Supplementary appendix to manuscript by Weaver et al., submitted January 2021:

Strategic infarct locations predict post-stroke cognitive impairment: a multicenter cohort study in 2950 patients with acute ischemic stroke

Contents

Supplementary Methods

Definition of stroke subtypes

Four stroke subtypes were defined: (A) Small subcortical infarcts: single supratentorial infarct without cortical involvement, with a lesion volume of ≤4.19 ml (i.e. a sphere of ≤2 cm diameter; following the STRIVE criteria).[1] (B) Large subcortical infarcts: supratentorial infarct(s) without cortical involvement, with a lesion volume of >4.19 ml. (C) Cortical infarcts: supratentorial infarct(s) of any volume with cortical involvement. (D) Infratentorial infarcts: any brain stem and/or cerebellar infarct(s).

Patients with multiple infarcts in both supra- and infratentorial regions could be included in categories B/C (i.e. supratentorial, but not a single small subcortical infarct) and D (i.e. infratentorial) at the same time. Whether an infarct had cortical or infratentorial involvement was determined using brain masks for the MNI structural atlas (supratentorial cortical regions and cerebellum)[2] and Harvard-Oxford brain atlas (brain stem).[3]

Manual adaptations of registration errors

For three cohorts (CASPER, CROMIS-2 and STROKDEM), we registered the lesion maps as part of the current project. Visual control of the registration results was performed by an experienced rater (N.A.W.), and manual adaptations were made in case of minor displacements. The most common errors in the registration were: 1) imperfect alignment due to the mass effect caused by the lesion in the acute stage; 2) misalignment of the tentorium cerebelli, in which case an occipital infarct can overlap with the cerebellum in the brain template; 3) misalignment or deformation of periventricular infarcts in patients with enlarged ventricles; and 4) incomplete coverage of cortical areas due to presence of brain atrophy. Manual adaptations were made by an experienced rater (N.A.W) who followed a previously published protocol.[4] An in-house developed brush tool in MeVisLab was used to add or remove voxel clusters manually in three-dimensional orientation.[5]

Lesion data quality control procedure

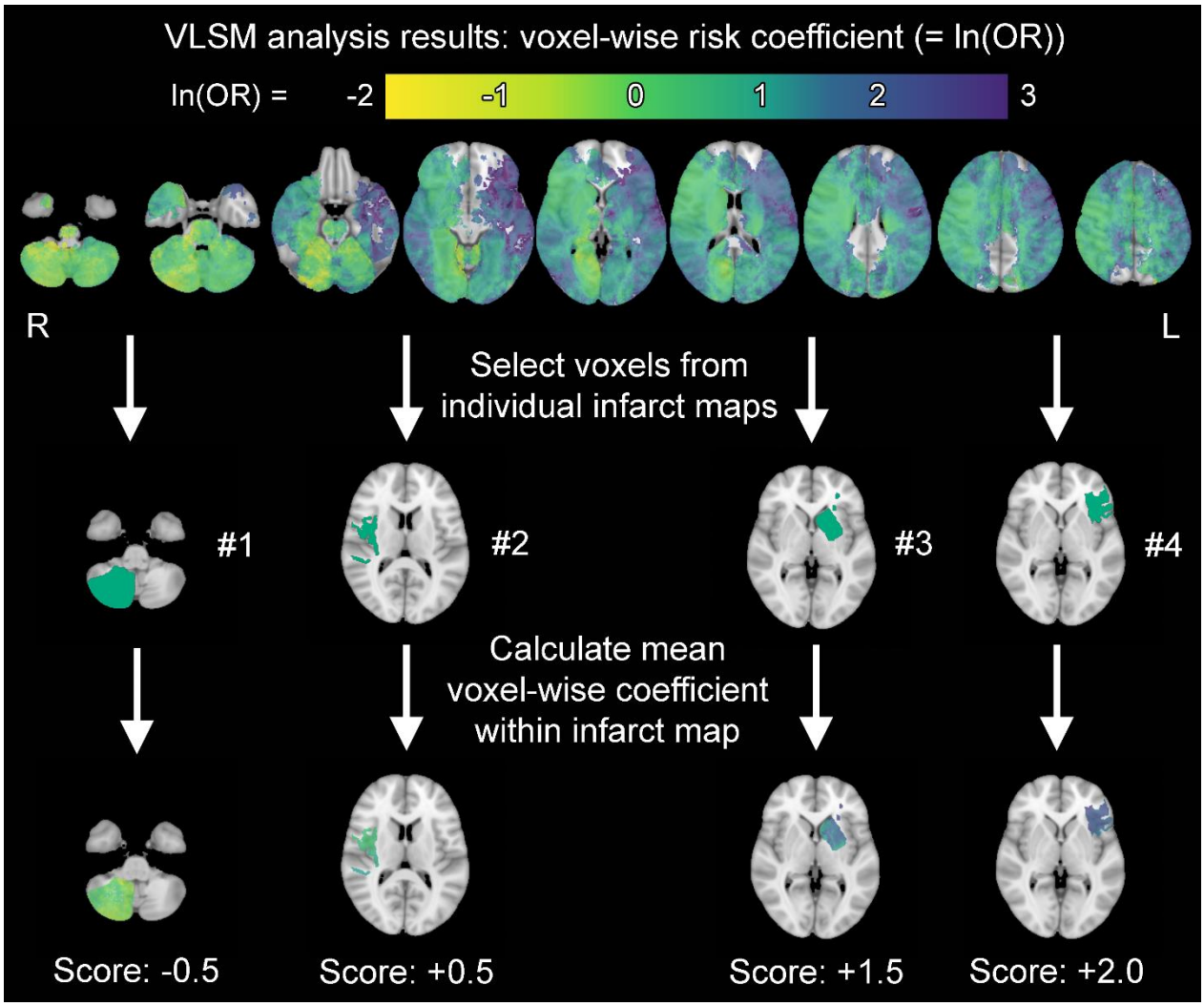
Standard operation procedures were followed to ensure that the fully processed lesion data matched the original imaging data and the clinical dataset provided by the participating center. For each cohort, the Utrecht team selected a random subset of 10 subjects and extracted a selection essential variables from the project dataset: age, sex, education, and three cognitive scores or MoCA score (depending on availability) from the collective dataset. If the dataset contained variables that described infarct location (e.g. left/right lateralization), this was also included. This selection of clinical data, along with the fully processed infarct maps of these subjects, was returned to the research team at each participating centers. They were asked to check: (1) whether the clinical data match up with the source data; (2) whether the infarct map properly represent the visible lesion on the original MRI or CT scan regarding size, shape, and location.

Missing data in prediction models

The following seven variables were used in the prediction models: age, sex, level of education, time interval after stroke onset, history of stroke, total infarct volume, and the location impact score. Data was complete except for time interval after stroke onset and history of stroke. Missing data was dealt with using the following approaches:

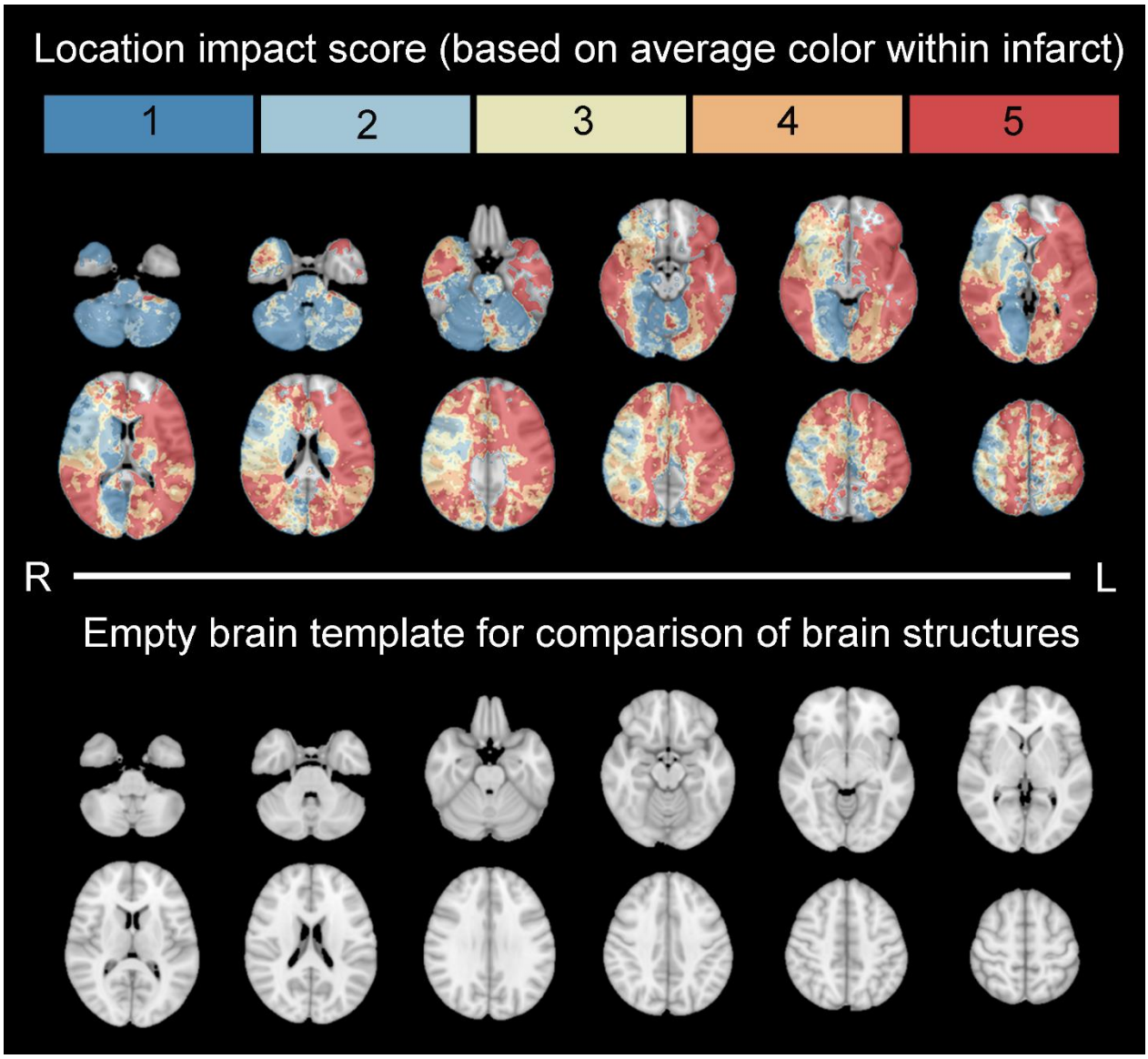
- Time interval after stroke: missing for a total of 7 subjects (0.2% of total), from the CROMIS-2 (N=1/97), Hallym VCI (N=3/641), and Mild Stroke Study 2 cohorts (N=3/100). Missing values were filled with the median of each respective cohort, as this would most correctly reflect the time intervals from individual study protocols.
- History of stroke: missing for a total of 13 subjects (0.4% of total), from the CROMIS-2 (N=1/97) and Hallym VCI cohorts (N=12/641). Missing values were filled with "no" if the clinical history was unknown, to avoid falsely attributing this risk factor to these patients.

Supplementary Figure 1. Calculation of individualized location impact score



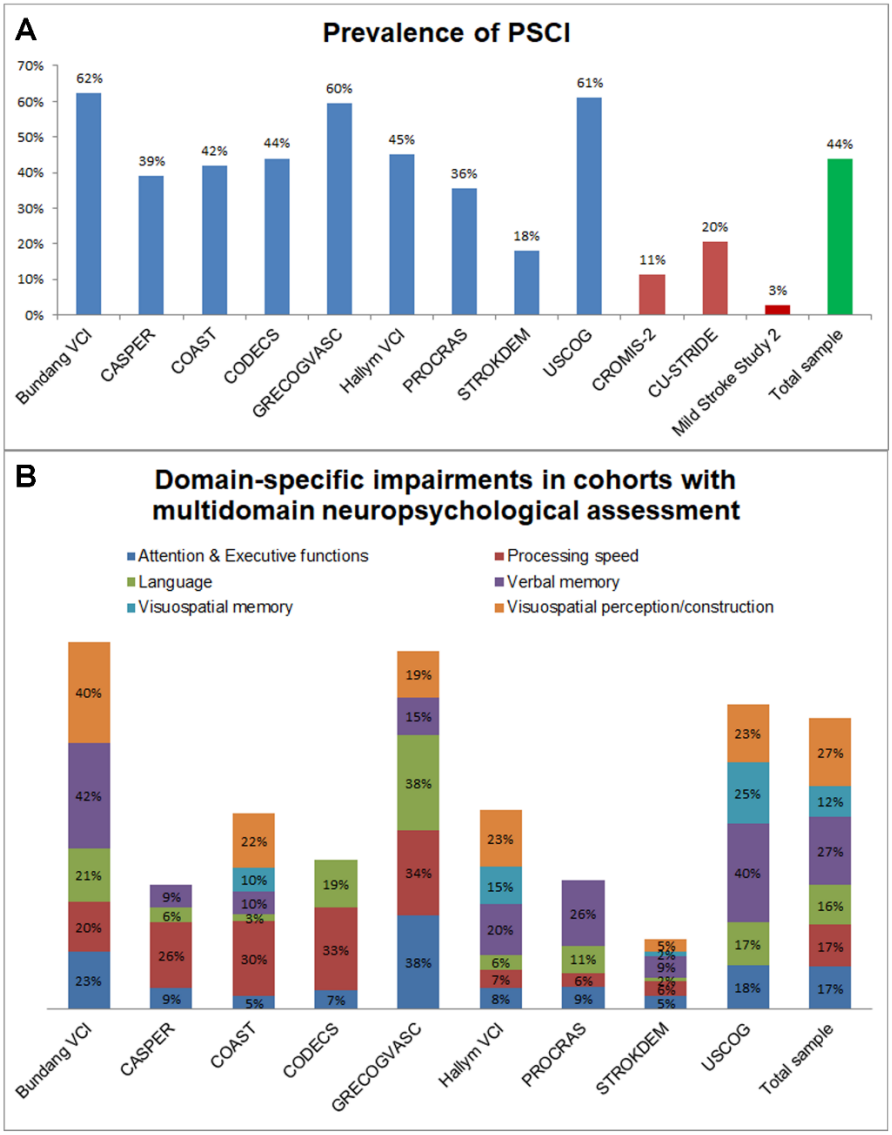
Schematic overview of how the individualized location impact score was calculated. First, the voxel-wise odds ratios of the voxel-based lesion-symptom mapping (VLSM) analysis (Fisher's exact test; see Figure 2) were converted into risk coefficients, to achieve a more practical scaling of the values, with a coefficient of 0 indicating no directionality, positive values indicating increased risk and negative values indicating decreased risk. Next, all voxels from the infarct segmentations of each patient (middle row; infarct indicated in dark green) were selected and given the value of the coefficients of the VLSM results (bottom row). Finally, the mean value of all affected voxels was calculated and comprises the individualized location impact score, with higher values indicating a higher risk of PSCI. The numbers in the middle and bottom row are four examples from the actual dataset. The "viridis" color scale was used for visualization of ORs (based on https://cran.r-project.org/web/packages/viridis/index.html).

Supplementary Figure 2. Brain slices provided for test ratings of the location impact score



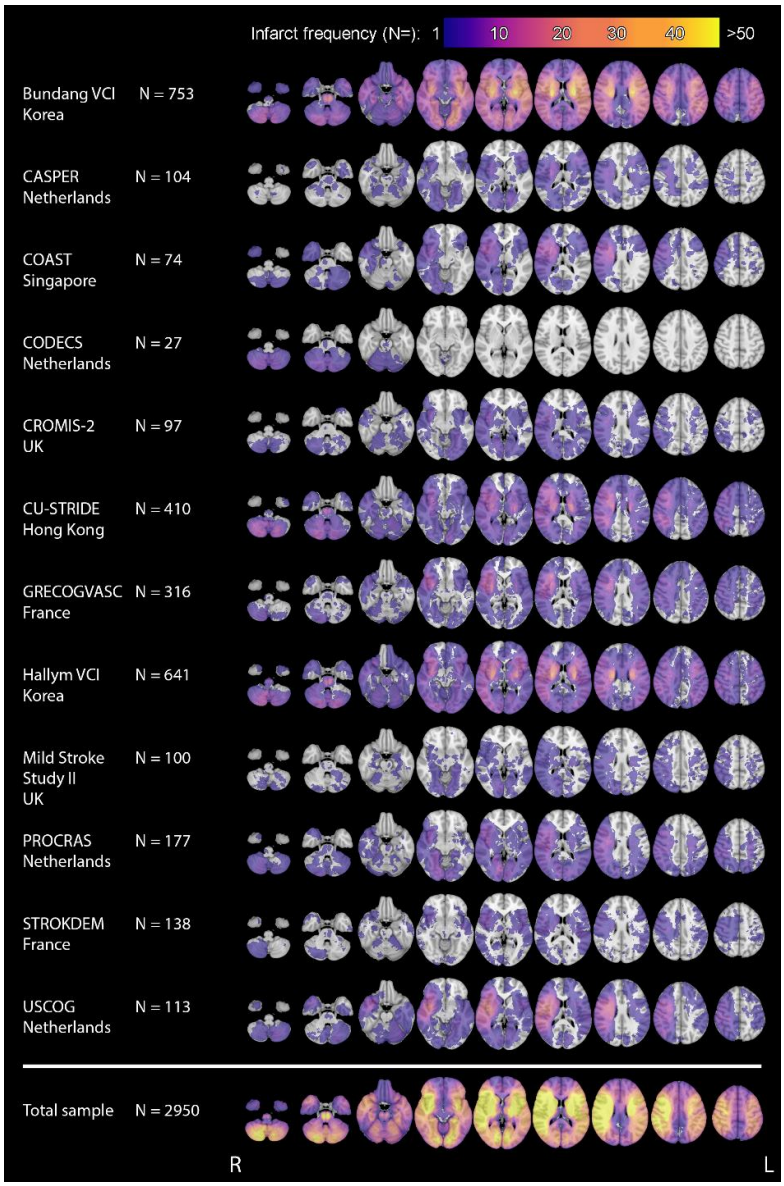
These 12 brain slices showing the five-point location impact score were provided for the test ratings. This was accompanied by a brief description of the rating method. Raters were asked to estimate the "average score of the voxels located within the infarct", based on the color scale. The same slices of the MNI-152 template were also provided without the visual rating scale, as reference, because it can be difficult to judge the underlying anatomical structures when the colors are projected onto the template. A 5-class RdYlBu color scale was used, which is colorblind- and printer-friendly.

Supplementary Figure 3. Cognitive profiles of the participating cohorts



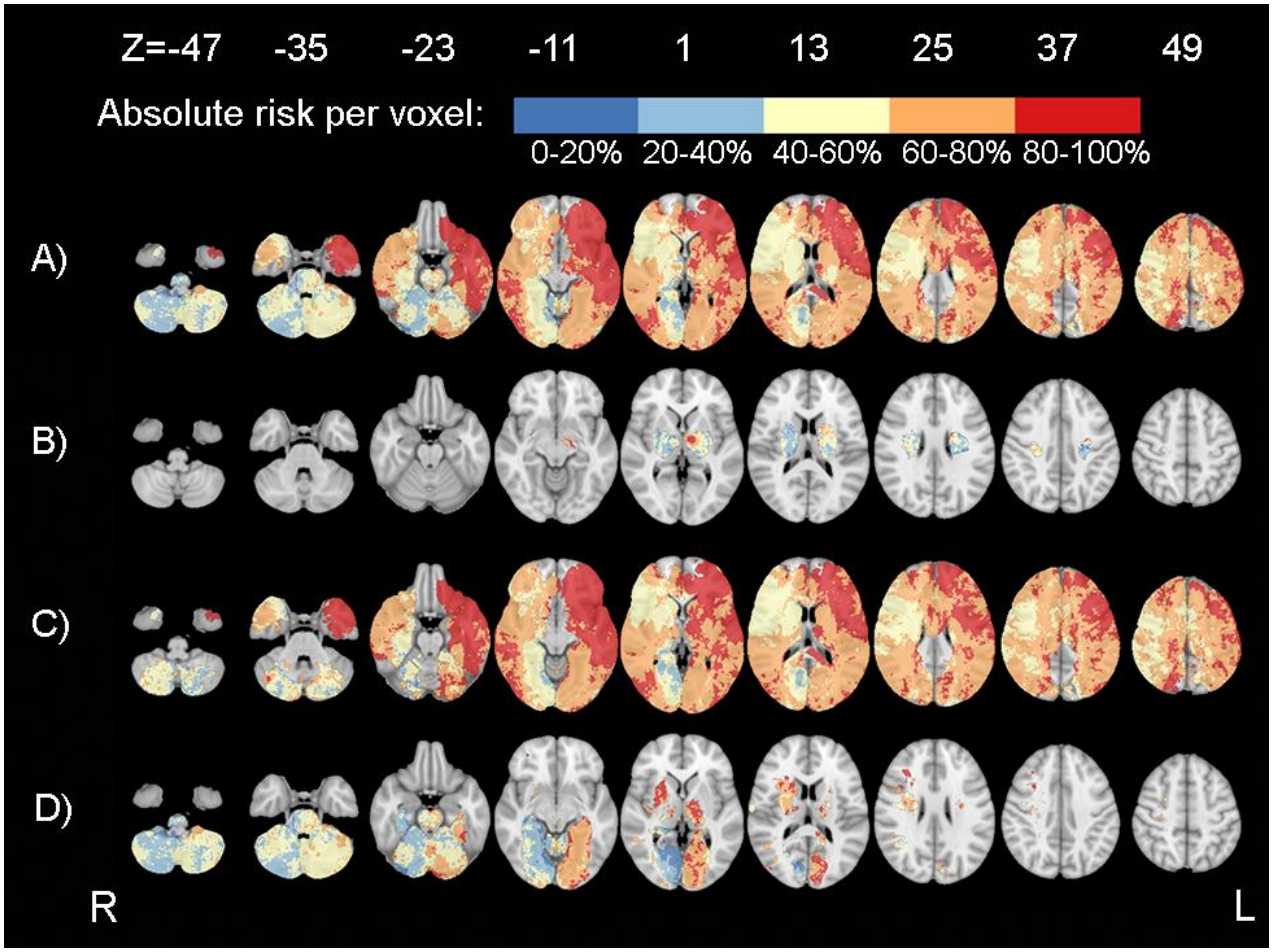
Panel A: Prevalence of PSCI in each cohort. The color of the bar indicates the type of cognitive data used to define PSCI: blue indicates cohorts with a formal neuropsychological test battery, red indicates cohorts with the Montreal Cognitive Assessment (MoCA). Differences in PSCI occurrence reflect heterogeneity in inclusion criteria and study protocols, particularly preselection based on severity of symptoms (STROKDEM and Mild Stroke Study 2) and lower sensitivity of MoCA as cognitive screener. Panel B: Stacked bar chart showing the occurrence of impairment across six cognitive domains. Percentages indicate the valid percent, i.e. patients with impairment as portion of all patient with scores for that specific domain available. Domain impairment was based impairment on >50% of available tests in each domain, using the 5th percentile as cut-off. Patients could be impaired in multiple domains, therefore each column may add up a to higher percentage than the total PSCI occurrence per cohort. Note that some cohorts did not assess all six domains, thus availability of data per domain varied. Attention and executive functioning data was available for 93% of patients (N=2195/2343), processing speed for 89% (N=2091/2343), language for 98% (N=2304/2343), verbal memory for 98% (N=2286/2343), visuospatial memory for 34% (N=806/2343), and visuoconstruction/-perception for 80% (N=1875/2343).

Supplementary Figure 4. Lesion prevalence map for individual cohorts and the combined dataset.



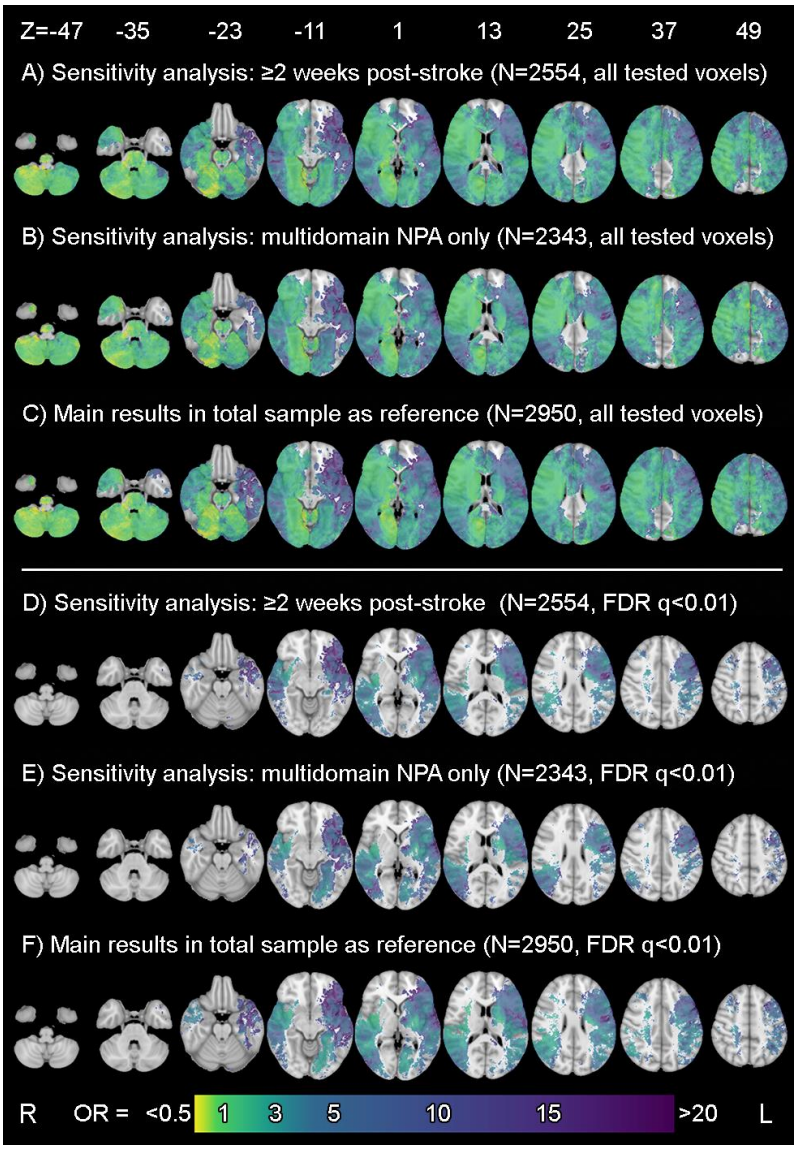
Prevalence maps depicted on the Montreal Neurological Institute 152 (MNI-152) brain template. Voxels damaged in one or more patients are shown in colors ranging from dark blue (N=1) to yellow (N>50). Lesion-symptom mapping analyses require sufficient "brain lesion coverage", meaning that every possible location in the brain must be damaged in a sufficient number of subjects to be analyzed (N≥5). As shown in the combined map in the bottom row, merging of datasets allows many more voxels to pass this threshold for inclusion than in individual cohorts. Note that the left hemisphere is underrepresented in most cohorts, because patients with large left-hemispheric infarcts more commonly suffer from (severe) aphasia that precludes neuropsychological assessment. The "plasma" color scale from the viridis color palette was used for visualization of ORs (based on https://cran.r-project.org/web/packages/viridis/index.html). L = left, R = right. Z-coordinates (axial slices) of MNI-152 template: -47, -35, -23, -11, 1, 13, 25, 37, 49.

Supplementary Figure 5. Absolute risk of PSCI per voxel in the total sample and stratified per stroke subtype



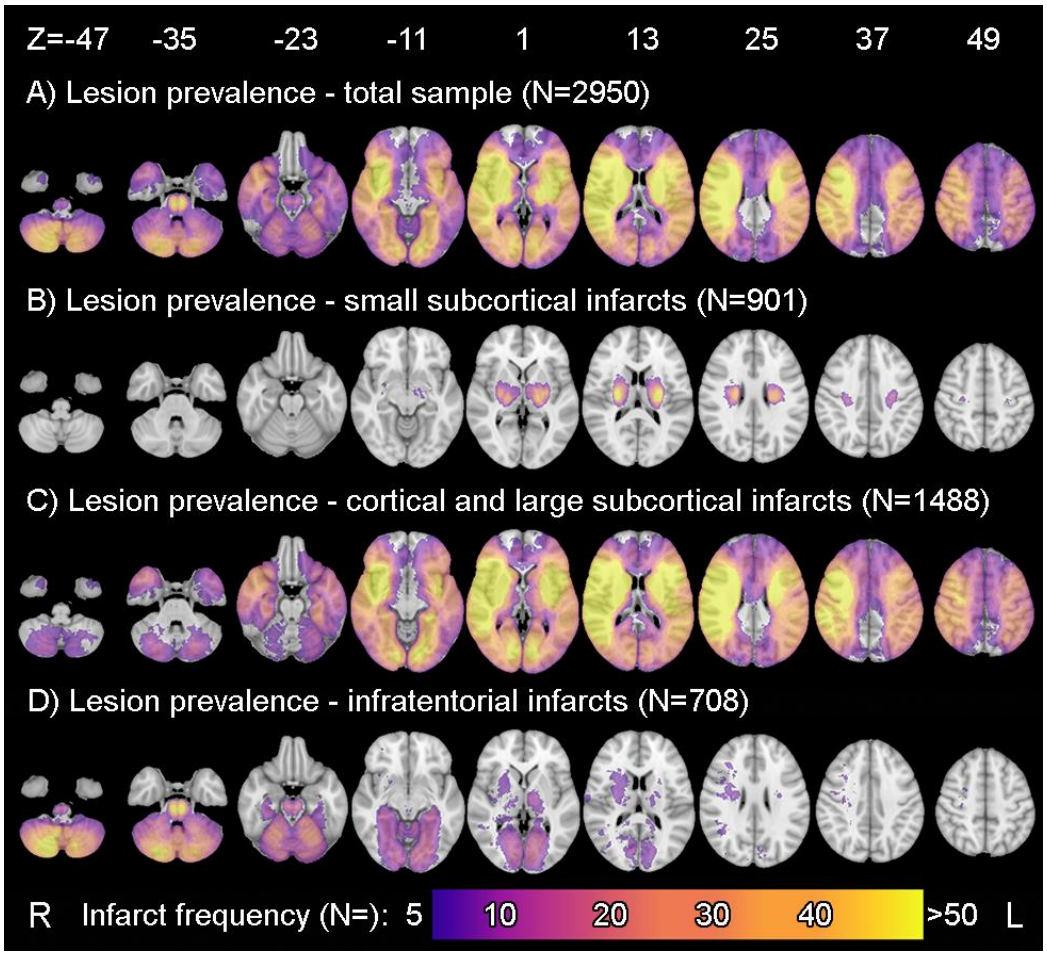
Voxels damaged in N≥5 are shown for the total sample (panel A; N=2950; PSCI occurrence: 44%) and stratified per stroke subtype: small subcortical infarcts (panel B; N=901; PSCI occurrence: 37%), large subcortical or cortical infarcts (panel C; N=1488; PSCI occurrence: 49%), and infratentorial infarcts (panel D; N=708; PSCI occurrence: 43%). The absolute risk was calculated for each voxel individually, by dividing the number of patients with PSCI and damage to a voxel by the total number of subjects with damage to the same voxel. Of note, while this figure provided an intuitive approach to assessing PSCI risk (i.e. given that a patient has an infarct in location X, PSCI occurs in Y% of patients), it provides no statistical certainty due to its descriptive nature. A 5-class RdYlBu color scale was used, which is colorblind- and printer-friendly. Coordinates of the MNI-152 template (Z; axial orientation) are indicated at the top of the figure. L = left, R = right.

Supplementary Figure 6. Sensitivity analysis results



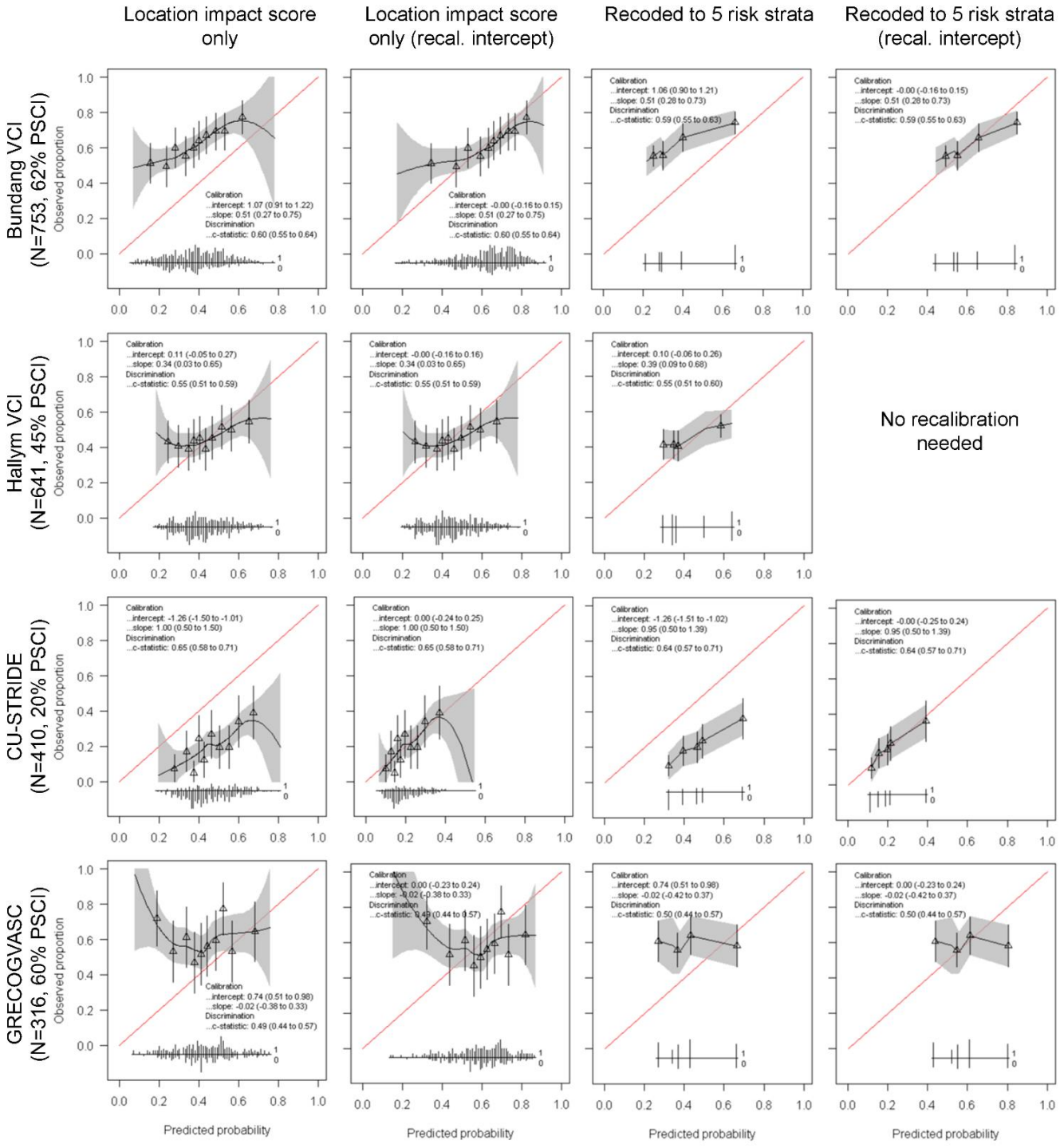
Sensitivity analyses were performed on: 1) patients with cognitive assessment ≥2 weeks post-stroke, to limit the effect of factors in the acute stage (e.g. delirium) on cognition (panels A and D), and 2) only patients with detailed neuropsychological assessment, i.e. excluding patients that only underwent MoCA, to determine whether the use of a cognitive screening instrument instead of detailed assessment influenced the primary results (panels B and E). Results from the main analysis (Figure 2 in main text) are shown in Panel C and F as reference. Voxel-wise odds ratios (ORs) for PSCI occurrence are shown, calculated using the Fisher's exact test. The color indicates the OR per voxel: dark green to blue indicates that presence of an infarct in that voxel is associated with an increased OR for cognitive impairment compared to absence of an infarct in that voxel, lime green indicates no association (OR=1), and yellow indicates a decreased OR. Panels A-C show the ORs for all tested voxels (i.e. damaged in N≥5; no threshold for statistical significance). Panels D-F only show voxels with p<0.01 after False Discovery Rate correction. In these sensitivity analyses patterns of odds ratios and significant voxels are essentially the same as the main results. The "viridis" color scale was used for visualization of ORs (based on https://cran.r-project.org/web/packages/viridis/index.html). Coordinates of the MNI-152 template (Z; axial orientation) are indicated at the top of the figure. L = left, R = right.

Supplementary Figure 7. Lesion prevalence maps stratified per stroke subtype

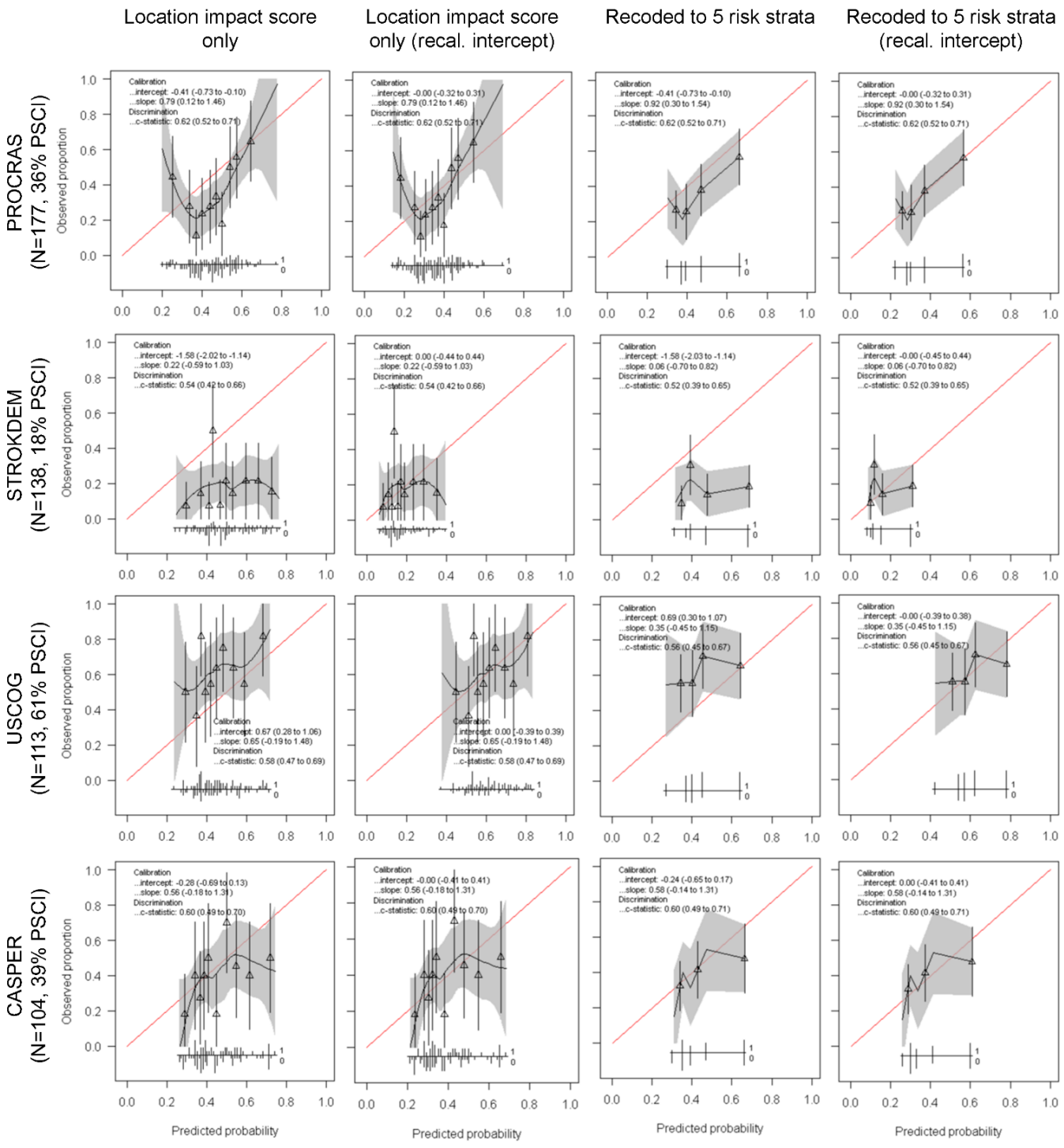


Prevalence maps are shown for the total sample as reference (panel A; N=2950), small subcortical infarcts (panel B; N=901), large subcortical or cortical infarcts (panel C; N=1488), and infratentorial infarcts (panel D; N=708). Small subcortical infarcts were defined as single supratentorial infarcts without cortical involvement, with lesion volume of ≤4.19 ml (i.e. a sphere of ≤2 cm diameter). Other supratentorial infarcts were categorized as large subcortical (>4.19 ml) or cortical infarcts (any volume). Infratentorial infarcts included brain stem and cerebellar infarcts (any volume). If a patient had both supra- and infratentorial infarcts (in 147 cases), the entire infarcted area was included; hence, some supratentorial regions were included in the infratentorial subgroup analysis (panel D), and vice versa (panel C). The "plasma" color scale from the viridis color palette was used for visualization of ORs (based on https://cran.r-project.org/web/packages/viridis/index.html). L = left, R = right.

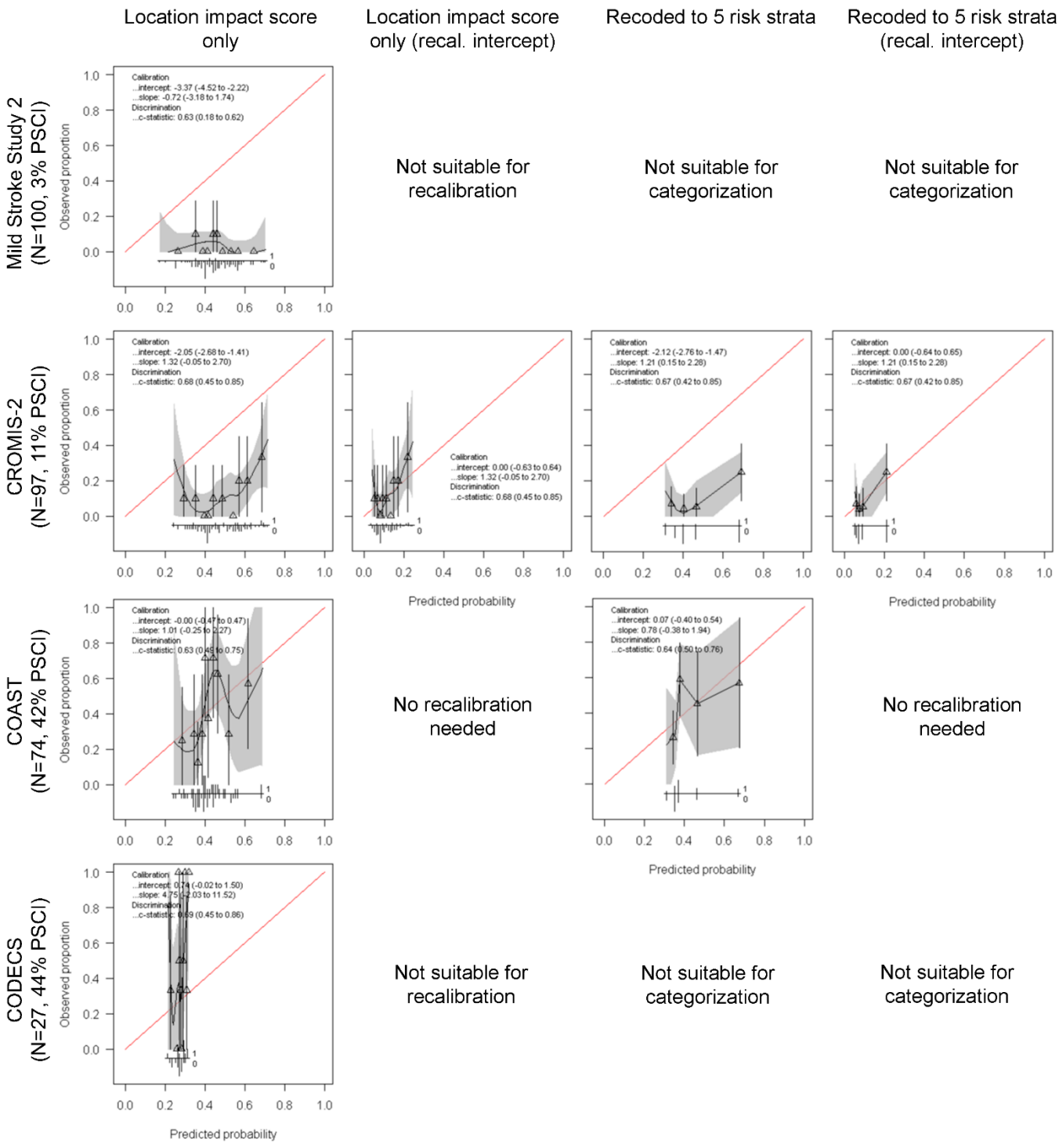
Supplementary Figure 8. Calibration plots for continuous and five-point location impact score as single predictor (1/3)



Supplementary Figure 8. Calibration plots for continuous and five-point location impact score as single predictor (cont., 2/3)



Supplementary Figure 8. Calibration plots for continuous and five-point location impact score as single predictor (cont., 3/3)

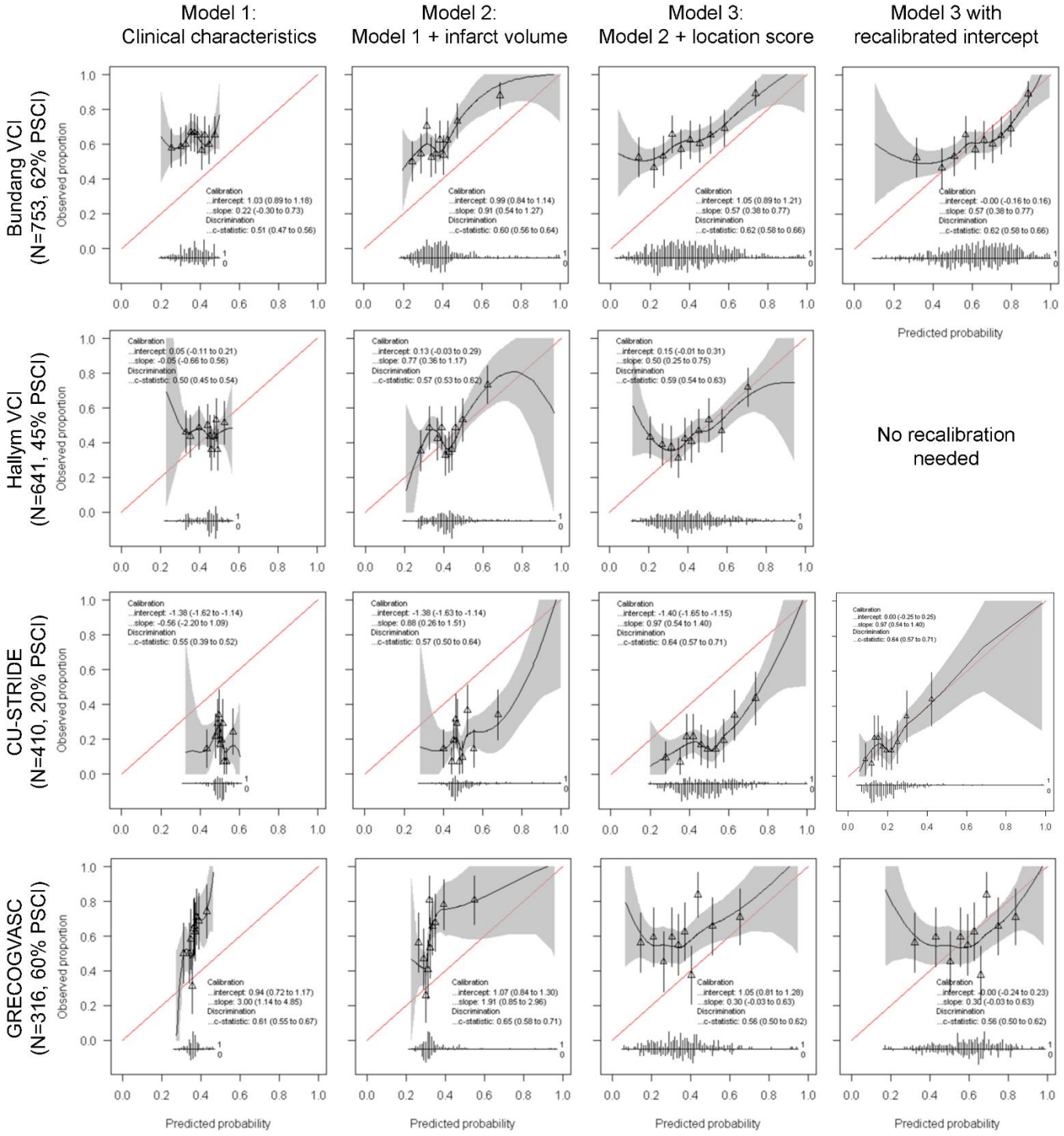


Calibration plots of predicted probabilities (x-axis) versus actual PSCI occurrence (y-axis) based on three logistic regression models. Each row indicates the cohort that was left out of the model derivation in the leave-one-cohort-out cross-validation and served as external validation sample. Cohorts are listed in descending order based on sample size; statistically well-powered cohorts (i.e. with approximately N=100 cases with PSCI [6]) are shown on page 1/3; the other cohorts (pages 2 and 3) might suffer from less stable estimates and wider confidence intervals.

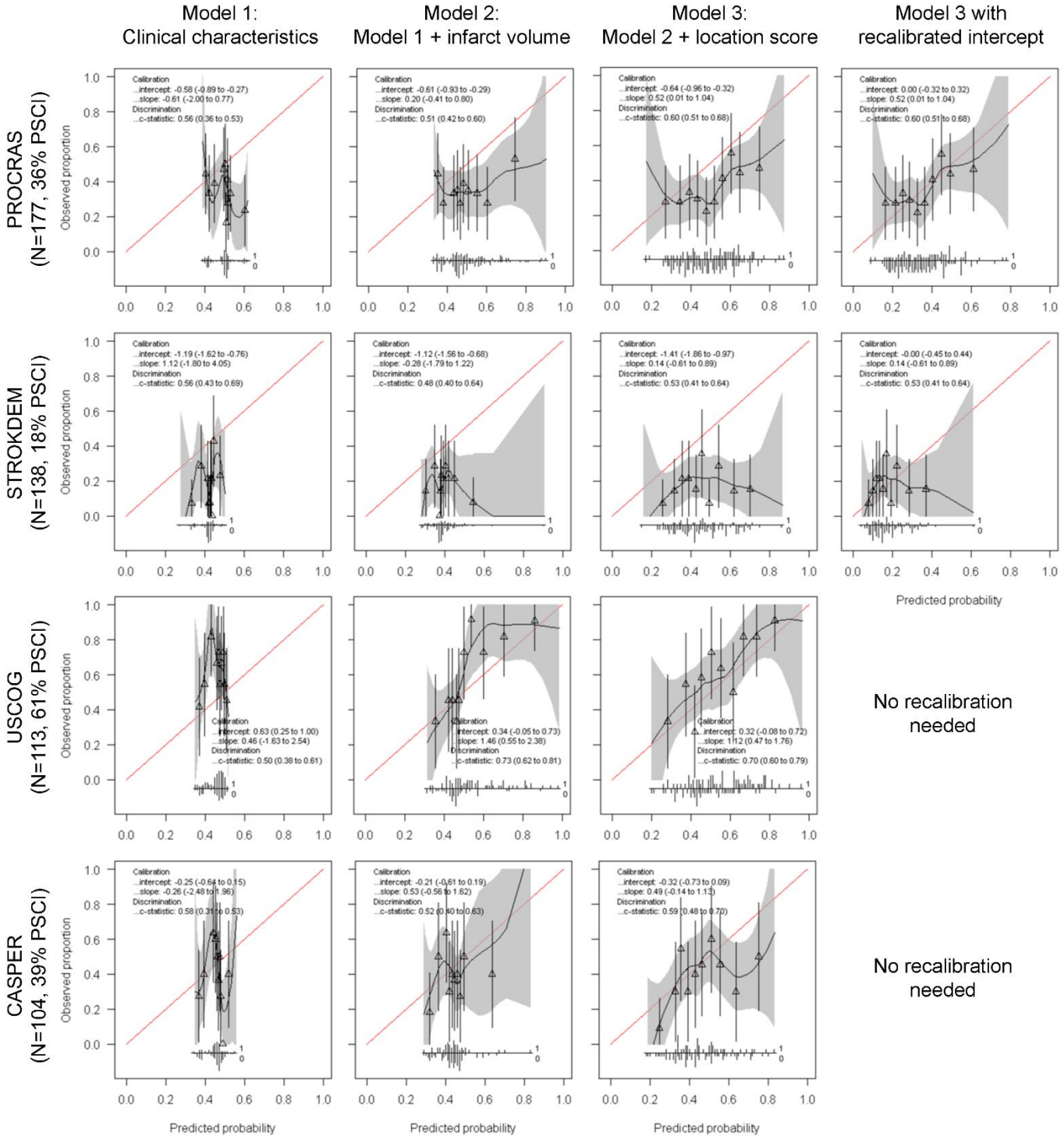
The distributions of actual 0 and 1 values are shown at the bottom of the graph; the *loess* smoother (with 95% confidence band) is shown in black; the ideal 45-degree line is shown in red. The actual outcomes are stratified according to risk groups (20% of validation sample per location impact score stratum) are indicated by triangles. Calibration and discrimination measures are shown in the upper left or bottom right corner of the plots.

First, performance of the location impact score as continuous measure was tested (column 1). The intercept was recalibrated to adjust for the wide range of PSCI occurrence across cohorts (column 2). Next, the continuous location impact score was recoded into a five-point score based on quintiles (1 = 0-20th percentile, 2 = 20-40th percentile, etc.). This five-point location impact score showed similar model calibration as the continuous score after recalibration (columns 3 and 4). Recalibration of the intercept was performed if the 95% confidence interval of the intercept did not overlap with zero; this was not necessary for two cohorts (Hallym VCI and COAST). Two cohorts had insufficient data to provide meaningful results: the Mild Stroke Study 2 sample (N=100) only included 3 patients with PSCI, and the CODECS sample (N=27; 44% had PSCI) only included cerebellar infarcts and therefore suffered from insufficient range of predictions (location impact score range: 1-2). Hence these cohorts were deemed unsuitable for recalibration based on the initial model (column 1), and were also not converted to five-point version of the location impact score.

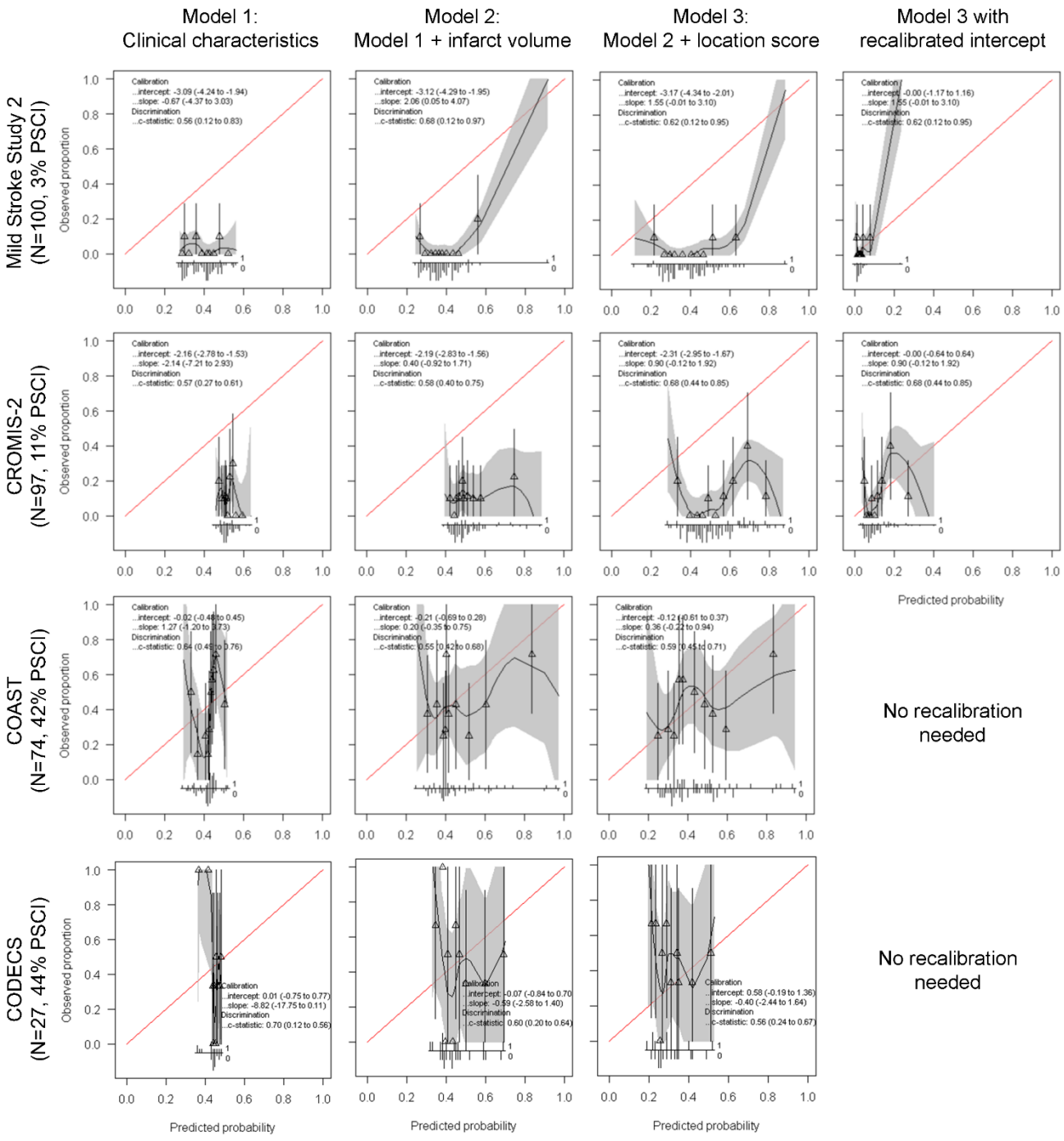
Supplementary Figure 9. Calibration plots for location impact score on top of other predictors (1/3)



Supplementary Figure 9. Calibration plots for location impact score on top of other predictors (cont.,2/3)



Supplementary Figure 9. Calibration plots for location impact score on top of other predictors (cont.,3/3)

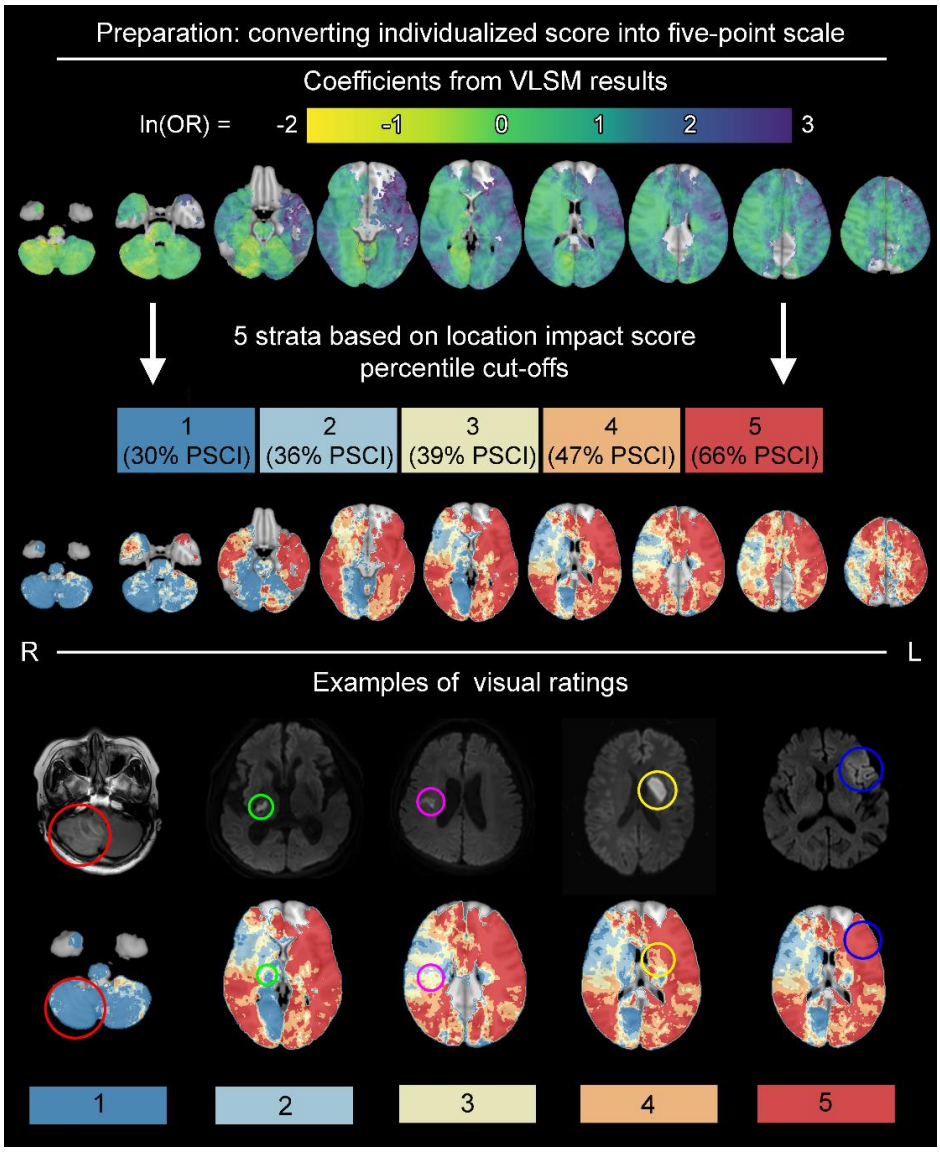


Calibration plots of predicted probabilities (x-axis) versus actual PSCI occurrence (y-axis) based on three logistic regression models. Each row indicates the cohort that was left out of the model derivation in the leave-one-cohort-out cross-validation and served as external validation sample. Cohorts are listed in descending order based on sample size; statistically well-powered cohorts (i.e. with approximately N=100 cases with PSCI [6]) are shown on page 1/3; the other cohorts (pages 2 and 3) might suffer from less stable estimates and wider confidence intervals.

The distributions of actual 0 and 1 values are shown at the bottom of the graph; the *loess* smoother (with 95% confidence band) is shown in black; the ideal 45-degree line is shown in red. The actual outcomes are stratified according to risk groups (10% of validation sample per stratum) are indicated by triangles. Calibration and discrimination measures are shown in the upper left or bottom right corner of the plots.

Model 1 (column 1) consisted of age, sex, level of education, history of stroke, and time interval between stroke onset and cognitive assessment. Model 2 (column 2) included infarct volume as additional variable. Model 3 (column 3) further added the location impact score, which is the marker of interest. As final step, calibration-in-the-large was performed by adapting the intercept to adjust for cohort-specific PSCI occurrence (column 4). This was only done if the 95% confidence interval of the intercept did not overlap with zero; this was not necessary for three cohorts (COAST, CODECS, and Hallym VCI). Note that model calibration was generally poor in Model 1, with a narrow and unstable range of predictions. Addition of infarct volume (Model 2) provided a wider range of predictions, but still showed unstable estimates in most cohorts. Final addition of the location impact score (Model 3) provided the best model calibration, with the widest range of predictions and best correspondence between predicted and actual probabilities.

Supplementary Figure 10. Visual rating procedure of the location impact score



The visual scale consists of a color map with five colors, each indicating a risk strata. A 5-class RdYlBu color scale was used for the location impact score, which is colorblind- and printer-friendly. To calculate the five-point location impact score, the continuous location impact score (i.e. the mean voxel-wise coefficient within a patient's infarct) was categorized into quintiles. Predicted probabilities are shown for each of the five-point location impact score categories; note that this prediction is based on the total dataset (with 44% PSCI in the total sample), but PSCI occurrence varied strongly across cohorts (see also Figure 4). To enable visual rating of the five-point location impact score, the same percentile cut-offs were applied to categorize individual voxels into five categories, corresponding with five different colors in the figure. This allows for visual estimation of the patient's location impact score based on the "average" color of the voxels: for example, if the infarct is located in a region with mostly red voxels (i.e. in the 80-100th percentile range), the overall location impact score will also be in the highest percentile category. Ratings can be performed using the original brain scan. Some examples of ratings are shown in the bottom panel. Note that these percentile cut-offs were determined at a patient level, not at a voxel level, thus each of the five color categories can contain more or less than 20% of all voxels.

Supplementary Table 1. In- and exclusion criteria of participating cohorts

	Inclusion criteria	Exclusion criteria
Bundang VCI [7,8]	• Ischemic stroke, hospitalized within 1 week of onset • acute ischemic lesions on diffusion-weighted imaging • Informed consent obtained	• Severe concomitant medical or neurological conditions (persistent impairment of consciousness or visual impairment) • Severe dysphasia • Death within 2 weeks of stroke onset
CASPER [9]	• Ischemic or hemorrhagic stroke • MMSE score ≥ 15 • Written informed consent • Sufficient knowledge of the Dutch language	• Subarachnoid hemorrhage, traumatic hemorrhage, primary intraventricular hemorrhage and transient ischemic attack • Age < 40 years • Severe aphasia • Evidence for pre-stroke dementia (based on clinical diagnosis or IQ-CODE) in the 5 years prior to the stroke • Other existing psychiatric and neurological diagnoses that are known to affect cognition (Parkinson's disease, bipolar disorder, epilepsy, schizophrenia, or substance abuse)
COAST [10]	• Age ≥21 years • Acute ischaemic stroke or TIA with onset within the preceding 14 days • Stable clinical and neurological status within the preceding 24 hours • Written consent obtained from patient or legally acceptable representative	• Significant aphasia and/or dysarthria that impedes performance of cognitive assessment • Major and active psychiatric illness • Acute delirium • Pre-existing dementia • Major physical disability with modified Rankin Scale score >4
CODECS [N/A]	• Age ≥18 years • Isolated cerebellar stroke	• Significant aphasia or severe dysarthria • Prior cognitive impairment
CROMIS-2 [11]	• Age ≥18 years • Clinical diagnosis of non-valvular atrial fibrillation (verified by ECG) with intention to treat with best practice oral anticoagulants • Previous ischemic stroke or TIA diagnosed by treating clinician • All patients must be able to have GRE MRI before (or within 1 week) of starting best practice oral anticoagulant	• Any MRI contraindications • Previous use of oral anticoagulation • Definite contra-indication to oral anticoagulation • Serious head injury (resulting to loss of consciousness)
CU-STRIDE [12,13]	• Patients admitted to the acute stroke unit of a university-affiliated hospital because of stroke/TIA • Chinese ethnicity • Fluency in Cantonese • Ability to participate in cognitive assessments • Provision of signed informed consent	• Severe language impairment precluding cognitive assessment • Terminal illness • Clinically significant psychiatric comorbidity • Known history of dementia before the index stroke
GRECogVASC [14]	• Age between 40 and 80 years • Hospitalized for acute (<30 days) cerebral infarct or hemorrhage with initial positive imaging • No previously diagnosed conditions affecting cognition (except for previous stroke) • French-speaking • Reliable informant, agreeing to participate in the study	• Mental retardation, illiteracy • Known dementia • Schizophrenia or psychosis or history of psychiatric illness requiring a stay > 2 days in a psychiatry unit • Persistent disturbance of consciousness • Contraindication to MRI • For the present analysis: subset of 316 patients with infarct and MR assessment in Amiens center
Hallym VCI [7,8]	• Ischemic stroke, hospitalized within 1 week of onset • Acute ischemic lesions on diffusion-weighted imaging • Informed consent obtained	• Severe concomitant medical or neurological conditions (persistent impairment of consciousness or visual impairment) • Severe dysphasia • Death within 2 weeks of stroke onset

Mild Stroke Study 2 [15]	• Lacunar or mild cortical ischemic stroke • Age ≥18 years • Able to consent • Within 4 weeks of mild ischemic stroke (i.e., NIHSS ≤5, unlikely to cause physical dependency) • MR diffusion-weighted imaging (DWI) infarct compatible with the index stroke symptoms, or no other cause of symptoms • No life-threatening illness to preclude 1 year follow-up	• Contraindications to MRI
PROCRAS [16]	• Clinical diagnosis of ischemic stroke • Age ≥50 years	• Pre-stroke dementia: Known diagnosis of dementia or Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) ≥3.6 • Life expectancy <1 year • Severe stroke expected to require long-term nursing care facilities • History of major neurological disease interfering with cognitive functioning • Pre-stroke dependence in activities of daily living (Barthel Index<18) • Insufficient command of the Dutch language to participate and understand questionnaires • Impossibility to participate in a neuropsychological assessment • An absolute contraindication to undergo an MRI scan of the brain
STROKDEM [17]	• Age >40 years • Hemispheric stroke • Stroke dating from less 72h • IQCODE < 64 • Patient (or his family) given an informed consent	• Malformed cerebral hemorrhage, traumatic cerebral hemorrhage, pure meningeal or intraventricular hemorrhage • Contraindications to MRI • Insufficient mastery of the French language • No informed consent
USCOG [18]	• First-ever ischemic stroke • Brain infarction on follow-up CT or MRI	• Pre-existent neurologic conditions that might interfere with cognition: history of cognitive impairment, traumatic brain injury, brain tumor, epilepsy, multiple sclerosis, moyamoya disease, or severe cerebral small vessel disease (i.e. Fazekas grade 3)

Supplementary Table 2. Overview of cohorts and available neuropsychological data per cohort

Study	N=	Cognitive screening	Attention & Executive Functioning	Information processing speed	Language	Verbal memory	Visuospatial memory	Visuoperception and -construction
Bundang VCI	753	N/A	1. TMT B 2. Phonemic fluency	1. TMT A 2. Digit Symbol Coding	1. Boston Naming Test 2. Semantic fluency – animals	Seoul Verbal Learning Test: 1. Immediate recall 2. Delayed recall 3. Recognition	N/A	1. Rey Complex Figure Test: copy
CASPER	104	N/A	1. TMT B 2. Digit span forward 3. Digit span backward	1. TMT A	1. Semantic fluency – animals	Rey Auditory Verbal Learning Test 1. Immediate recall 2. Delayed recall 3. Recognition	N/A	N/A
COAST	74	N/A	1. Visual memory span forward 2. Visual memory span backward 3. Auditory Detection test 4. Digit cancellation task 5. Maze task 6. Digit span forward 7. Digit span backward	1. Symbol Digit Modalities Test	1. Boston Naming Test 2. Semantic fluency – animals	Word-List Recall 1. Immediate 2. Delayed 3. Recognition Story Recall 4. Immediate 5. Delayed	Picture Recall 1. Immediate 2. Delayed 3. Recognition Visual Reproduction 4. Immediate 5. Delayed 6. Recognition	1. Clock-drawing 2. Block design 3. Visual reproduction copy
CODECS	27	N/A	1. TMT B 2. Phonemic fluency 3. Stroop	1. TMT A	4. Semantic fluency – animals	N/A	N/A	N/A
CROMIS-2	97	MoCA	N/A	N/A	N/A	N/A	N/A	N/A
CU-STRIDE	410	MoCA	N/A	N/A	N/A	N/A	N/A	N/A
GRECogVASC	316	N/A	1. TMT B 2. Phonemic fluency	1. TMT A 2. Digit Symbol Coding	1. Boston Naming Test 2. Semantic fluency – animals	Free and Cued Selective Reminding Test 1. Immediate 2. Delayed 3. Sum 3 total recall 4. Recognition	N/A	1. Rey Complex Figure Test: copy
Hallym VCI	641	N/A	1. TMT B 2. Phonemic fluency	1. TMT A 2. Digit Symbol Coding	1. Boston Naming Test 2. Semantic fluency – animals	Seoul Verbal Learning Test 1. Immediate recall 2. Delayed recall 3. Recognition	1. Rey Complex Figure Test: delayed recall	1. Rey Complex Figure Test: copy

Mild Stroke Study 2	100	MoCA	N/A	N/A	N/A	N/A	N/A	N/A
PROCRAS	177	N/A	1. TMT B 2. Phonemic fluency 3. Hayling test 4. Reaction time test, Vienna Test System S3 5. Digit span forward 6. Digit span backward	1. TMT A 2. Symbol Digit Modalities Test 3. Reaction time test, Vienna Test System S1 4. Reaction time test, Vienna Test System S2	1. Boston naming Test 2. Semantic fluency – animals	Rey Auditory Verbal Learning Test 1. Immediate recall 2. Delayed recall	N/A	N/A
STROKDEM	138	N/A	1. TMT B 2. Phonemic fluency 3. Stroop	1. TMT A 2. Digit Symbol Coding	1. Semantic fluency – animals 2. D080 – picture naming	Free and Cued Selective Reminding Test 1. Immediate recall 2. Delayed free recall	1. Rey Complex Figure Test: immediate recall	1. Rey Complex Figure Test: copy Visual object and space perception battery 2. Incomplete letters 3. Number location
USCOG	113	N/A	1. Phonemic fluency 2. BADS zoo test 3. Digit span forward 4. Digit span backward	N/A	1. Boston naming Test 2. Semantic fluency – animals 3. Token test	Rey Auditory Verbal Learning Test 1. Immediate recall 2. Delayed recall 3. Recognition	1. Rey Complex Figure Test: delayed recall	1. Rey Complex Figure Test: copy 2. Judgment of Line Orientation

Categorization of neuropsychological tests was based on previous work by Lezak.[19] The length of the numbered list indicates the maximum number of tests available in a cohort. Note that for some tests, individual subscores were separately included (e.g. immediate recall, delayed recall and recognition counting as 3 separate components in the verbal memory domain). For determining presence or absence of post-stroke cognitive impairment, availability of tests was determined on a per-subject basis. Normative data for each cohort is shown in Supplementary Table 3.

Abbreviations: BADS, Behavioral Assessment of the Dysexecutive Syndrome; MoCA, Montreal Cognitive Assessment; N/A, not applicable or not available; TMT, Trail Making Test.

Supplementary Table 3. Normative data for detailed neuropsychological assessment

Study name	N of control group	Population
Studies that recruited their own control group		
GRECogVASC	1003	General population not presenting any condition known to impair cognitive abilities stratified according to age and schooling levels.[14,20]
Studies that provided control group data from a separate local study		
COAST	279	A subset without cognitive impairment from the EDIS study. EDIS is a Singapore study with participants drawn from the Singapore Epidemiology of Eye Disease study, a multiethnic population-based study among persons aged 40–85 years, which included Chinese, Malays and Indians.[21]
Studies that calculated standardised scores based on published local norms or studies		
Bundang VCI and Hallym VCI	Varied	Age, sex and education matched community dwelling elderly.[7]
CASPER	1823	Maastricht Aging Study. Participants were drawn from a patient register of collaborating general practitioners.[22]
CODECS	Varied	Dutch population-based normative data adjusted for age, sex and level of education. Published in 2012 on website of The Dutch Association of Psychologists (https://www.psynip.nl/wp-content/uploads/2016/07/Handleiding-normen-Np-tests-2012.pdf).
PROCRAS	Varied	• Phonemic fluency, semantic fluency, TMT A and B, Rey Auditory Verbal Learning Test: Dutch population-based normative data adjusted for age, sex and level of education. Published in 2012 on website of The Dutch Association of Psychologists (https://www.psynip.nl/wp-content/uploads/2016/07/Handleiding-normen-Np-tests-2012.pdf). • Boston Naming Test: Heesbeen 2002 [23], adjusted for age and education. • Digit Span forward/backward, Vienna Test System, SDMT: Dutch normative data from official manuals. • Hayling: international normative data from official manual.
STROKDEM	Varied	• Verbal Fluency and Trail Making Test: Based on the work of Roussel and Godefroy,[24] z-scores were calculated by age and education group. Note that these scores were not adjusted for sex. • Rey Complex Figure Test: Expected scores for copy and immediate recall were computed using equations from Tremblay et al. [25] adjusted for sex, age, and education. Then, z-scores were computed from the expected scores.
USCOG	Varied	• Phonemic fluency, semantic fluency, and Rey Auditory Verbal Learning Test: Dutch population-based normative data adjusted for age, sex and level of education. Published in 2012 on website of The Dutch Association of Psychologists (https://www.psynip.nl/wp-content/uploads/2016/07/Handleiding-normen-Np-tests-2012.pdf). • Boston Naming Test: Heesbeen 2002 [23], adjusted for age and education. • Digit Span forward/backward and Token Test: Dutch normative data from official manuals, adjusted for age. • Token Test: Dutch normative data from official manuals, adjusted for age and IQ. • Rey Complex Figure Test: copy: normative data adjusted for age and education.[26] • Judgment of Line Orientation: normative data adjusted for age and education.[27]

Supplementary Table 4. Normative data for the Montreal Cognitive Assessment

Study	Country	Best available normative population	Calculation
CROMIS-2	United Kingdom (England)	Irish population from the The Irish Longitudinal Study on Ageing (TILDA) [28]: 5,802 individuals aged 50 and older representative of the community-dwelling population of Ireland, without known dementia, Parkinson's disease or severe cognitive impairment.	Age- and education adjusted cutoff scores were applied from The Irish Longitudinal Study on Ageing study [28]. To harmonize education level, education data was recoded from "school leaving age" and "higher education leaving age" (available for CROMIS-2) to three categories of "highest educational attainment" (TILDA): 1) primary or no education; 2) secondary education; 3) tertiary or higher education. The following calculations were used: <u>1) primary or no education completed</u> • Birth year <1934*: left school <14 years • Birth year ≥1934*: left school <15 years <u>2) secondary education completed*</u> • Birth year <1934*: left school ≥14 years + left higher education < 20 years • Birth year ≥1934*: left school ≥15 years + left higher education < 20 years <u>3) tertiary or higher education completed</u> • Left higher education ≥20 years
CU-STRIDE	Hong Kong	Local Hong Kong population [29]: 794 functionally independent and stroke- and dementia-free healthy controls aged ≥65 years. MRI was used to exclude people with significant brain pathology and medial temporal lobe atrophy.	Age- and education-adjusted percentile scores were derived from original study data from Wong et al. [29]
Mild Stroke Study 2	United Kingdom (Scotland)	Irish population from the The Irish Longitudinal Study on Ageing (TILDA) [28]: 5,802 individuals aged 50 and older representative of the community-dwelling population of Ireland, without known dementia, Parkinson's disease or severe cognitive impairment.	Age- and education adjusted cutoff scores were applied from The Irish Longitudinal Study on Ageing study [28]. To harmonize education level, education data was recoded from "years of education" (available for the Mild Stroke Study 2) to three categories of "highest educational attainment" (TILDA): 1) primary or no education; 2) secondary education; 3) tertiary or higher education. The following calculations were used: <u>1) primary or no education completed</u> • Birth year <1959**: education <10 years • Birth year ≥1959**: education <12 years <u>2) secondary education completed*</u> • Birth year <1959**: education ≥10 and <16 years • Birth year ≥1959**: education ≥12 and <16 years <u>3) tertiary or higher education completed</u> • Education ≥ 16 years For some of the Mild Stroke Study 2 subjects the highest educational attainment was recorded as an open field (e.g. "secondary school completed"); if available, this variable was used to make final adaptations to the categorization.

* The official school leaving age in England was 14 years before 1947, and 15 years from 1947 to 1976. ** The official school leaving age in Scotland was 14 years before 1973, and 16 years from 1973 onwards.

Supplementary Table 5. Overview of acute symptomatic infarct segmentation methods

Study name	Time point of imaging	Segmentation scan/sequence	Reference scan/sequence	Segmentation method	Software	Reference with details on MRI protocols
Infarct segmentation performed by the UMCU Utrecht (for Meta VCI Map pilot study or other projects)						
Bundang VCI	<1-2 weeks	DWI or FLAIR (if no DWI available)	T1, ADC, FLAIR (for DWI)	Manual segmentation by trained rater(s), and subsequent revision by a second rater. Acute infarcts were identified and segmented according to a published protocol.[4]	MeVisLab	Yu et al. 2013; Lim et al. 2014[7,8]
COAST	MRI: varied CT: >24 hours	DWI, T2, or CT (depending on availability)	MRI: varied CT: CT at hospital admission (<24h)		MeVisLab	Weaver et al. 2019[30]
CODECS	3 months	DWI, FLAIR, or CT (depending on availability)	MRI: varied CT: varied		MeVisLab	Weaver et al. 2019 [30]
Hallym VCI	<1-2 weeks	DWI or FLAIR (if no DWI available)	T1, ADC, FLAIR (for DWI)		MeVisLab	Yu et al. 2013; Lim et al. 2014[7,8]
PROCRAS	3-6 weeks	FLAIR	DWI, T1, T2		MeVisLab	Weaver et al. 2019[30]
USCOG	MRI: varied CT: >48 hours	FLAIR or CT	MRI: DWI, ADC; CT: CT at hospital admission (<24h)		MeVisLab	Biesbroek et al. 2014[18]
Infarct segmentation performed by individual participating centers						
CASPER	3 months	FLAIR	N/A	Manual segmentation by trained rater(s). Stroke location was determined by an experienced neurologist prior to segmentation.	FSL	Douven et al. 2020[31]
CROMIS-2	<2 weeks	DWI	T1, T2	Manual segmentation by a trained rater. Acute infarcts were identified and segmented according to a published protocol.[4]	ITK-SNAP	Wilson et al. 2018[11]
CU-STRIDE	<1 week	DWI or CT	MRI: T1, ADC CT: CT at hospital admission (<24h)	Manual segmentation by trained rater(s). Acute infarcts were defined as hyperintense DWI lesions with corresponding hypointense ADC signal, or hypodense lesions on CT that were relevant to the acute neurological signs and symptoms.	ITK-SNAP	Zhao et al. 2018[12]
GRECogVASC	6 months	T1	DWI, T2* and T1 from initial post-stroke MRI	Manual segmentation by trained investigators. Stroke lesion was defined as cavitation with a diameter >4mm, and no arguments for other causes	MRIcron	Puy et al. 2018[14]

				of cavitation (especially perivascular dilatation). Lesions were defined by reference to the initial poststroke MRI and especially the DWI and T2* sequences.		
Mild Stroke Study 2	<11 days	FLAIR	DWI, T2, T2*, T1	Manual segmentation by an experienced rater. The DWI sequence was used as a guidance to delineate the index stroke lesions on the FLAIR sequence. All stroke lesions (old and new) were delineated following the stroke classification and subtype given by the neuroradiologist.	Matlab	Wardlaw et al. 2017[15]
STROKDEM	3 days	DWI	T1	Semi-automated segmentation using the semi-automated tool using ITK-SNAP software described by Yushkevich et al. 2006.[32] B1000 images were reconstructed from the DTI acquisition. Infarcts were pre-segmented using an intensity threshold adapted for each patient. Then, seeds were placed on the lesion and an active contour algorithm was launched. The quality of the segmentation was checked and corrected manually if necessary.	ITK-SNAP	Bournonville et al. 2018[17]

Supplementary Table 6. Harmonisation of education level data: recoding of original education data into a 4-category variable

Study	**Original values used**	**Original value → STROKOG education category** [33] **1. Less than high school completion** **2. High school completion** **3. Technical or college diploma*** **4. University degree and above**
Bundang VCI	Years of education	<12 → 1 12 → 2 >=13 and <16 → 3 =>16 → 4
CASPER	Education is scored according to Dutch national categorization (Central Bureau of Statistics).	Study lead converted the original education variable into a 4-category variable as listed above.
COAST	Years of education	<10 → 1 =10 → 2 >=11 and <16 → 3 =>16 → 4
CODECS	Years of education	<10 → 1 =10 → 2 >=11 and <15 → 3 =>15 → 4
CROMIS-2	School leaving age & higher education leaving age	Birth year <1934*: left school <14 years → 1 Birth year ≥1934*: left school <15 years → 1 Birth year <1934*: left school ≥14 years + left higher education < 20 years → 2 Birth year ≥1934*: left school ≥15 years + left higher education < 20 years → 2 Left higher education ≥20 years → 4
CU-STRIDE	Years of education	<13 → 1 13 → 2 14-15 → 3 ≥16 → 4
GRECogVASC	NSC score	<12 → 1 12 → 2 >= 13 and <16 → 3 => 16 → 4
Hallym VCI	Years of education	<12 → 1 12 → 2 >=13 and <16 → 3 =>16 → 4
Mild Stroke Study 2	Years of education	Birth year <1959**: education <10 years → 1 Birth year ≥1959**: education <12 years → 1 Birth year <1959**: education ≥10 and <16 years → 2 Birth year ≥1959**: education ≥12 and <16 years → 2 Education ≥ 16 years → 4
PROCRAS	Verhage scale [34]	1-4 → 1 5 → 2 6 → 3 7 → 4
STROKDEM	NSC score	<12 → 1 12 → 2 >= 13 and <15 → 3 => 15 → 4
USCOG	Verhage scale [34]	1-4 → 1 5 → 2 6 → 3 7 → 4

* The official school leaving age in England was 14 years before 1947, and 15 years from 1947 to 1976. ** The official school leaving age in Scotland was 14 years before 1973, and 16 years from 1973 onwards.

Supplementary Table 7. Demographics and clinical characteristics of individual cohort and the total sample (extended table)

Characteristics	Bundang VCI (N=753)[7,8]	CASPER (N=104)[9]	COAST (N=74)[10]	CODECS (N=27)[30]	CROMIS-2 (N=97)[11]	CU-STRIDE (N=410)[12]	GRECogVASC (N=316)[14]	Hallym VCI (N=641)[7,8]	MSS-2 (N=100)[15]	PROCRAS (N=177)[16]	STROKDEM (N=138)[17]	USCOG (N=113)[18]	All studies (n = 2950)
Demographics													
Country of inclusion	Republic of Korea	NL	Singapore	NL	UK	Hong Kong	France	Republic of Korea	UK	NL	France	NL	
Ethnicity	Korean	Caucasian*	Singaporean Chinese (70%), Malay (22%), Indian (8%)	Caucasian	Caucasian**	Chinese	Caucasian	Korean	Caucasian	Caucasian	Caucasian	Caucasian	36% Caucasian; 47% Korean; 16% Chinese; 1% other
Age in years, mean (SD)	69.8 (10.8)	64.1 (10.8)	58.4 (10.5)	59.2 (16.5)	73.7 (9.2)	68.6 (10.4)	63.7 (10.6)	65.1 (11.9)	65.7 (11.5)	69.6 (9.4)	64.9 (12.1)	60.0 (14.9)	66.8 (11.6)
Female, n (%)	306 (40.6)	27 (26.0)	21 (28.4)	12 (44.4)	43 (44.3)	163 (39.8)	121 (38.3)	268 (41.8)	38 (38.0)	58 (32.8)	53 (38.4)	47 (41.6)	1157 (39.2)
Years of education, mean (SD)	9.6 (5.2)	N/A	6.8 (3.7)	13.4 (4.1)	N/A	6.0 (4.7)	10.4 (2.7)	9.2 (5.0)	12.2 (3.1)	N/A	11.5 (4.0)	N/A	9.2 (4.9)***
Education category[a], n (%)													
- Less than high school	402 (53.4)	42 (40.4)	52 (70.3)	8 (29.5)	6 (6.2)	381 (92.9)	233 (73.7)	351 (54.8)	19 (19.0)	79 (44.6)	86 (62.3)	44 (38.9)	1703 (57.7)
- High school	146 (19.4)	19 (18.3)	14 (18.9)	4 (14.8)	78 (80.4)	5 (1.2)	30 (9.5)	154 (24.0)	62 (62.0)	53 (29.9)	16 (11.6)	27 (23.9)	608 (20.6)
- Technical/college	37 (4.9)	35 (33.7)	7 (9.5)	5 (18.5)	N/A	8 (2.0)	35 (11.1)	31 (4.8)	N/A	39 (22.0)	11 (8.0)	26 (23.0)	234 (7.9)
- University or higher	168 (22.3)	8 (7.7)	1 (1.4)	10 (37.0)	13 (13.4)	16 (3.9)	18 (5.7)	105 (16.4)	19 (19.0)	6 (3.4)	25 (18.1)	16 (14.2)	405 (13.7)
Clinical characteristics													
NIHSS baseline, median (IQR)	3 (2-5)	N/A	3 (1-7)	0 (0)	3 (2-6)	4 (2-6)	3 (1-6)	2 (1-4)**	1 (0-2)	3 (2-4)	0 (0-1)	N/A	3 (1-5)***
IQCODE, median (IQR)	3.3 (3.1-3.7)**	3.1 (3.0-3.3)**	3.0 (3.0-3.1)	N/A	3.0 (3.0-3.3)	N/A	0% impaired	3.1 (3.0-3.3)***	N/A	3.0 (3.0-3.1)**	3.0 (3.0-3.1)	N/A	3.1 (3.0-3.4)***
Handedness, R / L / A, n	726 / 7 / 18*	95 / 6 / 3	N/A	20 / 5 / 0**	87 / 8 / 0**	380 / 7 / 7**	285 / 31 / 0	609 / 6/ 5**	89 / 11 / 0	167 / 6 / 4	64 / 10 / 0***	98 / 12 / 2*	2620/109 /39**
Cognitive assessment timing, n days after event, median (IQR)	104 (10-170)	87 (81-99)	121 (105-152)	90 (N/A)	4 (2-9)	154 (129-176)	178 (161-186)	98 (90-105)	142 (53-383)	35 (29-40)	189 (178-199)	6 (4-9)	105 (74-170)*
Medical history, n (%)													
Hypertension	175 (23.2)	80 (76.9)	56 (75.7)	15 (55.6)	54 (56.3)*	305 (74.4)	185 (58.5)	385 (60.2)*	76 (76.0)	132 (74.6)	76 (55.1)	20 (38.5)***	1962 (68.0)**
Hyperlipidemia	201 (26.7)	88 (84.6)	59 (79.7)	9 (33.3)	48 (50.0)*	242 (59.0)	136 (43.0)	246 (38.9)**	64 (64.0)	167 (94.4)	60 (43.5)	12 (23.1)***	1332 (46.3)**
Diabetes mellitus	246 (32.7)	14 (13.5)	36 (48.6)	7 (25.9)	11 (11.5)*	151 (36.8)	66 (20.9)	195 (30.5)*	12 (13.3)*	52 (29.4)	18 (13.0)	6 (10.7)***	814 (28.3)**
Smoking (past or present)	307 (40.8)	79 (76.0)	26 (35.1)	7 (25.9)	53 (54.6)*	175 (42.7)	133 (42.1)	24 (38.3)**	61 (61.0)	122 (68.9)	31 (22.5)	28 (57.1)***	1267 (44.5)**
Obesity[b]	250 (33.4)*	N/A	N/A	4 (14.8)	N/A	89 (27.7)***	216 (68.4)*	219 (35.8)**	N/A	46 (26.1)*	35 (25.4)	N/A	859 (36.8)***
Atrial fibrillation	134 (19.7)**	N/A	7 (9.5)	N/A	97 (100)	80 (19.5)	36 (11.4)	66 (10.3)**	N/A	32 (18.2)*	N/A	N/A	452 (19.0)***
Coronary heart disease	59 (8.0)	N/A	18 (24.3)	N/A	8 (8.2)	47 (11.5)	25 (7.9)	32 (5.1)**	8 (8.0)	N/A	13 (9.4)	N/A	210 (8.7)***
Peripheral arterial disease	7 (0.9)*	N/A	2 (2.7)	N/A	1 (1.1)**	N/A	N/A	2 (0.3)**	N/A	N/A	4 (2.9)	N/A	16 (1.0)***
History of stroke	104 (13.8)	5 (4.8)	10 (13.5)[c]	0 (0.0)	6 (6.2)*	50 (12.2)	22 (7.0)	85 (13.5)**	10 (10.0)	23 (13.0)	12 (8.7)	0 (0.0)	327 (11.1)*
History of TIA	15 (2.0)	2 (1.9)	N/A[c]	0 (0.0)	9 (9.3)	6 (1.7)	N/A	5 (0.9)**	8 (8.0)	23 (13.0)	7 (5.1)	19 (17.3)**	94 (3.2)***
Brain imaging													
Scan sequence/modality used for infarct segmentation	DWI (97%), FLAIR (3%)	FLAIR	DWI (41%), T2 (5%), CT (54%)	DWI (19%), FLAIR (63%), CT (19%)	DWI	DWI (75%), CT (25%)	T1	DWI (98%), FLAIR (2%)	FLAIR	FLAIR	DWI	FLAIR (34%), CT (66%)	DWI (66%), T2/FLAIR (16%), CT (8%), T1 (11%)

Normalized acute infarct volume in ml, median (IQR)	3.8 (1.2-16.5)	3.4 (0.9-13.2)	6.8 (2.0-32.6)	10.3 (1.1-26.2)	4.5 (1.5-16.1)	2.3 (0.9-12.9)	1.3 (0.3-5.7)	2.0 (0.9-11.3)	2.6 (1.2-11.3)	4.4 (1.3-21.0)	1.6 (0.6-8.6)	19.6 (3.5-51.9)	2.7 (1.0-14.1)
Imaging timing, n days after event, median (IQR)	5 (4-6)	87 (81-99)	2 (1-4)	34 (5-98)**	5 (3-9)	1 (0-2)	178 (161-186)	1 (1-2)	4 (2-9)	33 (27-40)	3 (3-3)	5 (3-8)	4 (1-9)*

* Missing in <1%; ** Missing in 1-10%; *** Missing in >10%; [a] Education categories defined by the STROKOG consortium[33]; categorization per cohort is shown in Supplementary Table 6. [b] Body Mass Index for obesity differed between countries, local definitions were followed. [c] Combined variable for stroke and/or TIA. Abbreviations: CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; IQR, interquartile range; NL, the Netherlands; SD, standard deviation; TIA, transient ischemic attack; UK, United Kingdom.

Supplementary Table 8. Logistic regression model for continuous location impact score (N=2950)

Variable	Continuous location impact score	
	Odds ratio	**95% confidence interval**
Age (years)	1.00	1.00-1.01
Female sex	1.03	0.88-1.2
Education category (reference = less than high school)		
- High school completion	0.67	0.54-0.82***
- Technical/college completion	1.02	0.76-1.37
- University or higher	1.03	0.82-1.31
Clinical history of stroke	1.34	1.06-1.71*
Interval stroke – cognitive assessment (days)	0.998	0.997-0.999***
Total infarct volume (mL)	1.01	1.01-1.02***
Location impact score - continuous (range: -1.3 to 2.4)	2.15	1.87-2.47***

Supplementary Table 9. Logistic regression model for five-point location impact score (N=2950)

Variable	Five-point location impact score	
	Odds ratio	**95% confidence interval**
Age (years)	1.00	1.00-1.01
Female sex	1.03	0.87-1.21
Education category (reference = less than high school)		
- High school completion	0.67	0.54-0.82***
- Technical/college completion	1.02	0.76-1.37
- University or higher	1.04	0.82-1.31
Clinical history of stroke	1.39	1.06-1.71**
Interval stroke – cognitive assessment (days)	0.998	0.997-0.999***
Total infarct volume (mL)	1.01	1.01-1.02***
Location impact score -five-point (reference = 1)		
2 (20-40th percentile)	1.33	1.04-1.70*
3 (40-60th percentile)	1.33	1.04-1.70*
4 (60-80th percentile)	1.82	1.42-2.32***
5 (80-100th percentile)	3.87	3.02-4.97***

Logistic regression models were built to explore whether the location impact score (continuous and categorized) was an independent predictor of post-stroke cognitive impairment (PSCI), before using this score for predictive modeling. Statistically significant variables are indicated with an asterix: *p<0.05; **p<0.01; ***p<0.001.

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