SVD analysis plan

Small vessel disease burden in acute ischemic stroke - the role of physical activity and vascular risk factors

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# Introduction

Physical activity (PA) may reduce the development of Small Vessel Disease (SVD). The effect of PA and more classical cerebrovascular risk factors (CVRF) such as hypertension and diabetes in the development of SVD is debated, however.

We aim to investigate if PA can counter the effects of hypertension, diabetes and other traditional CVRF on the development of cerebral small vessel disease among ischemic stroke patients.

# Methods

## Study population

This study is a pooled, post-hoc, cross-sectional study on acute ischemic stroke (AIS) patients pooled from two large randomized, clinical trials, the Efficacy of Citalopram Treatment in Acute Ischemic Stroke (TALOS) and the Remote Ischemic Conditioning for Acute Stroke (RESIST) trials.(Kraglund et al. 2018; Blauenfeldt et al. 2023)

The TALOS trial included first-time stroke within seven days after stroke onset and randomized to citalopram or placebo treatment. More detailed inclusion criteria has already been published.(Kraglund et al. 2018)

In the RESIST trial, patients presenting with a prehospital putative acute stroke within four hours of symptom onset were randomized in the ambulance to ischemic preconditioning treatment or sham.(Blauenfeldt et al. 2023)

In this current trial, we included patients with a final diagnosis of AIS included at Aarhus University Hospital, with available, acute magnetic resonance imaging and prestroke PA assessment.

## MRI sequences and feature annotation

Obtained magnetic resonance imaging (MRI) sequences are from the initial acute stroke protocol scan at the time of stroke admission. These include FLAIR as well as T2\* or SWI sequences depending on the time of inclusion. All with a magnetic field strength of 3 T.[[1]](#footnote-22)

The MRI sequences were evaluated by two independent assessors. On disagreement, consensus scoring was performed by a third assessor.

## Prestroke data

Clinical data include age and sex.

Prestroke data is retrieved from the Danish Stroke Registry. Variables included are hypertension, diabetes, prior AIS, prior transitory ischaemic attack (TIA) and regular smoking, and are all binary (yes/no).[[2]](#footnote-24)

## Physical activity

Prestroke PA was assessed using the Physical Activity Scale for the Elderly (PASE) questionnaire on trial enrolment. The PASE is a validated 12-item self-assessed questionnaire on overall PA including work, leisure time, household, and sports activities during the past 7 days. The score ranges from 0 to 793, with a higher score indicating a higher level of PA. The PASE questionnaire was completed by the patient or next of kin, and possibly with the assistance of study personnel.

## Statistics

Evaluation of effect modification(Corraini et al. 2017) of PA on CVRFs (e.g. diabetes, hypertension, smoking, previous ischemic cerebrovascular event (AIS and/or TIA)) and the burden of SVD will be performed using Ordinal logistic regression (OLR).

Separate OLR models with individual CVRF as the independent variable and SVD score as the dependent variable without and with PA quartiles will be created. All analysis will be adjusted for age and sex. In [Table 1](#tbl-main) the combined analyses for the simple SVD score is showed.

The outcome SVD score will be evaluated using a full scale and a simplified scale, as well as each sub score. In [Table 2](#tbl-other) an overview of the other analyses, that will be performed.

### Analyses

Below is listed the main analyses to give an overview.

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| | Reference | Model | Dependent variable | Independent variables | Other adjustment | | --- | --- | --- | --- | --- | | 01a | OLR | SVD score (0-4) | Diabetes (yes/no) | Age, sex | | 01b | OLR | SVD score (0-4) | Diabetes (yes/no) | Age, sex, PA quartile | | 02a | OLR | SVD score (0-4) | Hypertension (yes/no) | Age, sex | | 02b | OLR | SVD score (0-4) | Hypertension (yes/no) | Age, sex, PA quartile | | 03a | OLR | SVD score (0-4) | Smoking (yes/no) | Age, sex | | 03b | OLR | SVD score (0-4) | Smoking (yes/no) | Age, sex, PA quartile | | 04a | OLR | SVD score (0-4) | Ischemic event (yes/no) | Age, sex | | 04b | OLR | SVD score (0-4) | Ischemic event (yes/no) | Age, sex, PA quartile |   Table 1: Main analyses reference table |

Below is listed the sub analysis on sub scores and the full SVD score.

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| |  |  |  | | --- | --- | --- | | **Reference** | **Model** | **Dependent variable** | | **11-14** | OLR | Microbleeds (0,1-10,>10) | | **21-24** | OLR | Lacunes (0,1,>1) | | **31-34** | OLR | white matter hyperintensity (WMH) (0,1,2,3) | | **41-44** | OLR | Atrophy (0,1,2,3) | | **51-54** | OLR | SVD score (0-14) |   Table 2: Sub-score analyses |

All planned tables and figures to be included.

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| |  |  | | --- | --- | | **Reference** | **Description** | | **Table 1** | Baseline characteristics. | | **Table 2** | Merged tables with primary analyses of simplified SVD score for each CVRF with and without PA. | | **Figure 1** | Odds ratios from the main OLR analyses. | | **Table 3** | Merged table of each SVD sub score as outcome for each CVRF. | | **Supplementary tables** | Merged tables with analyses of full SVD score. |   Table 3: Planned tables and figures |

# References

Blauenfeldt, Rolf Ankerlund, Niels Hjort, Jan Brink Valentin, Anne-Mette Homburg, Boris Modrau, Birgitte Forsom Sandal, Martin Faurholdt Gude, et al. 2023. “Remote Ischemic Conditioning for Acute Stroke: The RESIST Randomized Clinical Trial.” *JAMA* 330 (13): 1236–46. <https://doi.org/10.1001/jama.2023.16893>.

Corraini, Priscila, Morten Olsen, Lars Pedersen, Olaf M. Dekkers, and Jan P. Vandenbroucke. 2017. “Effect Modification, Interaction and Mediation: An Overview of Theoretical Insights for Clinical Investigators.” *Clinical Epidemiology*, June. <https://www.tandfonline.com/doi/abs/10.2147/CLEP.S129728>.

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1. Other metadata can be exported from MR database. [↑](#footnote-ref-22)
2. Other factors include cohabitation, atrial fibrilation, myocardial infarction and alcohol consumption. They are left out to keep the focus, but can be included like the already listed risk factors in the suplementary material as “other risk factors”. [↑](#footnote-ref-24)