring energy expenditure. The PASE score was positively and significantly correlated with the the doubly labeled water method (r=0.68, 95% confidence interval 0.35 to 0.86).[25] In a random sample of 49 participants in ExStroke we tested if PASE score reflected their physical capacity[29]. We found a significant correlation between PASE score and Senior Fitness Test[30] that reflects the capacity to perform everyday activities during functional examination of strength, aerobic capacity, and balance.

Objectives

The objective was to assess if repeated verbal encouragement and instruction in being physically active would result in a long-term improvement in the level of physical activity. Further, to explore the effect of the intervention on mortality and new cerebrovascular and cardiovascular events, on falls and fractures, and on modified Rankin scale[22,23].

Outcome measures

The primary outcome was the difference in PASE score between the two groups. The secondary outcome was the time from randomisation to recurrent stroke, or to myocardial infarction (MI), or to all-cause mortality. Stroke was defined as sudden onset of a neurological deficit with symptoms continuing for more than 24h or leading to death with no apparent cause other than vascular. In all cases CT- or MR-scan were compatible with stroke diagnosis. Other outcomes were time to stroke, MI, or vascular death, frequency of recurrent stroke, modified Rankin Scale, and falls and fractures. Diagnosis of MI followed international guidelines. Vascular death was defined as death due to stroke, MI, other vascular causes or sudden unexpected death. Falls were defined as sudden unintentional contact with the floor or ground. All events were adjudicated by an independent adjudication committee, which was blinded to the randomisation of the patient.

Sample size

The sample size calculation assumed a minimal relevant mean difference of 20 PASE points between the intervention and the control groups and a standard deviation of 50 PASE points. Based on the sample size calculation (alpha = 0.05; beta = 0.20), 99 patients would be needed in each group.[21] A total of 300 patients were planned to be included to take into account that dropouts could occur.

Randomisation

The ExStroke Pilot Trial is a randomized, multi-center, multi-national, clinical trial with masked outcome assessment in patients with ischaemic stroke. The participants were centrally randomized to intervention group or control group. Generation of allocation sequences was computer based. Allocation concealment was achieved through centralised randomisation by telephone or e-mail stratified with regard to sex, age, stroke severity, and centre. Stratification was conducted into two groups for age (40 – 70 year; 70+ years), two groups for stroke severity (Scandinavian Stroke Scale 20 – 39 points, 40 – 58 points), and two groups for centre (Danish, or non-Danish) in blocks of 10 randomising patients 1:1 to experimental and control intervention. Block size was unknown to investigators.

Randomisation implementation

The investigator, who was informed from the Copenhagen Trial Unit via telephone or e-mail, whether the patient was randomised to intervention or control group, told the patient the result of the randomisation. For those in the intervention group the investigator arranged an appointment with the physiotherapist, or provided the intervention herself.

Masking and blinding

In each centre an interviewer masked to the randomisation of the patient obtained the PASE score at the follow up visits. These investigators were physicians, medical students, or secretaries, who were otherwise uninvolved in the conduct of the trial. They were instructed in how to use the PASE questionnaire and were told not to ask the patients about the group assignment. These investigators also obtained information about recurrent stroke, myocardial infarction and falls, events that were adjudicated by a blinded adjudication committee.

Statistical methods

The data were analysed by the intention-to-treat and the per-protocol principles. A mixed model (proc mixed SAS 9.1) including the repeated measures option was used to assess the time course of PASE. It proved necessary to code the data by using a square-root transformed PASE scale (the variability of the PASE increased with increasing PASE; the square-root scale eliminated this variability and improved normality). To obtain an estimate of the effect of the intervention from the mixed model program, the mean square-root PASE in each group was calculated. By squaring the two mean values and calculating their difference we obtained the difference between the two groups in the original scale. The standard error of difference in mean PASE score was then calculated by utilizing the fact that the standard error of the difference between the two mean values comprises (almost exactly) the same percentage of this difference whether the original scale or the square root scale is used.
The per-protocol analysis included the patients who attended all six follow-up visits. To compensate for differences in pre-stroke PASE score between the two groups we included the square root transformed pre-stroke PASE score as a co-variate.

The difference in modified Rankin Scale between the two groups at 3, 6, 12, and 24 months after randomisation was assessed using a non-parametric test (Mann Whitney). Cox-analyses were used to assess the effect of the intervention on time to a clinical event.

Registration of the trial

The protocol was approved by local ethics committees in Denmark (KF11006/04) and in the countries of the participating centres. The trial was registered with the Danish Data Protection Agency (J. no. 2003-41-3564) and at www.ClinicalTrials.gov (NCT00132483).

Independent Safety and Monitoring Board

The Independent Safety and Monitoring Board conducted one interim analysis. There was no safety concern as to continuing the trial.

Results

Fig. 1 shows the participant flow in the trial. The estimated number of individuals assessed for eligibility is based on data from one department in which 15% of patients admitted for cerebrovascular disease were enrolled in the trial.

Protocol deviations. In one participant randomised to intervention group PASE score before stroke was not obtained. Two patients randomised to the intervention group were not instructed in physical activity, they were followed up as if belonging to the control group but analysed according to randomisation. Two other participants did not get instruction in physical activity due to intercurrent illness. Participants who sustained a recurrent stroke continued in the trial if possible or were withdrawn if neurological deficits were severe. The latter was the case in 3 participants in the intervention group and 2 in the control group.

Dates of recruitment

A total of 314 patients fulfilled the entry criteria, agreed to participate, and were randomised between August 2003 and October 2005.

Baseline demographics

Entry characteristics of the patients appear in Table 1. At entry the two groups were similar regarding sex, age, and stroke severity measured by Scandinavian Stroke Scale, which was median 54 (51-58) points in both groups corresponding to mild strokes. Pre-stroke PASE score tended to be higher in the intervention group, median 76 (IQR 50-124) than in the control group, 65 (50-106). Distribution of atrial fibrillation, diabetes, mean arterial blood pressure, blood glucose, hypercholesterolaemia, pre-stroke modified Rankin Scale, and habits of smoking and alcohol were comparable in the two groups.

Number of participants at each follow up is given in figure 1 and in table 2. In participants who were unable to visit the clinic at 24 months, a telephone interview was made. Ten participants in the intervention group and 2 in the control group could not be reached and were considered lost to follow up, but they were known to be alive and not having been hospitalised for stroke or myocardial infarction. In the intervention group 80 participants had all planned intervention sessions, 22 had 5 intervention sessions, 19 had 4, 11 had 3, 12 had 2, 9 had 1, and 4 had none.

Summary of results

The mean PASE scores in the intervention group versus the control group, estimated as stated above, were 69.1 vs 64.0, respectively. The difference was +5.0 (95% C.I., –5.8 to +15.9) PASE units, p = 0.36.

Figure 2a shows the median PASE-scores with interquartile range in the two groups by the intention-to-treat analysis.

The development over time was not different between the groups, although the intervention group at 6 and 9 months showed a non-significant increase in PASE. The control group maintained the pre-stroke level throughout the trial. Table 2 shows that the small difference in PASE-score, which was apparent during the week preceding the stroke, was maintained during most of the trial period but vanished at 24 months. There was no significant effect of centre and no significant interactions between protocol-specified variables and the intervention indicator.

The per-protocol analysis, Fig. 2b, of the patients who attended all planned follow-up visits, 80 patients in the intervention group and 81 patients in the control-group, showed a significant (p = 0.03) difference in pre-stroke PASE-score. Overall, there was no significant difference between the two groups, when adjusted for pre-stroke PASE score.

Of the points that constituted the PASE score 15% originated from walking outside the home, 46% from household activities, 13% from yard work. Sports activities accounted for only 10%, caring for another person for 7%, and work for 8%. There were no significant differences between the groups in the distribution of activities.

Other analyses

Recurrent stroke occurred in 14 participants in the intervention group and 11 in the control group (Table 3). Participants were readmitted for these events of which 7 were fatal. There was no significant difference in modified Rankin scale between the two groups at any time points (table 4). Although the qualifying strokes were mild, they did cause a shift in the modified Rankin scale from before stroke. At 3 months about 15% to 18% had a modified Rankin scale of 3 points or more.

Adverse events

The number of first falls was 53 in the intervention group and 54 in the control group (table 3). Several participants fell more than once, the total number of falls were 93 in the intervention group and 94 in the control group. Falls resulting in fractures were not significantly different in the two groups. The recurrent strokes and fractures contributed to the worsening of modified Rankin scale over time.

Discussion

Interpretation of results

The main finding of our trial was that repeated encouragement and verbal instruction did not appear to result in a measurable increase in physical activity in the intent-to-treat analysis, nor in the per-protocol analysis among patients who attended all visits. The intervention did not seem to have any effect on recurrent vascular events, nor on activity of daily living as measured by the modified Rankin scale.

The strengths of our trial are that it is a multicentre, multinational, randomised clinical trial with masked outcome assessors. The patients had mild strokes and had the physical possibility to increase their physical activity. The mixed-model analysis is optimal in the presence of missing data (see figure 1) since all observations are utilised to improve the precision as compared to a conventional complete-patient analysis, and the mixed-model analysis will not be biased even if missing PASE scores depend on observed quantities like, e.g., the choice of intervention used.[31] It was a weakness that we did not test during the trial whether the participants actually increased their physical activity as measured by the PASE score. To confront the patients with the fact that they were not increasing their activity might have given a stronger stimulus to exercise. However, the physiotherapists and other investigators were unaware of the PASE-score. Masked assessors, who did not know how the score was calculated, obtained answers to the PASE questionnaire. The repeated questioning about physical activity in the control group may have contributed to a higher PASE score in this group. This may have made the course in the control group become better, than if they had not been reminded about physical activity, and could make our possibility to find an effect less likely. We cannot exclude that some of the PASE assessors regarding some of the participants could have been demasked, but this is unlikely to have affected our results.

At the time when this trial was planned, the literature on counselling on physical activity had shown some positive results in elderly sedentary people and in various non-stroke patients groups.[9-11] However, systematic reviews from recent years did not find the intervention effective in non-stroke patients.[32,33] Our results in ischaemic stroke confirm the ineffectiveness of counselling on physical activity.

Stroke survivors might be expected to be motivated to improve their level of physical activity. However, that was not apparent in this trial. More than half of the PASE score derived from household activities, while walking outside home and sports activities only accounted for one fourth. In a previous study[28] a random sample from the general population with similar age had a mean PASE score of about 120, while patients in this trial had a pre-stroke PASE score that was 35% to 45% lower. The lessons to be learned are that stroke patients are inclined to low levels of physical activity. A contributing reason could be that power in the legs was found to be low bilaterally in a study of muscle power in ambulatory stroke patients.[34] Verbal encouragement possibly have an effect in some, but the majority of this group of patients with mild strokes did not seem to be responsive to our suggestions of change in level of physical activity.

This pilot study was not powered to show an effect of physical training on recurrent stroke or survival, which would need more than ten times the sample size. A Cochrane review[35] of 12 trials including 289 participants randomised to fitness training versus control concluded that although it improved walking ability there were too few data for reliable conclusions to be drawn.

Generalisability

The results of the ExStroke Pilot Trial are probably generalisable to patients with mild ischaemic stroke. Although most of the included participants were Danes, there was no indication that patients from the other countries responded differently. A possible selection bias existed since some patients declined to participate because they were not interested in physical training.

General interpretation

The best and most cost effective way of increasing physical activity after stroke has not been found.

The aim of our study was to explore the value of a comparatively low-cost intervention of repeated verbal encouragement to be physically active. This type of intervention failed to have the desired effect. Group training has been shown to work over short periods of time.[9-13] Supervised group training of long duration might be an avenue to be explored. As of yet, it is unknown if increased physical activity will influence risk of recurrent vascular events in stroke survivors. A one-time recommendation to exercise at the time of discharge from hospital, as it is most often done in stroke units, is unlikely to have any long-term effect on behaviour. The trial testifies to the difficulty of promoting physical activity in stroke patients, who on average had a low level of PASE-score before and after their stroke. However, absence of evidence for an effect is not evidence of absence of an effect.[36] We therefore need more randomised trials assessing the impact of more compelling interventions designed to improve physical activity among stroke patients.

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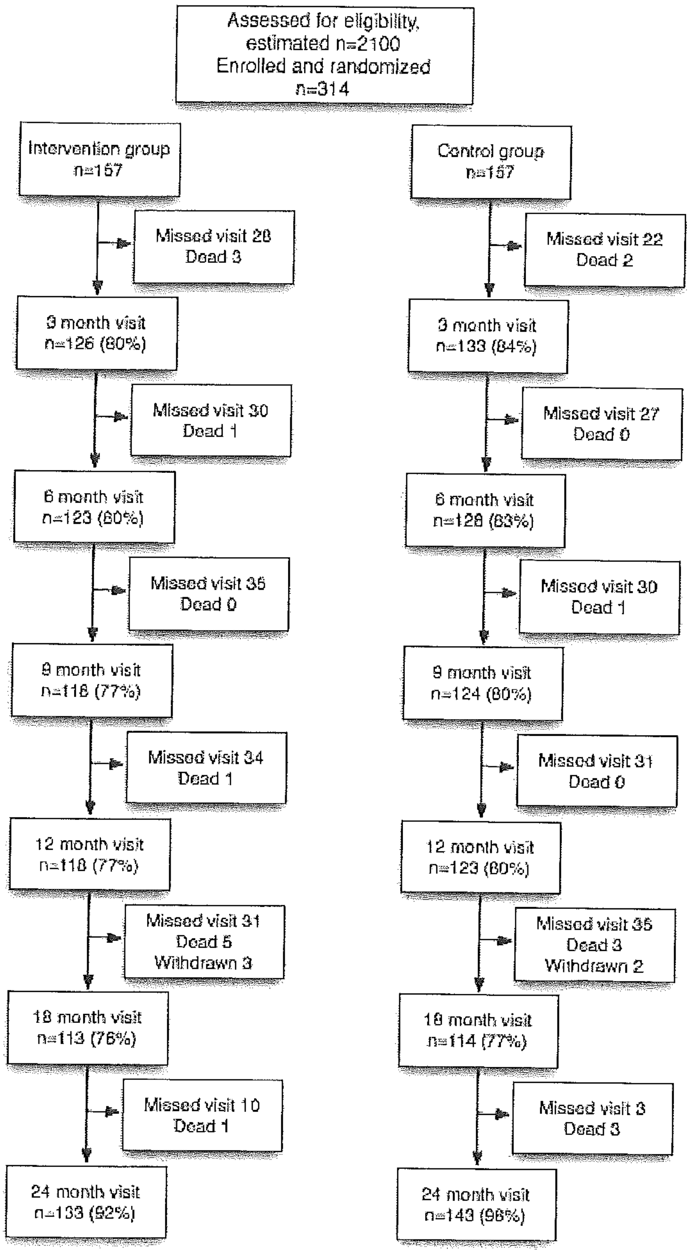
Figure legends:

Fig. 1: Participant flow chart of ExStroke Pilot Trial. Withdrawn denotes patients withdrawn due to severe recurrent stroke.

Fig. 2: The figure shows the median (interquartile range) Physical Activity Scale for the Elderly (PASE) score at each follow up visit. Data are shown for the intention-to-treat (fig 2a) and the per-protocol (fig 2b) group for participants who attended all planned visits.



Assessed for eligibility,
estimated n=2100
Enrolled and randomized
n=314
Intervention group
n=157
Control group
n=157
Missed visit 28
Dead 3
Missed visit 22
Dead 2
3 month visit
n=126 (80%)
3 month visit
n=133 (84%)
Missed visit 30
Dead 1
Missed visit 27
Dead 0
6 month visit
n=123 (80%)
6 month visit
n=128 (83%)
Missed visit 35
Dead 0
Missed visit 30
Dead 1
9 month visit
n=118 (77%)
9 month visit
n=124 (80%)
Missed visit 34
Dead 1
Missed visit 31
Dead 0
12 month visit
n=118 (77%)
12 month visit
n=123 (80%)
Missed visit 31
Dead 5
Withdrawn 3
Missed visit 35
Dead 3
Withdrawn 2
18 month visit
n=113 (76%)
18 month visit
n=114 (77%)
Missed visit 10
Dead 1
Missed visit 3
Dead 3
24 month visit
n=133 (92%)
24 month visit
n=143 (96%)

Median (IQR) PASE score

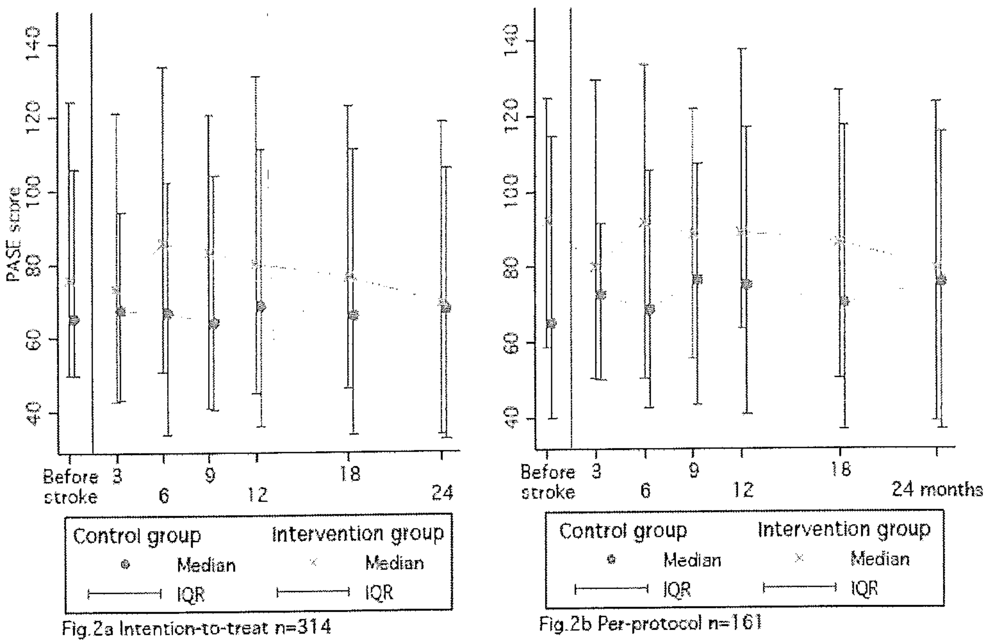


Fig 2. The figure shows the median (IQR) Physical Activity Scale for the Elderly (PASE) score at each follow-up visit. Data are shown for the intention-to-treat (fig 2a) and the per-protocol (fig 2b) group.

Table 1: Entry characteristics for all patients in the ExStroke Pilot Trial

	Intervention group (n=157)	Control group (n=157)
Age – median (IQR)	69.7 (60.0-77.7)	69.4 (59.6-75.8)
PASE score – median (IQR) before stroke	76 (50-124)	65 (50-106)
Women – n(%)	68 (43.3)	69 (43.6)
Scandinavian Stroke Scale – median (IQR)	54 (51-58)	54 (51-57)
Body Mass Index –mean (SD)	25.8 (4.2)	25.9 (4.5)
Systolic blood pressure – mean (SD)	152.7 (21.1)	150.2 (29.2)
Prior diseases – n (%)		
Stroke	22 (14.0)	27 (17.2)
Transient ischaemic attack	14 (8.9)	15 (9.6)
Atrial fibrillation	25 (15.9)	16 (10.2)
Myocardial infarction	13 (8.3)	13 (8.3)
Diabetes mellitus	28 (17.8)	17 (10.8)
Intermittent claudication	15 (9.6)	11 (7.0)
Depression	21 (13.4)	14 (8.9)
Hypertension	93 (59.2)	78 (49.7)
Coronary artery bypass grafting	5 (3.2)	0 (0)
Percutaneous transluminal coronary angioplasty	4 (2.6)	1 (0.6)
Blood		
Total cholesterol (mmol/l) – mean (SD)	5.3 (1.2)	5.3 (1.3)
Glucose (mmol/l) – median (IQR)	5.6 (5.1-6.4)	5.6 (5.1-6.3)
C-reactive protein (mg/l) – median (IQR)	5.0 (2.4-12.0)	6.0 (3.0-11)
Modified Rankin score		
0	114 (72.6)	116 (73.9
1	28 (17.8)	20 (12.7)
2	13 (8.3)	18 (11.5)
3	2 (1.3)	3 (1.9)
Education n (%)		
8 years or less	71 (45.2)	73 (46.5)
9-12 years	53 (33.8)	63 (40.1)
13 years or more	33 (21.0)	21 (13.4)
Smoking – n (%)		
Current smoker	49 (31.2)	66 (42.0)
Former smoker	62 (39.5)	46 (29.3)
Never smoked	46 (29.3)	45 (28.7)
Alcohol – n (%)		
Never drinking	32 (20.4)	46 (29.5)
<14/21(w/m)†	108 (68.8)	89 (57.1)
>14/21(w/m)	17 (10.8)	21 (13.4)
Stroke diagnosis – n (%)		
Large-artery disease	40 (25.5)	29 (18.5)
Cardioembolism	21 (13.4)	19 (12.1)
Small-vessel disease	51 (32.5)	51 (32.5)
Other determined cause	0 (0)	2 (1.3)
Undetermined aetiology	45 (28.7)	56 (35.7)

† Units of alcohol according to sex (women/men); SD standard deviation; IQR, interquartile range; PASE, the Physical Activity Scale for the Elderly; SSS, Scandinavian stroke scale.

Table 2: Median and interquartile range (IQR) of Physical Activity Scale for the Elderly and number of patients attending the follow-up visits in the intention-to-treat analysis of the ExStroke Pilot Trial

Visit		Intervention group	Control group
Before stroke	Median	76	65
	IQR	50-124	50-126
	n (%)	156 (99)	157 (100)
3 month	Median	73	68
	IQR	42-120	43-94
	n (%)	126 (80)	133 (84)
6 month	Median	86	67
	IQR	50-133	33-102
	n (%)	123 (80)	128 (83)
9 month	Median	83	64
	IQR	41-120	41-104
	n (%)	118 (77)	124 (80)
12 month	Median	80	69
	IQR	45-130	36-111
	n (%)	118 (77)	123 (80)
18 month	Median	76	66
	IQR	46-123	33-111
	n (%)	113 (74)	114 (74)
24 month	Median	69	68
	IQR	33-118	32-106
	n (%)	133 (91)	143 (97)

the Elderly and number
of the ExStroke Pilot Trial

Table 3 Number and percentage of clinical events in intervention and control group, hazard ratio (HR) between groups with 95% confidence interval (CI), and P of difference from 1 in ExStroke Pilot Trial.

Event	Number (%) in intervention group	Number (%) in control group	HR of group (95% CI)	P of group effect
Strokes	14 (8.9)	11 (7.0)	1.30 (0.59-2.87)	0.51
Myocardial infarction (MI)	2(1.3)	2(1.3)	1.01 (0.14-7.17)	0.99
Death	11 (7.0)	9 (5.7)	1.41 (0.57-3.50)	0.46
Vascular death	3(1.5)	4(2.5)	0.76 (0.17-3.41)	0.72
Fall fracture (FF)	5 (3.2)	12 (7.6)	0.46 (0.16-1.31)	0.14
Stroke, MI, or death	24 (15.3)	19 (12.1)	1.37 (0.74-2.52)	0.31
Stroke, MI, or vascular death	18 (11.5)	14 (8.9)	1.32 (0.66-2.65)	0.44
Stroke, MI, death, or FF	28 (17.8)	29 (18.5)	1.01 (0.60-1.70)	0.98
First falls	53 (34)	54 (34)	1.08 (0.73-1.58)	0.70

Table 4 Distribution of modified Rankin scale (mRS) by intervention group in the ExStroke Pilot Trial

Time	Group	mRS=0 N (%)	mRS=1 N (%)	mRS=2 N (%)	mRS=3 N (%)	mRS=4 N (%)	mRS=5 N (%)	P
Before stroke	1	114(72.6)	28(17.8)	13(8.3)	2(1.3)	0(0.0)	0(0.0)	n.a.
	2	116(73.9)	20(12.7)	18(15.5)	3(1.9)	0(0.0)	0(0.0)	
3 m	1	23(18.0)	30(23.4)	51(39.8)	17(13.3)	4(3.1)	3(2.3)	0.10
	2	28(20.9)	43(32.1)	43(32.1)	18(13.4)	1(0.7)	1(0.7)	
6 m	1	20(16.5)	46(38.0)	38(31.4)	14(11.6)	3(2.5)	0(0.0)	0.25
	2	27(21.4)	50(39.7)	33(26.2)	14(11.1)	2(1.6)	0(0.0)	
12 m	1	30(24.8)	37(30.6)	36(29.8)	12(9.9)	4(3.3)	2(1.7)	0.66
	2	28(22.4)	49(39.2)	31(24.8)	11(8.8)	6(4.8)	0(0.0)	
24 m	1	32(23.4)	46(33.6)	35(25.5)	15(10.9)	7(5.1)	2(1.5)	0.88
	2	34(23.1)	49(33.3)	38(25.9)	12(8.2)	11(7.5)	3(2.0)	

A non-parametric test was used to compare the two distributions (Mann Whitney test).

m = months
1 = intervention group
2 = control group

<u>What is already known on this subject</u>

Observational studies have suggested that physical activity reduces risk of first stroke.
In stroke patients there is little evidence on the effect of physical activity on recurrent stroke or other cardiovascular events.
Several smaller trials had shown that supervised group training can result in improved fitness and walking ability in stroke patients over periods of 3 to 6 months.

<u>What this study adds</u>

The aim of this trial was to evaluate if counselling and repeated encouragement on being physically active would lead to increased physical activity after mild stroke over a period of 24 months. We wanted to test if participants, when advised to do so, would increase their physical activity.
Repeated encouragement did not result in improvement of physical activity.
Probably trials on supervised training programmes will be needed.

Physical activity after ischemic stroke improves insulin sensitivity

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Physical activity after ischemic stroke improves insulin sensitivity

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Physical activity improves insulin sensitivity

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Ischemic stroke, physical activity, insulin sensitivity, Homeostasis model assessment, insulin resistance.

Abstract
Objective
To examine if stroke patients randomized to repeated encouragement to be physically active through a 2-year period could improve insulin sensitivity compared with control patients receiving usual care.
Methods
Patients included in the ExStroke Pilot Trial in the Copenhagen area were eligible. Participants had fasting blood samples taken at the end-of-trial visit. Blood samples were analyzed for glucose and insulin. Insulin sensitivity was calculated according to the homeostasis model assessment for insulin sensitivity (HOMA2-S%). Two-sample t-test was used to compare HOMA2-S% in the two groups and multiple linear regression was used to adjust for differences in pre-stroke physical activity level.
Results
A total of 107 (59%) of 180 eligible patients were included. Median (IQR) age was 69 years (58-76), and 54 (51%) were female. Geometric mean (SD) HOMA2-S% was 128.2 (1.6) in the intervention group vs. 100.9 (1.8) in the control group, P=0.049. Adjusting for pre-stroke level of physical activity did not alter the result, P=0.043.
Conclusion
Insulin sensitivity was significantly better in the group encouraged to be physically active than in the control group.

Introduction

In stroke survivors decreased insulin sensitivity and abnormal glucose metabolism is highly prevalent[1]. Decreased insulin sensitivity is linked to changes in the vascular system, including thickening of the carotid media intima[2] and to induce hypercoagulability[3]. These changes might explain the association between impaired insulin sensitivity and the risk of stroke[4,5].

Physical exercise can improve insulin sensitivity in healthy non-obese and non-diabetic people[6]. Therefore increasing stroke survivors' level of physical activity could be a way of improving insulin sensitivity and ultimately reduce the risk of recurrent stroke. In the present randomized trial we investigated if repeated encouragement to be physically active given by a physiotherapist through two years versus 'treatment as usual' could improve insulin sensitivity.

Materials and Methods

Study participants

Patients were eligible for the present study if they were participants of the ExStroke Pilot Trial registered at www.ClinicalTrials.gov (NCT00132483), randomized in the Copenhagen area, able to understand the purpose of the trial, and did not suffer from diabetes mellitus or had a history of diabetes mellitus. All patients had to give verbal and written informed consent prior to inclusion. Participating patients were scheduled to have fasting blood samples taken at the end-of-trial visit in the ExStroke Pilot Trial. The present study is registered at www.clinicaltrials.gov (NCT00376207) and approved by the local ethics committee (KF) 01 282361.

The ExStroke Pilot Trial

The design of the ExStroke Pilot Trial has previously been published[7]. In brief, the ExStroke Pilot Trial is a randomized, multi-center, multi-national intervention trial comparing repeated encouragement by a physiotherapist to increase ischemic stroke patients' level of physical activity plus 'treatment as usual' versus 'treatment as usual'. Patients could be included if they were 40 years or older, had an ischemic stroke, were able to walk unassisted, and could be included within 90 days of stroke symptom onset. Patients were excluded if they were bedridden, reluctant to provide informed consent, or suspected of cerebral pathology other than ischemic stroke.

Patients randomized to the intervention group were scheduled to meet with a physiotherapist soon after randomization. An individual training program was designed for each patient taking into account the patient's prior training status and resources. The control group did not meet with a physiotherapist but was given information on the possible benefits of being physically active. Both groups were seen for follow-up visits at regular intervals through a maximum of 2 years. The primary outcome measure was level physical activity obtained by an investigator masked to the randomization.

Blood samples and insulin sensitivity

Fasting blood samples were analyzed for insulin, glucose, glycosylated hemoglobin (HbA1c), total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, and C-reactive protein. After collection of blood samples serum was kept in an -80 degrees Celsius freezer to allow for insulin to be analyzed when all samples were collected. Insulin was analyzed using an enzyme linked immunosorbent assay (DakoCytomation). All insulin samples were analyzed in duplicates and the mean value was used for statistical analyses. Other blood samples were analyzed using routine laboratory methods

Insulin sensitivity, HOMA2-S%, was calculated using the homeostasis model assessment (HOMA) calculator developed by Matthews et al.[8]. The HOMA2 calculator uses the HOMA2 model for calculation of insulin resistance, which takes into account the non-linear approximation between insulin and glucose. The HOMA calculator is available for download at www.dtu.ox.ac.uk (last accessed November 2007).

Physical activity measurement

Physical activity was measured using the Physical Activity Scale for the Elderly (PASE)[9], which quantifies the amount of physical activity done in the last seven days. The PASE questionnaire is a 12-item scale that measures the average number of hours per day spent on leisure, household, and occupational activities over the previous seven days. Each item has an activity weight, which is multiplied by the amount of time spent on the item. The activity weights and the PASE scoring algorithm was derived from studies where physical activity was measured using movement counts from an electronic physical activity monitor, activity diaries, and self assessed activity level. The activities (weight) scored on the PASE questionnaire is as follows: walk outside home (20); light sport (21); moderate sport (23); strenuous sport (23); muscle strength (30); light housework (25); heavy housework or chores (25); home repairs (30); lawn work or yard care (36); outdoor gardening (20); caring for another person (35); work for pay or as a volunteer (21). The PASE-score may range from zero to more than 400. When tested in the general population it ranged from 0-361. PASE has been validated in different populations: Healthy persons with no cardiac risk factors, sedentary people, patients with knee pain, and patients with cardiac risk factors[10-12]. Furthermore, PASE has been correlated to the doubly labeled water method[13], which is considered the gold standard when measuring energy expenditure.

The PASE-score was obtained at entry into the study, which refers to the week preceding stroke, and six times throughout the intervention period by investigators masked to randomization.

Statistics

Univariate analyses were conducted using the two-sample t-test for normally distributed and transformed data, Wilcoxon ranksum test for non-normally distributed data, and ^{2} test for categorical data. Variables, which were not normally distributed, were transformed. The logarithm was used for all transformed variables except pre-stroke PASE score and fasting insulin, which were transformed using the square root. Mean (SD) for transformed data is presented as geometric mean (SD). Multivariate analyses were done using linear regression. Variance-homogenecity was checked visually by plotting the residuals against the fitted values and normal distribution of the residuals was checked using a standardized normal probability plot. The level of physical activity through the intervention period was estimated by calculating the area under the activity curve (PASE-AUC) using cubic splines for all PASE score measures. For patients with a missed visit we interpolated between neighboring values to obtain a value for the missed visit. No extrapolation was done. A two-tailed P-value below 0.05 was considered significant. STATA version 9.2 was used for all calculations.

Results

Of the 314 patients were included in the ExStroke Pilot Trial, 237 (75%) patients were included in the Copenhagen area. Seventeen (7%) of these patients died before the end of the follow-up period, and 40 (17%) patients had a history of diabetes mellitus. In total there were 180 patients, who were eligible for this study. Seventy-three (41%) patients did not give informed consent so in total 107 (59%) of the 180 eligible patients were included, figure 1. Blood samples were taken from 100 (53%) patients, as seven patients did not show up to have blood samples taken. Forty-nine patients (46%) were from the intervention group and 58 patients (54%) were from the control group. There were no differences in age, sex, prior diseases, stroke severity, smoking, alcohol, fasting glucose or C-reactive protein between the two groups, table 1. The mean (SD) pre-stroke PASE score differed in favor of the intervention group, 95.9 (8.1) compared to 72.5 (5.0) in the control group, P=0.01.

At the end of the follow-up period there was a significant difference in PASE-AUC (529.5 vs. 394.2, P=0.006) and fasting insulin (39.6 vs. 52.3, P=0.04) between the two groups, table 2. When adjusting the PASE-AUC for the difference in pre-stroke PASE-score the difference was no longer significant, P=0.14. Fasting insulin remained significantly different between the two groups after adjusting for the difference in pre-stroke PASE score.
There were no differences in waist circumference, modified Rankin score, mean arterial blood pressure, glycosylated hemoglobin, cholesterol levels, and triglyceride levels, table 2.

Patients from the intervention group had a significantly better insulin sensitivity compared with patients from the control group (geometric mean (SD) HOMA2-S% 128.2 (1.6) vs. 100.9 (1.8), P=0.049). Due to the difference in pre-stroke PASE score between the two groups the result was adjusted by including the pre-stroke PASE score as a covariate. The result remained significant, P=0.043.

We tested the association between the integrated level of physical activity (PASE-AUC) and insulin sensitivity in all patients through the 2-year period using uni- and multivariate linear regression analyses. The multivariate model was adjusted for the following confounders: waist circumference, betablockers, thiazide, angiotensin II receptor blockers, educational level, age, sex, and randomization group. Both in uni- and multivariate analyses the PASE-AUC was significantly associated to HOMA2-S%. An increase in PASE-AUC by 50% increased HOMA2-S% by 12% (3-21%, P=0.01) and 14% (4-27%, P=0.009), respectively. Of the other co-variables only waist circumference, use of betablockers, and age was significantly and inversely associated with insulin sensitivity.

Discussion

In the present subgroup study of a larger randomized trial we found that patients randomized to an intervention of repeated encouragement to be physical active obtained significantly better glucose control two years following stroke. Further, we found that increased level of physical activity (PASE-AUC) after stroke was associated with better insulin sensitivity (HOMA2-S%). These results show that stroke patients can reduce insulin resistance by increasing their level of physical activity.

The association between insulin resistance and risk of stroke[4,5] is well established. Following stroke and transient ischemic attacks impaired insulin sensitivity is highly prevalent[1,14]. Therefore a reduction in insulin resistance could possible lower the risk of recurrent stroke. Ivey et al. have previously demonstrated that hemiparetic stroke patients could improve glucose tolerance through treadmill aerobic exercise[15]. In our randomized trial a different intervention was chosen. Patients were encouraged to engage in physical activities. The rational was to use a relatively low-cost intervention, which could be easily implemented in daily routine. The results in both studies showed a difference in fasting insulin and in insulin sensitivity between the intervention group and the control group, while there was no difference in fasting glucose.

The ExStroke Pilot trial failed to show an overall effect of the designed intervention on PASE score (Boysen et al. 2008 submitted). Still, in the present study we found an effect of the intervention on insulin sensitivity. One explanation for the present finding could be selection bias. The two groups differed in pre-stroke PASE score, which could lead to an imbalance in insulin sensitivity at baseline. However, adjusting for pre-stroke PASE score only strengthened the overall results of this study.
Another explanation could be that the intervention given exerted an effect on insulin sensitivity mediated through physical activity behavior, which was not picked up by the PASE questionnaire.
This is a subgroup study and the results should be interpreted as such. As any results obtained in analyses of subgroups they should be viewed more as hypothesis generating than as solid evidence[16].

Our present results are strengthened by the use of the randomized design. The use of a randomized design diminishes the possibility for selection bias. Due to the design of the present study, however, some of the advantages of randomization may have been lost due to selective drop out during the course of the trial.
The main limitation of our trial is the post-hoc design, which meant that no information on the baseline HOMA2-S% was collected at entry into the ExStroke Pilot Trial.

Conclusion

In conclusion patients randomized to the intervention group had significantly better insulin sensitivity two years following stroke. Insulin sensitivity can be improved by increasing stroke patients' level of physical activity, although the present results should be interpreted with caution as selection bias may have been introduced.

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Table 1: Baseline characteristics at time of randomization into the ExStroke Pilot Trial.

	Intervention (n=49)	Control (n=58)	P*
Age – mean (SD)	64.9 (12.4)	67.6 (12.5)	0.26
Pre-stroke PASE score*	95.9 (8.1)	72.5 (5.0)	0.01
Female – n (%)	23 (46.9)	31 (53.5)	0.50
Prior diseases – n (%)			
Stroke	6 (12.2)	10 (17.2)	0.50
Transient ischemic attack	6 (12.2)	5 (8.6)	0.36
Atrial fibrillation	6 (12.7)	4 (7.1)	0.48
Myocardial infarction	0 (-)	2 (3.5)	0.27
Intermittent claudication	3 (6.1)	3 (5.3)	0.48
Depression	6 (12.5)	6 (10.9)	0.96
Hypertension	23 (46.9)	25 (43.9)	0.87
Modified Rankin score prior to stroke			0.41
0	38 (77.5)	42 (72.4)	
1	7 (14.3)	7 (12.1)	
2	4 (8.2)	6 (10.3)	
3	0 (-)	3 (5.2)	
SSS – median (IQR)	55(52-56)	56 (51-58)	0.58
Body mass index	25.6 (1.2)	26.2 (1.2)	0.46
Education			0.88
8 years or less	22 (44.9)	25 (43.1)	
9-12 years	19 (38.8)	25 (43.1)	
13 years or more	8 (16.3)	8 (13.8)	
Smoking – n (%)			0.53
Current smoker	17 (34.7)	28 (48.3)	
Former smoker	19 (38.8)	14 (24.1)	
Never smoked	13 (26.5)	16 (27.6)	
Alcohol – n (%)			0.77
Never drinking	8 (16.3)	10 (17.2)	
<14/21(f/m)†	34 (69.4)	38 (65.6)	
>14/21(f/m)	7 (14.3)	10 (17.2)	
Stroke diagnosis – n (%)			0.13
Large-artery disease	10 (20.4)	8 (13.8)	
Cardioembolism	4 (8.2)	8 (13.8)	
Small-vessel disease	17 (34.7)	12 (20.7)	
Other determined cause	0 (-)	1 (1.7)	
Undetermined etiology	18 (36.7)	29 (50.0)	
Blood samples			
C-reactive protein – median (IQR)	4 (2.2-8)	5 (3-9)	0.22
Fasting glucose – geometric mean (SD)	5.4 (1.1)	5.6 (1.2)	0.40

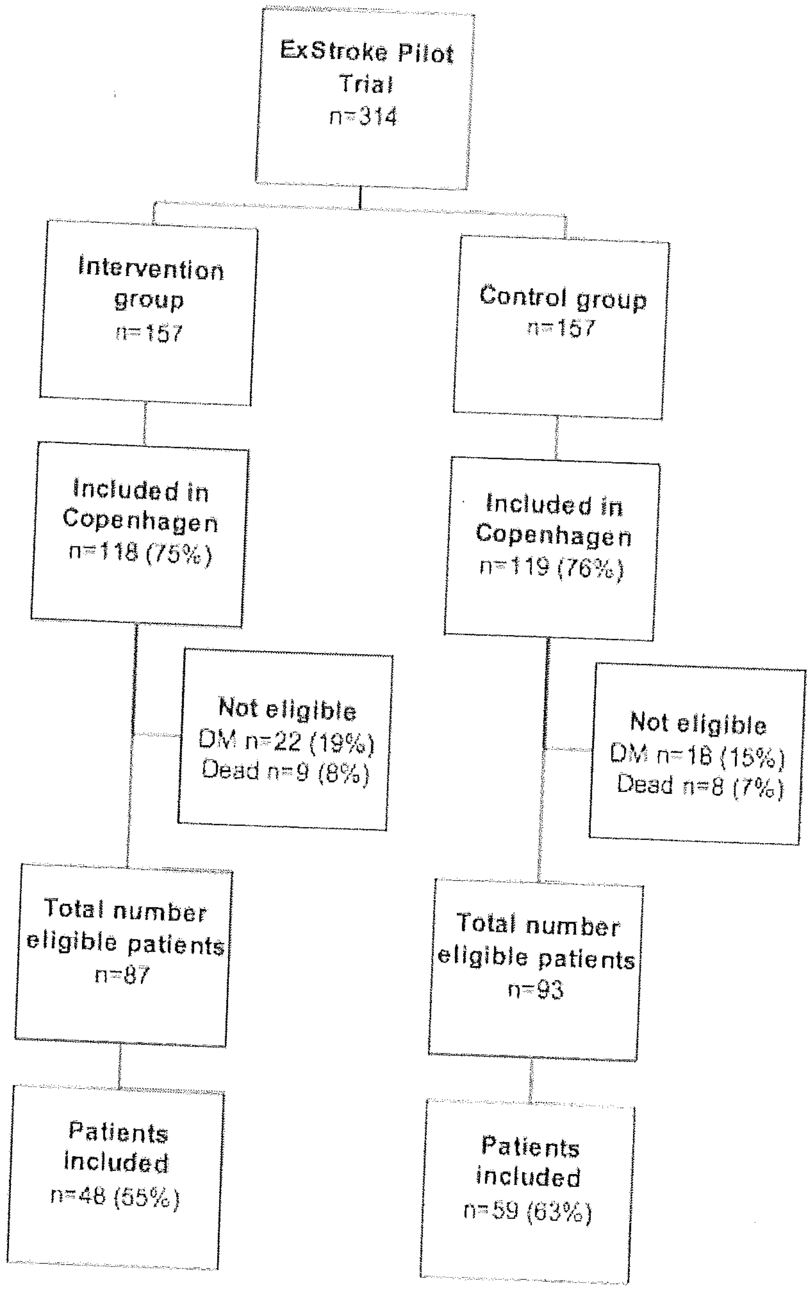
*Pre-stroke PASE score refers to the week preceding stroke onset.
†Units of alcohol per week according to sex (female/male);
SD = standard deviation; IQR, interquartile range; SSS, Scandinavian Stroke Scale.

Table 2. Characteristics for patients at the end of follow-up

	Intervention (n=49)	Control (n=58)	P
PASE-AUC* – geometric mean (SD)	516.5 (1.7)	394.2 (1.7)	0.01
Modified Rankin score			0.44
0	11 (22.4)	16 (27.6)	
1	22 (44.9)	18 (31.0)	
2	14 (28.6)	18 (31.0)	
3	2 (4.1)	4 (6.9)	
4	0 (-)	2 (3.5)	
Waist circumference (cm) – mean (SD)	93.4 (11.8)	92.7 (13.7)	0.81
BMI – geometric mean (SD)	26.8 (1.3)	27.1 (1.5)	0.86
Mean arterial blood pressure – mean (SD)	102.9 (12.5)	100.3 (14.2)	0.36
Medication			
Betablocker – n (%)	6 (13.6)	5 (10.2)	0.61
Thiazide diuretic– n (%)	12 (27.3)	18 (36.7)	0.33
Angiotensin II receptor blocker – n (%)	6 (13.6)	3 (6.1)	0.22
HOMA2-S%* – geometric mean (SD)	0.78 (1.6)	1.0 (1.8)	0.049
HOMA2-S% adjusted for pre-stroke PASE score	-	-	0.043
Fasting insulin (pmol/L) – geometric mean (SD)	39.6 (4.1)	52.3 (6.2)	0.04
Fasting glucose (mmol/l) – geometric mean (SD)	5.1 (1.1)	5.4 (1.2)	0.16
Fasting HgbA1c (%) – median (IQR)	5.8 (5.4-6)	5.8 (5.55-6.1)	0.43
Total cholesterol (mmol/L) – geometric mean (SD)	4.7 (1.2)	4.7 (1.2)	0.99
HDL-cholesterol (mmol/L) – geometric mean (SD)	1.5 (1.4)	1.5 (1.4)	0.87
LDL-cholesterol (mmol/L) – geometric mean (SD)	2.5 (1.4)	2.5 (1.4)	0.84
Triglycerid median (IQR)	1.12 (0.73-1.45)	1.17 (0.87-1.51)	0.69

*Insulin sensitivity was calculated using the HOMA2-S% calculator.
PASE – AUC = the Physical Activity Scale for the Elderly – Area Under the Curve. The AUC was calculated based on measurements of PASE scores during the intervention period.
SD = standard deviation; IQR = interquartile range.

Fig.1 Flow chart



Legend to figure 1.

Figure 1. Flowchart of patients in the study. Three (6%) patients from the intervention group and 5 (9%) patients from the control group did not show for blood sampling and could therefore not be included in the analyses.
DM = diabetes mellitus.

PASE - skema

(Physical Activity Scale for the Elderly)

Patient cpr.	|__|__|__|__|__|__|-|__|__|__|__|
Patient nr.	|__|__|__|__|__|
Dato for interview	|__|__|__|__|__|__| d d m m å å

Fritidsaktivitet

1. Hvor ofte har du foretaget stillesiddende aktiviteter, såsom at læse, se TV, håndarbejde eller lignende indenfor de sidste 7 dage før du blev indlagt?

☐ Aldrig – gå til spørgsmål 2.

☐ Sjældent (1-2 dage)

☐ Af og til (3-4 dage)

☐ Ofte (5-7 dage)

1a Hvilke aktiviteter? ____

1b Hvor mange timer har du gennemsnitlig været beskæftiget med disse aktiviteter pr. dag?

☐ Mindre end 1 time

☐ 1 time eller mere, men mindre end 2 timer

☐ 2 til 4 timer

☐ Mere end 4 timer

2. Hvor ofte har du gået en tur uden for hjemmet indenfor de sidste 7 dage? (f.eks. for fornøjelsens eller motionens skyld, til arbejde eller gået en tur med hunden)?

☐ Aldrig → gå til spørgsmål 3.

☐ Sjældent (1-2 dage)

☐ Af og til (3-4 dage)

☐ Ofte (5-7 dage)

2a Hvor mange timer har du gennemsnitligt været beskæftiget med disse aktiviteter pr. dag?

☐ Mindre end 1 time

☐ 1 time eller mere, men mindre end 2 timer

☐ 2 til 4 timer

☐ Mere end 4 timer.

3. Hvor ofte har du deltaget i lette sports- eller fritidsaktiviteter såsom bowling, minigolf, lystfiskeri, gymnastik i hjemmet eller lignende inden for de sidste 7 dage?

☐ Aldrig → gå til spørgsmål 4

☐ Sjældent (1-2 dage)

☐ Af og til (3-4 dage)

☐ Ofte (5-7 dage)

3a Hvilke aktiviteter? ______________________________

3b Hvor mange timer har du gennemsnitlig været beskæftiget med disse aktiviteter pr. dag?

☐ mindre end 1 time

☐ 1 time eller mere, men mindre end 2 timer

☐ 2 til 4 timer

☐ Mere end 4 timer

4. Hvor ofte har du deltaget i moderate sports- eller fritidsaktiviteter, såsom dans, double tennis, jagt, skøjteløb, golf, gymnastik på hold eller lignende inden for de sidste 7 dage?

☐ Aldrig → gå til spørgsmål 5

☐ Sjældent (1-2 dage)

☐ Af og til (3-4 dage)

☐ Ofte (5-7 dage)

4a Hvilke aktiviteter?______________________________

4b Hvor mange timer har du gennemsnitlig været beskæftiget med disse aktiviteter pr. dag?

☐ Mindre end 1 time

☐ 1 time eller mere, men mindre end 3 timer

☐ 2-4 timer

☐ Mere end 4 timer

5. Hvor ofte har du deltaget i anstrengende sports- eller fritidsaktiviteter, såsom jogging, gymnastik, svømning, cykling, single tennis, aerobic eller lignende aktiviteter inden for de sidste 7 dage?

☐ Aldrig → gå til spørgsmål 6.

☐ Sjældent (1-2 dage)

☐ Af og til (3-4 dage)

☐ Ofte (5-7 dage)

5a Hvilke aktiviteter? ______________________________

5b Hvor mange timer har du gennemsnitligt været beskæftiget med disse aktiviteter pr. dag?

☐ Mindre end 1 time

☐ 1 time eller mere, men mindre end 2 timer

☐ 2-4 timer

☐ Mere end 4 timer

6. Hvor ofte har du udøvet styrketræning specielt for at øge muskelstyrke og udholdenhed, såsom vægttræning, armbøjninger eller andre styrkekrævende aktiviteter inden for de sidste 7 dage?

☐ Aldrig → gå til spørgsmål 7.

☐ Sjældent (1-2 dage)

☐ Af og til (3-4 dage)

☐ Ofte (5-7 dage)

6a Hvilke aktiviteter? ______________________________

6b Hvor mange timer har du gennemsnitligt været beskæftiget med disse aktiviteter pr. dag?

☐ Mindre end 1 time

☐ 1 time eller mere, men mindre end 2 timer

☐ 2-4 timer

☐ Mere end 4 timer

7. Har du udført lette former for arbejde i hjemmet, såsom at vaske op eller tørre støv af indenfor de sidste 7 dage?

☐ Ja

☐ Nej

8. Har du udført anstrengende former for arbejde i hjemmet, såsom at støvsuge, vaske gulv, vaske vinduer eller bære brænde indenfor de sidste 7 dage?

☐ Ja

☐ Nej

9. Har du udført nogle af følgende aktiviteter inden for de sidste 7 dage?
   a: Vedligeholdelse af hjemmet så som at male, tapetsere, udføre el-installation eller lign.

   ☐ Ja

   ☐ Nej

   b. Slå græs, feje fortov, skovle sne eller blade, save brænde eller lignende.

   ☐ Ja

   ☐ Nej

   c. Udendørs havearbejde

   ☐ Ja

   ☐ Nej

   d. Pleje af personer såsom børn, afhængige familiemedlemmer eller andre voksne

   ☐ Ja

   ☐ Nej

10. Har du været på arbejde eller arbejdet som frivillig inden for de sidste 7 dage?

   ☐ Ja

   ☐ Nej

10a Hvor mange timer om ugen har du arbejdet – betalt eller frivilligt?

|__|__| timer om ugen

10b Hvilken af følgende kategorier beskriver bedst det niveau af fysisk aktivitet, som dit daglige arbejde kræver – betalt eller frivilligt?

☐ Hovedsageligt stillesiddende arbejde med begrænsede armbevægelser (f.eks. kontorarbejde, siddende samlebåndsarbejde, buschauffører eller lignende)

☐ Omkringgående arbejde med nogen håndtering af materialer, der vejer mindre end 25 kg (f.eks. postbud, tjener, vejarbejder, tung maskin- og værktøjsarbejder eller lignende).

☐ Omkringgående arbejde med tungt manuelt arbejde, der ofte kræver håndtering af materiale, der vejer mere end 25 kg (f.eks. smedearbejde, savværksarbejde, jord- og betonarbejder, landmand eller lignende)

Dato |__|__|__|__|__|__| og signatur:________________________
d d m m å å

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