ONLINE DATA SUPPLEMENT

Cerebrovascular Risk-Factors of Prevalent and Incident Brain Infarcts in the General Population:The AGES-Reykjavik Study

Table of Content

Data Supplement – Extended Methods

MRI acquisition and rating of infarcts

MR images were acquired on a single research-dedicated 1.5T Signa Twinspeed EXCITE system (General Electric Medical Systems, Waukesha, WI) using a multi-channel phased array head cap coil. The image protocol described in detail elsewhere included a T1-weighted three dimensional spoiled gradient echo (3D-SPGR) sequence with 1.5 mm slice thickness and in-plane pixel size of 0.94 mm x 0.94 mm, a proton density (PD)/T2-weighted fast spin echo (FSE) sequence, a fluid attenuated inversion recovery (FLAIR) sequence, a T2*-weighted gradient echo-planar imaging (GRE-EPI) and a diffusion weighted sequence. All these latter sequences were acquired with 3-mm thick slices and in-plane pixel size of 0.86 mm x 0.86 mm. All sequences were acquired using the same acquisition parameters at both time points. At the time of acquisition in the follow-up study the overview images (localizers) from the baseline study were retrieved and viewed for selecting the appropriate levels for examination so that slice positions and slice alignments from the baseline scan could be reproduced in the follow-up scan.

Brain infarcts from both time-points were rated semi-quantitatively by two trained radiographers who recorded the presence, number, and location of the lesions. The baseline and follow-up images were viewed together on a computer workstation using customized software developed in-house. As a general rule, the follow-up images were evaluated first, slice by slice without the baseline images on the computer screen. When a lesion was encountered on a follow-up image, a corresponding baseline image was brought up on the screen and assessed if the same lesion was present or not. Immediately following the characterization of the lesion, findings were registered and the baseline image screen closed again. This process was repeated until all follow-up images had been analyzed. This way, all lesions were grouped into prevalent lesions (lesions present on both follow-up and baseline scans) and incident lesions (lesions only present on the follow-up scans). An infarct was defined as a defect of the brain parenchyma with a signal intensity isointense to that of cerebrospinal fluid on all sequences used for the rating (FLAIR, PD/T2/T2*-w). All infarcts were included regardless of whether they were clinically apparent or not. Cortical infarcts were defined as defects involving or limited to the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images. Subcortical infarcts were defined as parenchymal defects not extending into the cortex, surrounded by an area of high signal intensity on FLAIR with a minimal size diameter of 4-mm. This minimal size was used, because for smaller parenchymal defects it is harder to assess reliably whether they are based on perivascular spaces or lacunar infarcts. Defects surrounded by a rim of hemosiderin were excluded since it is not possible to distinguish parenchymal hematomas from hemorrhagic infarcts. The presence of hemosiderin was defined as an area of signal loss on T2*-w scans that was invisible or smaller on T2- and PD-w images. Cerebellar infarcts were defined as parenchymal defects in the cerebellum. There were no size criteria for cortical- nor cerebellar infarcts. Infarcts that spanned two different anatomical areas were assigned to the location with the largest diameter of the defect. Defects in the subcortical area without a rim or area of high signal intensity on FLAIR, with a minimal size diameter of 4-mm and without evidence of hemosiderin were regarded as enlarged perivascular-spaces and excluded.
Intra- and inter-observer reliability was assessed for the two observers every 6 months and shown to be good. The intra-observer reliability (Kappa statistics) was 0.90 and 0.85 for cortical-; 0.85

and 0.87 for cerebellar- and 0.89 and 0.93 for subcortical infarcts. The inter-observer reliability for cortical-, cerebellar- and subcortical infarcts was 0.82, 0.70 and 0.76 respectively.

Statistical Analysis, interaction

To study if risk-factor effects on outcome differed depending on where the infarct is located, in subcortical-, cortical- and cerebellar regions, we set the data up as a multivariate panel data with an id-variable for subject and an indicator for region. Then regression equations were fitted using generalized estimating equations, with the robust variance estimator assuming unstructured 3x3 working correlation structure to account for correlation between regions by subject. Interaction terms between region and age, region and sex, and region and risk factor were put in the model to allow for the effect of the risk factor to depend on region. This approach is in the same spirit as seemingly unrelated regressions.[11] Then a score test was applied to test if the interaction term with the risk factor was statistically significant. The null hypothesis being that the effect of the risk factor is the same for the 3 brain infarct regions. As an example, to test if the effect of hypertension (1=yes/0=no) is the same for subcortical-, cortical- and cerebellar infarcts, this approach is equivalent to fitting the following three equations:

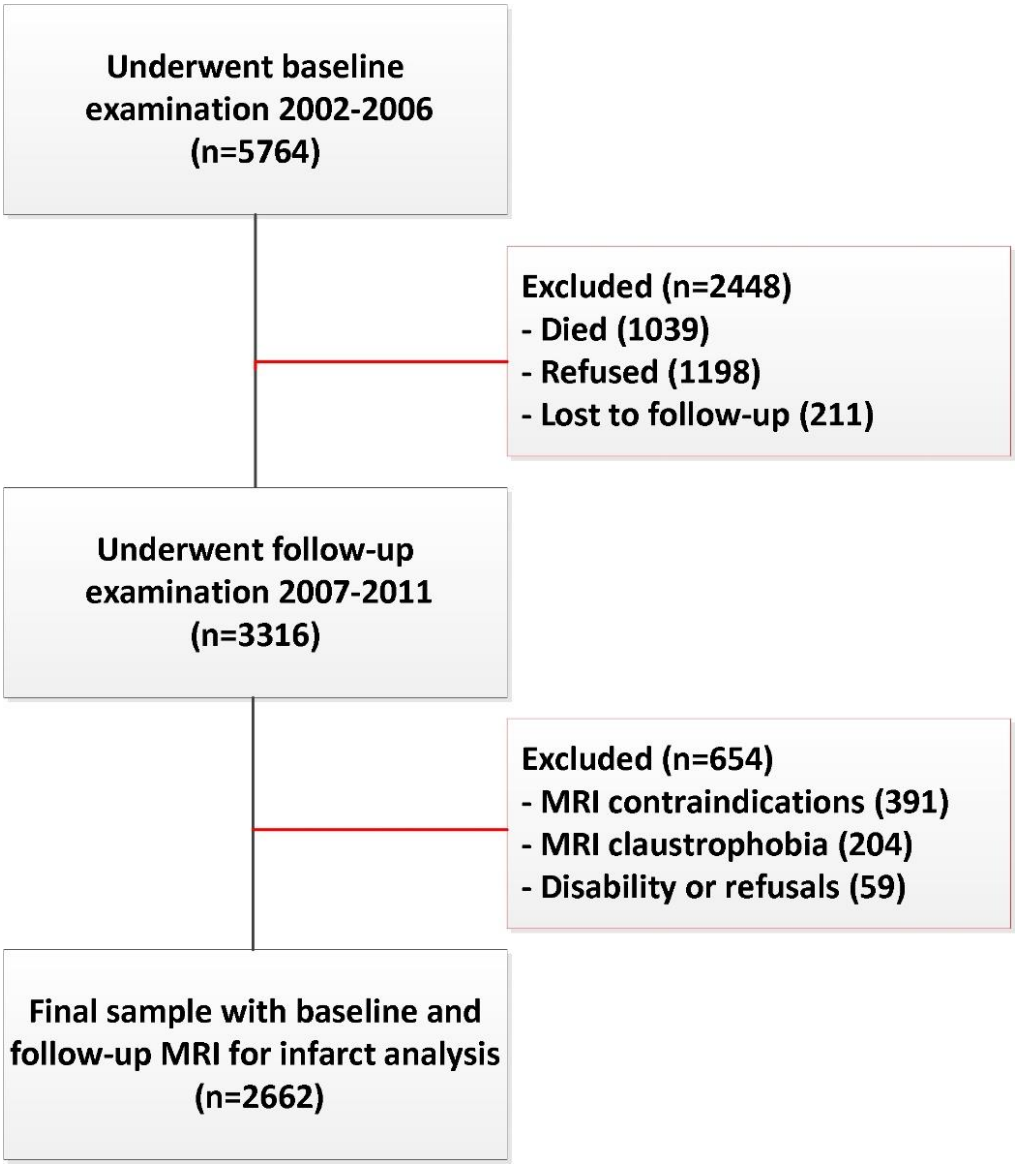
risk of subcortical = beta0,1 + beta1,1 * age + beta2,1 * sex + beta3,1 * Hypertension
risk of cortical = beta0,2 + beta1,2 * age + beta2,2 * sex + beta3,2 * Hypertension
risk of cerebellar = beta0,3 + beta1,3 * age + beta2,3 * sex + beta3,3 * Hypertension

The beta-coefficients are allowed to depend on regions. Then test for equal effect of hypertension on the risk of infarct for the different regions is: beta3,1 = beta3,2 = beta3,3.

This procedure was repeated for each risk-factor.

We additionally tested two-way interactions for all risk-factors (predictor variables) in the multivariable models using multiplicative terms. We also inspected separately if interactions with sex were statistically significant by including multiplicative terms between sex and other predictor variables in the model. A stricter level for statistical significance was set at 0.0005 for interactions to avoid overfitting, due to the many possible combinations between variables

Figure I, Study Flow Diagram



*STROBE Statement—Checklist of items that should be included in reports of **cohort studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4**
Methods			
Study design	4	Present key elements of study design early in the paper	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**5,7**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	**NA**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**5-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5-8**
Bias	9	Describe any efforts to address potential sources of bias	**8, 15**
Study size	10	Explain how the study size was arrived at **Also study flow diagram in supplemental material**	**7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**7,8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**7-8**
		(*b*) Describe any methods used to examine subgroups and interactions	**7**
		(*c*) Explain how missing data were addressed	**7**
		(*d*) If applicable, explain how loss to follow-up was addressed	**7**
		(*e*) Describe any sensitivity analyses	**8**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**7**
		(b) Give reasons for non-participation at each stage	**7**
		(c) Consider use of a flow diagram **Flow diagram in supplemental material**	**Suppl.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1 p.19**	**9, 20**
		(b) Indicate number of participants with missing data for each variable of interest	**7**
		(c) Summarise follow-up time (eg, average and total amount)	**9**

Outcome data	15*	Report numbers of outcome events or summary measures over time **Also in supplemental Tables I and II**	**9**
Main results	16	*(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Also Tables 3-4 and supplemental Tables IV-V**	**10-12**
		(b) Report category boundaries when continuous variables were categorized **Also Tables 3-4 and supplemental Tables IV-V**	**10-12**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**NA**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Also supplemental Tables VI-IX**	**12**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**12-16**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**16**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**12-16**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**12-17**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**17**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Data Supplement – Results, Tables

Table I
Number of prevalent infarcts per individual

Infarct region	Without infarcts	One infarct n (%)	Two infarcts n (%)	Three or more infarcts n (%)	Total n (%)	Mean±SD
Overall	1836 (69)	441 (17)	171 (6)	214 (8)	2662 (100)	0.7±1.6
Subcortical	2460 (92)	154 (6)	32 (1)	16 (1)	2662 (100)	0.1±0.4
Cortical	2364 (89)	190 (7)	55 (2)	53 (2)	2662 (100)	0.2±0.7
Cerebellar	2106 (79)	333 (12)	127 (5)	96 (4)	2662 (100)	0.4±1.1

Mean±SD: Mean and standard deviation of the number of prevalent infarcts per individual

Table II
Number of incident infarcts per individual

Infarct region	Without infarcts	One infarct n (%)	Two infarcts n (%)	Three or more infarcts n (%)	Total n (%)	Mean±SD
Overall	2103 (79)	335 (12)	120 (5)	104 (4)	2662 (100)	0.4±1.1
Subcortical	2543 (95)	90 (4)	24 (1)	5 (0)	2662 (100)	0.1±0.3
Cortical	2453 (92)	136 (5)	46 (2)	27 (1)	2662 (100)	0.1±0.6
Cerebellar	2316 (87)	242 (9)	57 (2)	47 (2)	2662 (100)	0.2±0.7

Mean±SD: Mean and standard deviation of the number of incident infarcts per individual

Table III
Risk-Factors and Risk of Incident Brain Infarcts
in Strata of Presence of Infarcts at Baseline, Univariate

	Risk Ratios of Incident Brain Infarcts (RR 95% CI)	
Potential Risk-Factor	Overall without prevalent (n=258 of 1836)	Overall with prevalent (n=301 of 826)
Age per 5 years	**1.41 (1.20-1.66)**	**1.32 (1.05-1.66)**
Sex (men vs. women)	**1.46 (1.10-1.96)**	**1.72 (1.30-2.27)**
Hypertension (yes vs no)	1.41 (0.80-2.49)	**2.19 (1.00-4.76)**
Systolic Blood Pressure	1.11 (0.98-1.26)	1.04 (0.91-1.18)
Diastolic Blood pressure	0.91 (0.77-1.07)	1.08 (0.93-1.27)
Diabetes Mellitus (yes vs no)	0.90 (0.59-1.36)	1.09 (0.71-1.67)
Smoking (current vs never)	1.21 (0.75-1.95)	0.80 (0.49-1.29)
Smoking (quit vs never)	1.04 (0.75-1.43)	0.88 (0.65-1.19)
Atrial Fibrillation	0.70 (0.40-1.22)	1.05 (0.67-1.66)
Carotid Plaque (≥mod stenosis)	1.20 (0.88-1.64)	1.14 (0.84-1.55)
Migraine (yes vs no)	1.16 (0.74-1.81)	1.26 (0.90-1.77)
Migraine with aura (yes vs no)	1.34 (0.63-2.85)	1.32 (0.83-2.08)
Use of lipid lowering medication (yes vs no)	1.16 (0.82-1.63)	0.78 (0.57-1.06)
Total Cholesterol†	1.08 (0.91-1.28)	0.89 (0.69-1.13)
High-Density Lipoprotein†	1.01 (0.86-1.18)	0.89 (0.74-1.07)
Agatston Coronary Calcium	**1.20 (1.00-1.43)**	1.07 (0.93-1.22)

For continuous risk-factors, the unit of difference was 1SD, except for age where it was 5 years. All Risk-Ratios are adjusted for age, sex and time interval between MR scans. †Additionally adjusted for use of lipid lowering medication.

Table IV. Relationship between Risk-Factors and Risk of Prevalent Brain Infarcts – Multivariate Analysis, Poisson Regression

	Risk Ratios of Prevalent Brain Infarcts (RR 95% CI)			
Potential Risk-Factor	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	**1.23 (1.12-1.34)**	**1.37 (1.19-1.57)**	**1.21 (1.03-1.43)**	**1.20 (1.07-1.35)**
Sex (men vs.women)	**1.64 (1.26-1.93)**	**1.73 (1.25-2.40)**	**2.50 (1.78-3.52)**	**1.33 (1.04-1.71)**
Hypertension (yes vs no)	**1.70 (1.16-2.50)**	2.11 (0.83-5.41)	1.10 (0.63-1.92)	**2.09 (1.24-3.52)**
Diabetes Mellitus (yes vs no)	1.20 (0.94-1.53)	**2.55 (1.67-3.89)**	1.10 (0.74-1.164)	0.94 (0.66-1.33)
Atrial Fibrillation	1.15 (0.86-1.54)	0.80 (0.39-1.66)	1.37 (0.89-2.11)	1.15 (0.80-1.65)
Carotid Plaque (≥mod plaque)	**1.34 (1.11-1.60)**	1.07 (0.74-1.54)	**1.68 (1.22-2.30)**	**1.28 (1.03-1.59)**
Migraine without aura (yes no)	0.91 (0.66-1.25)	0.87 (0.43-1.79)	0.85 (0.49-1.46)	0.95 (0.64-1.40)
Migraine with aura (yes vs no)	**1.50 (1.11-2.03)**	1.22 (0.60-2.50)	1.49 (0.77-2.89)	**1.56 (1.12-2.19)**
Use of lipid lowering medication (yes vs no)	**1.30 (1.07-1.59)**	1.05 (0.73-1.53)	**1.54 (1.13-2.10)**	1.27 (0.98-1.64)
Agatston Coronary Calcium	**1.17 (1.04-1.31)**	1.21 (0.99-1.49)	1.17 (0.96-1.42)	**1.16 (1.00-1.34)**

For continuous risk factors, the unit of difference was 1 SD, except for age where it was 5 years.

Table V. Relationship between Risk-Factors and Risk of Incident Brain Infarcts – Multivariate Analysis, Poisson Regression

	Risk Ratios of Incident Brain Infarcts (RR 95% CI)			
Potential Risk-Factor	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	**1.35 (1.16-1.58)**	1.18 (0.94-1.47)	**1.42 (1.16-1.74)**	**1.39 (1.16-1.65)**
Sex (men vs. women)	**1.61 (1.28-2.02)**	**1.88 (1.21-2.91)**	**2.20 (1.57-3.10)**	1.22 (0.91-1.63)
Presence at Baseline (1+ vs 0)	**3.04 (2.46-3.76)**	**5.95 (3.96-8.94)**	**3.98 (2.73-5.82)**	**2.84 (2.16-3.73)**
Hypertension (yes vs no)	1.60 (0.99-2.56)	1.05 (0.40-2.81)	1.17 (0.56-2.43)	**2.75 (1.30-5.82)**
Diabetes Mellitus (yes vs no)	1.04 (0.73-1.48)	1.31 (0.79-2.17)	0.86 (0.49-1.50)	1.16 (0.78-1.72)
Atrial Fibrillation	1.03 (0.69-1.54)	0.62 (0.25-1.52)	1.26 (0.65-2.44)	0.98 (0.62-1.57)
Carotid Plaque (≥mod plaque)	1.13 (0.90-1.42)	0.94 (0.64-1.37)	**1.68 (1.12-2.53)**	0.95 (0.71-1.27)
Migraine without aura (yes no)	1.15 (0.84-1.58)	0.75 (0.30-1.88)	0.83 (0.40-1.76)	1.37 (0.93-2.01)
Migraine with aura (yes vs no)	1.40 (0.93-2.10)	1.32 (0.55-3.18)	1.56 (0.87-2.80)	1.29 (0.77-2.17)
Use of lipid lowering medication (yes vs no)	**0.76 (0.59-0.98)**	0.86 (0.53-1.40)	0.88 (0.60-1.29)	**0.66 (0.49-0.90)**
Agatston Coronary Calcium	**1.13 (1.00-1.27)**	1.00 (0.79-1.28)	1.14 (0.92-1.41)	**1.19 (1.02-1.38)**

For continuous risk factors, the unit of difference was 1 SD, except for age where it was 5 years.

Table VI. Relationship between Risk-Factors and Risk of Prevalent Brain Infarcts - Univariate Sensitivity Analysis, Logistic Regression

	Odds Ratios of Prevalent Brain Infarcts (RR 95% CI)			
Potential Risk-Factor	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	**1.33 (1.22-1.45)**	**1.42 (1.23-1.64)**	**1.33 (1.17-1.50)**	**1.19 (1.08-1.31)**
Sex (men vs.women)	**1.59 (1.34-1.88)**	**1.63 (1.22-2.18)**	**2.48 (1.94-3.20)**	**1.33 (1.10-1.60)**
Hypertension (yes vs no)	**1.78 (1.19-2.72)**	**2.38 (1.06-6.81)**	1.07 (0.64-1.92)	**1.88 (1.17-3.17)**
Systolic BP	1.07 (0.98-1.16)	**1.19 (1.04-1.37)**	0.98 (0.86-1.10)	1.08 (0.98-1.18)
Diastolic BP	1.00 (0.92-1.09)	1.18 (0.97-1.29)	0.90 (0.79-1.02)	1.02 (0.92-1.12)
Diabetes Mellitus (yes vs no)	**1.59 (1.21-2.08)**	**2.65 (1.80-3.83)**	1.49 (1.02-2.13)	1.18 (0.86-1.60)
Smoking (current vs never)	1.11 (0.92-1.33)	1.34 (0.97-1.86)	0.93 (0.71-1.22)	1.06 (0.86-1.30)
Smoking (quit vs never)	1.17 (0.88-1.56)	1.45 (0.86-2.35)	1.30 (0.86-1.94)	1.02 (0.73-1.41)
Atrial Fibrillation	**1.80 (1.27-2.55)**	0.95 (0.50-1.67)	**1.87 (1.21-2.82)**	**1.73 (1.19-2.50)**
Carotid Plaque (≥mod plaque)	**1.30 (1.08-1.56)**	1.33 (0.97-1.86)	**1.65 (1.24-2.20)**	1.13 (0.92-1.38)
Migraine (yes vs no)	1.17 (0.91-1.50)	0.95 (0.58-1.48)	1.10 (0.73-1.61)	**1.40 (1.06-1.84)**
Migraine with aura (yes vs no)	**1.60 (1.13-2.25)**	1.10 (0.55-2.00)	1.36 (0.77-2.27)	**1.90 (1.31-2.71)**
Use of lipid lowering medication (yes vs no)	**1.53 (1.27-1.85)**	1.33 (0.96-1.82)	**2.13 (1.65-2.75)**	**1.34 (1.08-1.65)**
Total Cholesterol†	0.98 (0.90-1.08)	0.97 (0.83-1.14)	1.00 (0.87-1.15)	1.00 (0.91-1.11)
High-Density Lipoprotein†	1.02 (0.83-1.25)	0.93 (0.65-1.34)	0.91 (0.66-1.24)	1.05 (0.83-1.32)
Agatston Coronary Calcium	**1.20 (1.09-1.32)**	**1.26 (1.06-1.52)**	**1.32 (1.13-1.54)**	**1.14 (1.02-1.27)**

For continuous risk factors, the unit of difference was 1 SD, except for age where it was 5 years. All Risk-Ratios are adjusted for age and sex. †Additionally adjusted for use of lipid lowering medication.

Table VII. Relationship between Risk-Factors and Risk of Incidentent Brain Infarcts - Univariate Sensitivity Analysis, Logistic Regression

	Odds Ratios of Incident Brain Infarcts (RR 95% CI)			
Potential Risk-Factor	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	**1.39 (1.26-1.53)**	**1.21 (1.00-1.47)**	**1.46 (1.27-1.69)**	**1.36 (1.21-1.53)**
Sex (men vs. women)	**1.76 (1.46-2.14)**	**2.04 (1.41-2.98)**	**2.47 (1.85-3.32)**	**1.38 (1.10-1.73)**
Presence at Baseline (1+ vs 0)	**3.18 (2.61-3.87)**	**6.19 (4.01-9.40)**	**4.69 (3.39-6.46)**	**3.32 (2.61-4.22)**
Hypertension (yes vs no)	**1.58 (1.00-2.62)**	1.32 (0.58-3.80)	1.26 (0.66-2.73)	**2.60 (1.34-5.83)**
Systolic Blood Pressure	1.04 (0.94-1.14)	**1.18 (1.00-1.40)**	0.99 (0.86-1.14)	1.05 (0.94-1.17)
Diastolic Blood pressure	0.94 (0.85-1.03)	**1.23 (1.02-1.48)**	**0.79 (0.68-0.93)**	0.99 (0.88-1.11)
Diabetes Mellitus (yes vs no)	1.25 (0.92-1.69)	1.64 (0.95-2.72)	1.03 (0.63-1.62)	1.26 (0.87-1.80)
Smoking (current vs never)	0.90 (0.73-1.11)	0.93 (0.62-1.40)	1.02 (0.74-1.40)	0.99 (0.77-1.27)
Smoking (quit vs never)	0.99 (0.71-1.37)	1.14 (0.59-2.06)	1.14 (0.68-1.86)	1.03 (0.68-1.53)
Atrial Fibrillation	1.12 (0.75-1.64)	0.73 (0.28-1.58)	1.12 (0.63-1.88)	1.08 (0.66-1.70)
Carotid Plaque (≥mod plaque)	**1.28 (1.04-1.58)**	1.06 (0.71-1.60)	**2.18 (1.54-3.14)**	1.07 (0.83-1.37)
Migraine (yes vs no)	1.46 (1.10-1.92)	0.75 (0.36-1.39)	1.14 (0.71-1.76)	**1.56 (1.13-2.15)**
Migraine with aura (yes vs no)	1.59 (1.07-2.32)	1.08 (0.41-2.33)	1.83 (0.99-3.16)	1.41 (0.87-2.19)
Use of lipid lowering medication (yes vs no)	1.04 (0.84-1.30)	1.03 (0.67-1.56)	1.30 (0.94-1.77)	0.98 (0.74-1.27)
Total Cholesterol†	1.03 (0.93-1.14)	0.94 (0.77-1.16)	1.09 (0.93-1.27)	1.00 (0.89-1.13)
High-Density Lipoprotein†	0.86 (0.68-1.10)	0.97 (0.60-1.53)	0.89 (0.61-1.28)	0.86 (0.64-1.14)
Agatston Coronary Calcium	**1.21 (1.09-1.36)**	1.10 (0.89-1.37)	**1.32 (1.10-1.60)**	**1.20 (1.05-1.38)**

For continuous risk factors, the unit of difference was 1 SD, except for age where it was 5 years. All Risk-Ratios are adjusted for age and sex. †Additionally adjusted for use of lipid lowering medication.

Table VIII. Relationship between Risk-Factors and Risk of Prevalent Brain Infarcts – Multivariate Sensitivity Analysis, Logisitc Regression

	Odds Ratios of Prevalent Brain Infarcts (RR 95% CI)			
Potential Risk-Factor	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	**1.27 (1.16-1.40)**	**1.37 (1.17-1.60)**	**1.28 (1.11-1.47)**	**1.15 (1.04-1.28)**
Sex (men vs.women)	**1.46 (1.21-1.77)**	**1.45 (1.05-2.02)**	**2.39 (1.78-3.21)**	**1.30 (1.04-1.61)**
Hypertension (yes vs no)	1.39 (0.92-2.16)	1.92 (0.85-5.54)	0.77 (0.44-1.42)	1.60 (0.98-2.77)
Diabetes Mellitus (yes vs no)	**1.37 (1.03-1.83)**	**2.38 (1.57-3.53)**	1.20 (0.80-1.78)	1.08 (0.77-1.50)
Atrial Fibrillation	**1.47 (1.01-2.12)**	0.78 (0.38-1.44)	1.42 (0.87-2.24)	**1.53 (1.02-2.25)**
Carotid Plaque (≥mod plaque)	1.16 (0.95-1.41)	1.11 (0.79-1.58)	**1.45 (1.07-1.97)**	1.06 (0.85-1.32)
Migraine without aura (yes no)	0.93 (0.64-1.32)	0.91 (0.45-1.66)	0.96 (0.53-1.64)	1.10 (0.73-1.61)
Migraine with aura (yes vs no)	**1.71 (1.19-2.44)**	1.19 (0.58-2.19)	1.43 (0.79-2.46)	**1.99 (1.35-2.89)**
Use of lipid lowering medication (yes vs no)	**1.32 (1.06-1.63)**	0.99 (0.69-1.40)	**1.78 (1.33-2.39)**	1.25 (0.98-1.58)
Agatston Coronary Calcium	**1.11 (1.00-1.24)**	1.21 (0.99-1.49)	1.12 (0.94-1.34)	1.08 (0.95-1.22)

For continuous risk factors, the unit of difference was 1 SD, except for age where it was 5 years.

Table IX. Relationship between Risk-Factors and Risk of Incident Brain Infarcts – Multivariate Sensitivity Analysis, Logisitc Regression

	Odds Ratios of Incident Brain Infarcts (RR 95% CI)			
Potential Risk-Factor	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	**1.31 (1.17-1.46)**	1.20 (0.96-1.48)	**1.36 (1.16-1.60)**	**1.31 (1.15-1.49)**
Sex (men vs. women)	**1.56 (1.24-1.95)**	**1.67 (1.08-2.60)**	**2.06 (1.46-2.93)**	1.22 (0.93-1.60)
Presence at Baseline (1+ vs 0)	**3.09 (2.51-3.80)**	**6.27 (3.97-9.75)**	**4.33 (3.05-6.12)**	**3.18 (2.46-4.11)**
Hypertension (yes vs no)	1.25 (0.77-2.11)	0.95 (0.41-2.81)	1.07 (0.54-2.39)	**2.12 (1.07-4.83)**
Diabetes Mellitus (yes vs no)	1.09 (0.77-1.53)	1.40 (0.76-2.45)	0.83 (0.47-1.37)	1.20 (0.79-1.78)
Atrial Fibrillation	0.98 (0.63-1.48)	0.66 (0.22-1.56)	1.06 (0.57-1.85)	0.98 (0.58-1.60)
Carotid Plaque (≥mod plaque)	1.12 (0.89-1.41)	0.93 (0.60-1.45)	**1.99 (1.36-2.96)**	0.92 (0.70-1.22)
Migraine without aura (yes no)	**1.53 (1.03-2.23**)	0.77 (0.27-1.78)	0.77 (0.35-1.50)	**1.72 (1.10-2.62)**
Migraine with aura (yes vs no)	**1.68 (1.10-2.51)**	1.19 (0.45-2.66)	1.86 (0.98-3.33)	1.43 (0.86-2.28)
Use of lipid lowering medication (yes vs no)	**0.76 (0.58-0.97)**	0.93 (0.56-1.50)	0.89 (0.61-1.28)	**0.69 (0.50-0.94)**
Agatston Coronary Calcium	**1.18 (1.04-1.34)**	1.06 (0.83-1.37)	1.17 (0.95-1.45)	**1.23 (1.06-1.44)**

For continuous risk-factors, the unit of difference was 1 SD, except for age where it was 5 years.