Cognitive performance following stroke, transient ischaemic attack, myocardial infarction, and hospitalisation

Cognitive performance following stroke, transient ischaemic attack, myocardial infarction, and hospitalisation: an individual participant data meta-analysis of six randomised controlled trials

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Summary

Background Survivors of stroke are often concerned about cognitive problems, and information on the risk of cognitive problems often comes from small studies. We aimed to estimate years of cognitive ageing associated with stroke compared with transient ischaemic attack, myocardial infarction, and other hospitalisations in a large population.

Methods Using data from six randomised controlled trials (ORIGIN, ONTARGET, TRANSCEND, COMPASS, HOPE-3, and NAVIGATE ESUS), we completed an individual participant data meta-analysis using data requested from the Public Health Research Institute to estimate the association of stroke (by type and severity), transient ischaemic attack, myocardial infarction, and other hospitalisations with cognitive performance measured at the end of each trial. We included participants in any of these randomised controlled trials with a cognitive assessment at baseline and at least one other timepoint. Cognitive performance was measured with the Mini-Mental State Examination or the Montreal Cognitive Assessment, transformed into Z scores. We estimated Z score differences in end of trial cognitive performance between people with and without events and calculated corresponding years of cognitive ageing in these trials, and additionally calculated using a population representative cohort—the Cognitive Function and Ageing Study.

Findings In 64 106 participants from 55 countries, compared with no event, stroke was associated with 18 years of cognitive ageing (1487 strokes included in the model, 95% CI 10 to 28; p<0·0001) and transient ischaemic attack with 3 years (660 transient ischaemic attacks included in the model, 0 to 6; p=0·021). Myocardial infarction (p=0·60) and other hospitalisations (p=0·26) were not associated with cognitive ageing. The mean difference in SD compared with people without an event was –0·84 (95% CI –0·91 to –0·76; p<0·0001) for disabling stroke, and –0·12 (–0·19 to –0·05; p=0·0012) for non-disabling stroke. Haemorrhagic stroke was associated with worse cognition (–0·75, –0·95 to –0·55; p<0·0001) than ischaemic stroke (–0·42, –0·48 to –0·36; p<0·0001).

Interpretation Stroke has a substantial effect on cognition. The effects of transient ischaemic attack were small, whereas myocardial infarction and hospitalisation had a neutral effect. Prevention of stroke could lead to a reduction in cognitive ageing in those at greatest risk.

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See **Comment** page e653

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Introduction

Maintaining cognitive function is a priority for people affected by stroke.[1] People with stroke have twice the risk of subsequent cognitive impairment or dementia compared with those without stroke.[2] In some cohorts, more than one-third of participants experience post-stroke dementia,[3] with a similar proportion experiencing some cognitive impairment that does not reach a dementia threshold.[4]

Existing data on post-stroke cognitive impairment has several limitations. First, most studies recruited participants after stroke, and did not measure pre-stroke cognitive performance (also known as cognitive reserve). Cognitive impairment is associated with an increased risk of stroke[5] and approximately 9% of people with stroke have dementia before their stroke;[3] therefore, some of the estimated effect of stroke on dementia risk could be due to previous cognitive impairment. Second, hospitalisation, which often occurs after stroke, could independently affect cognition.[6] Third, most studies have been performed within one country, hence the international generalisability of existing data is unclear. Finally, controlling for other factors that could influence post-stroke cognition (eg, vascular risk factors and cognitive reserve[7]) is important, but sometimes not measured systematically.

To overcome these limitations, we aimed to estimate the effect of stroke on cognitive test performance in an

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Research in context

Evidence before this study

We searched PubMed on March 23, 2022, using the terms ("dementia" OR "cognition" OR "cognitive") AND ("stroke"). We searched for studies and systematic reviews published from Jan 1, 1952 to March 23, 2022, with no language restrictions, and found 65 relevant publications. In 2018, a systematic review reported that incident stroke doubled dementia risk (relative risk 2·18, 95% CI 1·90–2·50). However, of the 46 studies included, only four studies accounted for pre-stroke cognitive performance, and only one study completed a subgroup analysis by pre-stroke cognitive status (mild cognitive impairment *vs* no mild cognitive impairment). A 2007 systematic review of post-stroke memory dysfunction in patients with no dementia found that 31% of participants had memory problems one year after stroke; however, not one of the 65 studies that were included in the systematic review accounted for pre-stroke cognitive ability. Of the four studies we identified which had controlled for pre-stroke cognitive performance (The Rotterdam study, the Reasons for Geographic and Racial Differences in Stroke [REGARDS] study, the Health Retirement Study [HRS], and the Swedish Military Service Conscription Register), all four found that participants had poorer cognition post-stroke.

Added value of this study

In this pooled analysis of data from six large randomised controlled trials of vascular interventions, stroke was associated with 18 years of cognitive ageing, and had a greater effect than transient ischaemic attack, myocardial infarction, or other hospitalisations. We found poorer cognitive performance with increasing stroke severity, particularly for individuals with haemorrhagic stroke compared with ischaemic stroke, and in participants with the poorest cognitive performance pre-stroke.

Implications of all the available evidence

The prevention of severe stroke and, to a lesser extent, transient ischaemic attack, could reduce cognitive ageing in people with a high risk of stroke. The prevention of myocardial infarction is less likely to affect cognitive ageing.

See Online for appendix

individual-level participant meta-analysis of six large international randomised controlled trials conducted by the Public Health Research Institute, Canada. These trials included participants with cognitive measures before and after their stroke, had centres in 55 countries, with systematic measurement of important pre-stroke variables, and allowed for calculation of the effect of events on cognition independent of stroke, such as transient ischaemic attack, myocardial infarction, or hospitalisation. We estimated the years of cognitive ageing associated with stroke and compared these with the years of cognitive ageing attributable to transient ischaemic attack, myocardial infarction, and hospitalisation. We further estimated the effect of strokes of different types and severities on cognitive performance.

Methods

Search strategy and selection criteria

We conducted an individual participant data meta-analysis of observational data from randomised controlled trials. Our study complies with STROBE cohort reporting guidelines.[8]

We used data from six randomised controlled trials of vascular risk interventions conducted by the Public Health Research Institute: Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS),[9] Heart Outcomes Prevention Evaluation-3 (HOPE-3),[10] New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS),[11] Outcome Reduction With Initial Glargine Intervention (ORIGIN),[12] Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),[13] and Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND; appendix p 3).[14] As TRANSCEND recruited participants meeting the ONTARGET inclusion criteria but who were intolerant to ACE inhibitors, we considered ONTARGET and TRANSCEND as one dataset. We excluded HOPE-3 participants younger than 70 years as these participants did not complete cognitive assessments. We included participants in any of these randomised controlled trials with a cognitive assessment at baseline and at least one other timepoint.

We used data from the Medical Research Council Cognitive Function and Ageing Studies study (version 4 of the data; n=13 004)[15] to calculate years of cognitive ageing in a population representative cohort as a sensitivity analysis.

To measure cognitive performance, ORIGIN, ONTARGET, and TRANSCEND used the Mini-Mental State Examination,[16] and COMPASS, HOPE-3, and NAVIGATE ESUS used the Montreal Cognitive Assessment.[17] A shortened version of the Montreal Cognitive Assessment was administered to participants in HOPE-3 with a maximum possible score of 12, which we normalised to a scale of 0–30. A paper version of the cognitive test (Mini-Mental State Examination or Montreal Cognitive Assessment) was administered in person by site staff for all trials at varying times of administration (appendix p 3).

Mini-Mental State Examination and Montreal Cognitive Assessment scores were standardised to Z scores based on the trial-specific baseline scores, giving a mean of 0 and SD of 1 for each trial. We used participants' final cognitive Z score (from their last available assessment) as the outcome cognitive test performance. We pooled the Z scores across the Mini-Mental State Examination and Montreal Cognitive Assessment given previous evidence

that these Z scores are comparable by age.[18] In this study, we showed that the association between age and Z scores for the Mini-Mental State Examination and Montreal Cognitive Assessment were comparable across the two different assessments.

We calculated associated years of cognitive ageing by dividing cognitive Z score mean differences by the slope of the relationship between age and cognitive Z scores (ie, the rate of cognitive Z score decline per 1 year of age).[19]

As an exploratory outcome, we used country-specific baseline standardised Z scores to account for country-level variation in performance on cognitive assessments due to cultural and regional difference, as opposed to cognitive performance.[20] We further used a dichotomous outcome of the end of trial significant cognitive impairment, which was defined as having a Mini-Mental State Examination score of less than 24 or a Montreal Cognitive Assessment score of less than 26.[16,17]

We used the original trial definitions of stroke, transient ischaemic attack, myocardial infarction, and hospitalisation, which were similar. A post-stroke modified Rankin Scale score ranged between 0 and 6 was obtained in each trial by study investigators or, in the case of NAVIGATE ESUS, it was measured at 7 days post-stroke or at hospital discharge if discharged before 7 days. We defined non-disabling stroke as a modified Rankin Scale score that ranged between 0 and 2 and disabling stroke as a modified Rankin Scale score between 3 and 5. We analysed participants in categories of event versus everyone else, with the events divided into mutually exclusive categories of the first occurrence of: any stroke; any transient ischaemic attack; any myocardial infarction; any non-myocardial infarction, non-transient ischaemic attack or non-stroke hospitalisation with no subsequent hospitalisation for stroke, transient ischaemic attack, or myocardial infarction. Participants who had both a stroke and transient ischaemic attack (n=83) or stroke and myocardial infarction (n=87) were classified as having had a stroke only. Participants who had both a transient ischaemic attack and myocardial infarction were classified as having had transient ischaemic attack only (n=36). Any stroke, transient ischaemic attack, myocardial infarction, or hospitalisation that occurred after the participants' final cognitive assessment was excluded.

Potential confounders at baseline were: age, sex, cognitive score, education, BMI, current smoker, hypertension, diabetes, previous stroke, myocardial infarction, or transient ischaemic attack. We considered the same confounders across all randomised controlled trials.

Subgroups were analysed by age (51–60 years, 61–70 years, and 71–80 years), sex, baseline cognitive score (thirds based on the baseline cognitive Z scores), stroke type (haemorrhagic, ischaemic, and unknown or uncertain), stroke severity (disabling, non-disabling, and unknown or uncertain), and each modified Rankin Scale score (0–5).

Data analysis

We used linear regression to estimate the rate of cognitive Z score decline per 1 year of age in participants aged between 50 years and 80 years, excluding anyone who had a vascular event, adjusted for the confounders listed earlier, which was done using data pooled across the randomised controlled trials.

For comparison, we estimated the rate of cognitive Z score decline per 1 year of age in the Cognitive Function and Ageing Studies adjusting for sex and education, in the age range of 65 years (lower age limit of the Cognitive Function and Ageing Studies) to 80 years.

We used a two-step individual participant data meta-analysis for our primary analysis. In the first step, we used linear regression to estimate the effect of the events (stroke, transient ischaemic attack, myocardial infarction, or hospitalisation) on the final visit cognitive Z scores adjusted for baseline cognition. We ran models for each trial separately, with models unadjusted and adjusted for the additional confounders listed earlier. In the second step, we summarised the effects of events on cognitive performance across trials with an inverse variance-weighted random effects meta-analysis on the maximally adjusted event-cognition models. We estimated the years of cognitive ageing associated with each event by dividing the Z score estimates by the slope of the relationship between age and cognitive performance in those aged 50–80 years across our trials (appendix p 4).

We looked for interactions between our events and age, sex, and baseline cognition. We conducted subgroup analysis by age, sex, baseline cognition, stroke type, and stroke severity, with mixed effects linear models with a random intercept for trial.

We examined the effects of using mixed effects regression models for data pooled across trials, using each of the events (stroke, transient ischaemic attack, myocardial infarction, and hospitalisation) as the exposure, with fixed effects for covariates and random effects for trial, in comparison to the meta-analysis used as our primary analysis. We also evaluated the effect of time from the event to the final cognitive assessment on the Z scores, using mixed effects regressions for each of the events. We used mixed effects logistic regression to explore the association between each of the events with end of trial cognitive impairment (Mini-Mental State Examination <24 and Montreal Cognitive Assessment <26), adjusting for confounders. Finally, we used country-standardised rather than trial-standardised Z scores.

The mean differences (95% CI) were reported for continuous outcomes and the odds ratios (ORs; 95% CI) were reported for binary outcomes. Statistical analyses were performed in R (version 4.0.4).

Ethical approval was obtained for the original trials: HOPE-3 (NCT00468923), COMPASS (NCT01776424), NAVIGATE ESUS (NCT02313909), ORIGIN (NCT00069784), and ONTARGET and TRANSCEND

(NCT00153101 for both trials) and all participants provided written informed consent. Ethics for the Medical Research Council Cognitive Function and Ageing Studies were from the Eastern Multi-centre Research Ethics Committee (reference: 05/MRE05/37).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 81777 participants randomised into these six randomly assigned controlled trials, we excluded 17671 participants for missing either the baseline assessment or final cognitive assessment, leaving 64106 participants from 55 countries for analysis (appendix p 5). At baseline, participants had a mean age of 67 years (SD 7·9), 18597 (29·0%) of 64106 participants were female, 26483 (41·3%) participants had more than 12 years of education, 10089 (15·7%) participants were current smokers, mean BMI was 28 (SD 4·8), 6338 (9·9%) participants had a history of previous stroke, 1592 (2·5%) participants had previous transient ischaemic attack, and 30026 (46·8%) participants had previous myocardial infarction (table 1).

During follow-up (median 4·4 years [IQR 1·9–5·2]), 22862 (35·7%) of 64106 participants had an event and a post-event cognitive assessment: 1495 (6·5%) strokes of 22862 participants, 667 (2·9%) transient ischaemic attacks, 1657 (7·2%) myocardial infarctions, and 19043 (83·3%) other hospitalisations. Of the participants who had a stroke, 656 (43·9%) of 1495 participants were disabling, 827 (55·3%) participants non-disabling, and 12 (0·8%) participants were of unknown severity (table 2). Most strokes were ischaemic (n=1267 [84·7%]),

	COMPASS (n=23176)	HOPE-3 (n=1970)	NAVIGATE ESUS (n=4547)	ONTARGET and TRANSCEND (n=23924)	ORIGIN (n=10489)	Total (N=64106)
Sex						
Female	5003 (21·6%)	1168 (59·3%)	1685 (37·1%)	6992 (29·2%)	3749 (35·7%)	18597 (29·0%)
Male	18173 (78·4%)	802 (40·7%)	2862 (62·9%)	16932 (70·8%)	6740 (64·3%)	45509 (71·0%)
Age	68 (7·8)	74 (3·6)	67 (9·9)	66 (7·0)	63 (7·6)	67 (7·9)
Education (>12 years)	10849 (46·8%)	371 (18·8%)	2171 (47·7%)	9055 (37·8%)	4037 (38·5%)	26483 (41·3%)
Current smoker	4960 (21·4%)	237 (12·0%)	936 (20·6%)	2727 (11·4%)	1229 (11·7%)	10089 (15·7%)
BMI	28 (4·7)	26 (4·8)	27 (5·1)	28 (4·5)	30 (5·2)	28 (4·8)
Baseline medical history						
Stroke	805 (3·5%)	0	583 (12·8%)	3690 (15·4%)	1260 (12·0%)	6338 (9·9%)
Transient ischaemic attack	518 (2·2%)	0	233 (5·1%)	841 (3·5%)	NA	1592 (2·5%)
Myocardial infarction	14573 (62·9%)	0	172 (3·8%)	11640 (48·7%)	3641 (34·7%)	30026 (46·8%)
Heart failure	4983 (21·5%)	0	138 (3·0%)	0	NA	5121 (8·0%)
Angina	10642 (45·9%)	0	NA	10933 (45·7%)	3736 (35·6%)	25311 (39·5%)
Hypertension	17378 (75·0%)	852 (43·2%)	3492 (76·8%)	16615 (69·4%)	8292 (79·1%)	46629 (72·7%)
Atrial fibrillation	NA	0	0	658 (2·8%)	282 (2·7%)	940 (1·5%)
Diabetes	8564 (37·0%)	110 (5·6%)	1074 (23·6%)	8553 (35·8%)	8605 (82·0%)	26906 (42·0%)
Cardiovascular risk factors*						
0	2284 (9·9%)	299 (15·2%)	579 (12·7%)	2550 (10·7%)	197 (1·9%)	5909 (9·2%)
1	6954 (30·0%)	798 (40·5%)	1950 (42·9%)	6524 (27·3%)	1300 (12·4%)	17526 (27·3%)
2	7809 (33·7%)	641 (32·5%)	1488 (32·7%)	7895 (33·0%)	3339 (31·8%)	21172 (33·0%)
≥3	6129 (26·4%)	232 (11·8%)	530 (11·7%)	6955 (29·1%)	5653 (53·9%)	19499 (30·4%)
Cardiovascular disease†						
0	896 (3·9%)	1970 (100%)	3502 (77·0%)	2968 (12·4%)	3597 (34·3%)	12933 (20·2%)
1	11111 (47·9%)	0	898 (19·7%)	13105 (54·8%)	5010 (47·8%)	30124 (47·0%)
2	7689 (33·2%)	0	130 (2·9%)	6830 (28·5%)	1752 (16·7%)	16401 (25·6%)
≥3	3480 (15·0%)	0	17 (0·4%)	1021 (4·3%)	130 (1·2%)	4648 (7·3%)
Follow up time, years	1·9 (1·4–2·5)	5·7 (5·2–6·4)	1·2 (0·8–1·6)	4·9 (4·4–5·0)	6·2 (5·9–6·8)	4·4 (1·9–5·2)

Data are n (%), median (IQR), or mean (SD). COMPASS=Cardiovascular Outcomes for People Using Anticoagulation Strategies. HOPE-3=Heart Outcomes Prevention Evaluation. NA=not applicable. NAVIGATE ESUS=New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source. ONTARGET=Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial. TRANSCEND=Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. ORIGIN=Outcome Reduction with an Initial Glargine Intervention. *Defined as having hypertension, diabetes, being a current smoker, elevated cholesterol, or obesity at baseline. †Defined as having had at least one episode of transient ischaemic attack, stroke, myocardial infarction, angina, peripheral artery disease, or heart failure before baseline.

Table 1: **Baseline characteristics of individuals with a baseline and follow-up cognitive assessment by trial**

95 (6·4%) were haemorrhagic, and 133 (8·9%) were of unknown or uncertain type (table 2).

The mean (SD) Mini-Mental State Examination score in participants was 27·4 (SD 3·1) at baseline and 25·5 (5·2) at follow-up in individuals with a stroke, compared with 27·8 (2·8) at baseline and 27·6 (3·3) at follow-up in those without a stroke. The mean (SD) Montreal Cognitive Assessment score in participants with a stroke was 23·6 (4·7) at baseline and 22·6 (6·2) at follow-up, compared with 24·6 (4·1) at baseline and 24·4 (4·3) at follow-up in those without a stroke. Participants with stroke were more likely to have no final cognitive assessment (1288 [46%] of 2783) compared with those without stroke (16 383 (21%) of 78 994). The reasons for missing a final cognitive assessment in stroke participants were death (764 [59%] of 1288), disability (311 [24%]), and unknown reasons (213 [17%]; figure 1; appendix p 5).

When examining the association between age and cognitive performance, the cognitive Z scores of participants between the ages of 50 years and 80 years decreased by a mean difference of 0·025 SD per year of ageing (95% CI –0·026 to –0·024; p<0·0001). A linear model provided an adequate fit to the data. Changes were similar for the Montreal Cognitive Assessment (0·027 SD per year) and Mini-Mental State Examination (0·025 SD per year). Changes were similar in studies recruiting only people with stroke (NAVIGATE ESUS: –0·021 SD), those with stroke and other cardiovascular diseases (ORIGIN, ONTARGET, TRANSCEND, and COMPASS: –0·024 SD), and those with no cardiovascular diseases at study entry (HOPE-3; –0·031 SD). Z score mean differences with ageing were similar in the Medical Research Council Cognitive Function and Ageing Studies (–0·032 SD, 95% CI –0·035 to –0·030; p<0·0001).

When looking at the association between in-trial stroke and post-stroke cognitive performance, after adjustment for baseline cognition and additional confounders listed earlier, stroke compared with no stroke was associated with a Z score difference of –0·46 SD (95% CI –0·69 to –0·24; p<0·0001), corresponding to 18 years (95% CI 10 to 28; p<0·0001) of cognitive ageing, with significant heterogeneity between trials (I^2=93·5%; figure 2). However, differences in cognitive performance between trials attenuated after adjustment for stroke severity. The Z score difference for stroke versus no stroke was –0·12 SD (95% CI –0·19 to –0·05; p=0·0012)

	COMPASS (n=23 176)	HOPE-3 (n=1970)	NAVIGATE ESUS (n=4547)	ONTARGET and TRANSCEND (n=23 924)	ORIGIN (n=10 489)	Total (N=64 106)
Any event*	5671 (24·5%)	373 (18·9%)	836 (18·4%)	10 705 (44·7%)	5277 (50·3%)	22 862 (35·7%)
Stroke	182/5671 (3·2%)	16/373 (4·3%)	180/836 (21·5%)	741/10 705 (6·9%)	376/5277 (7·1%)	1495/22 862 (5·2%)
Transient ischaemic attack	82/5671 (1·4%)	11/373 (2·9%)	48 180/836 (5·7%)	516/10 705 (4·8%)	10/5277 (0·2%)	667/22 862 (2·3%)
Myocardial infarction	369/5671 (6·5%)	23/373 (6·2%)	17 180/836 (2·0%)	828/10 705 (7·7%)	420/5277 (8·0%)	1657/22 862 (5·7%)
Hospitalisation only	5038/5671 (88·8%)	323/373 (86·6%)	591 180/836 (70·7%)	8620/10 705 (80·5%)	4471/5277 (84·7%)	19 043/22 862 (66·0%)
Time from event to final assessment, weeks	46 (24–74)	129 (69–210)	31 (16–53)	90 (39–150)	110 (46–210)	73 (32–140)
Incidence of event per 1000 person-years†						
Stroke	4·0	1·4	32·3	6·5	5·7	6·2
Transient ischaemic attack	1·9	1·0	9·7	5·1	0·2	3·1
Myocardial infarction	8·4	2·0	3·8	7·9	6·8	7·3
Hospitalisation	125·0	32·2	144·3	92·4	79·9	93·4
Stroke subtype						
Haemorrhagic stroke	20/182 (11%)	1/16 (6·2%)	8/180 (4·4%)	38/741 (5·1%)	28/376 (7·4%)	95/1495 (6·4%)
Ischaemic stroke	157/182 (86·2%)	13/16 (81·3%)	171/180 (95·0%)	613/741 (82·7%)	313/376 (83·2%)	1267/1495 (84·7%)
Unknown, uncertain, or other	5/182 (2·7%)	2/16 (12·5%)	1/180 (0·6%)	90/741 (12·1%)	35/376 (9·3%)	133/1495 (8·9%)
Stroke severity						
Non-disabling stroke	141/182 (77·5%)	10/16 (62·5%)	138/180 (76·7%)	350/741(47·2%)	188/376 (50·0%)	827/1495 (55·3%)
Disabling stroke	41/182 (22·5%)	4/16 (25·0%)	35/180 (19·4%)	390/741 (52·6%)	186/376 (49·5%)	656/1495 (43·9%)
Unknown or uncertain stroke severity	0	2/16 (12·5%)	7/180 (3·9%)	1/741 (<1%)	2/376 (1%)	12/1495 (1%)

Data are n (%) or median (IQR). COMPASS=Cardiovascular Outcomes for People Using Anticoagulation Strategies. HOPE-3=Heart Outcomes Prevention Evaluation. NAVIGATE ESUS=New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source. ONTARGET=Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial. TRANSCEND=Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. ORIGIN=Outcome Reduction with an Initial Glargine Intervention. *We analysed participants in groups of event versus everyone else, with the events divided into mutually exclusive categories of any stroke, any transient ischaemic attack, any myocardial infarction, or any non-myocardial infarction, non-stroke, non-transient ischaemic attack hospitalisation with no subsequent hospitalisation for stroke, transient ischaemic attack or myocardial infarction. Participants who had both a stroke and a transient ischaemic attack or myocardial infarction were classified as having had a stroke only. Participants who had both a transient ischaemic attack and myocardial infarction were classified as transient ischaemic attack only. The total (N) shown are counts of participants who have had one or more event. Time from event to final assessment is the time from the event until the cognitive examination following the event. †Only the first events of each event type are counted, but multiple event types are counted per person (eg, someone who had a myocardial infarction and stroke during the trial is counted for both categories). Calculated as number of events divided by the total number of follow-up years multiplied by 1000.

Table 2: **Event characteristics of individuals with a baseline and follow-up cognitive assessment**

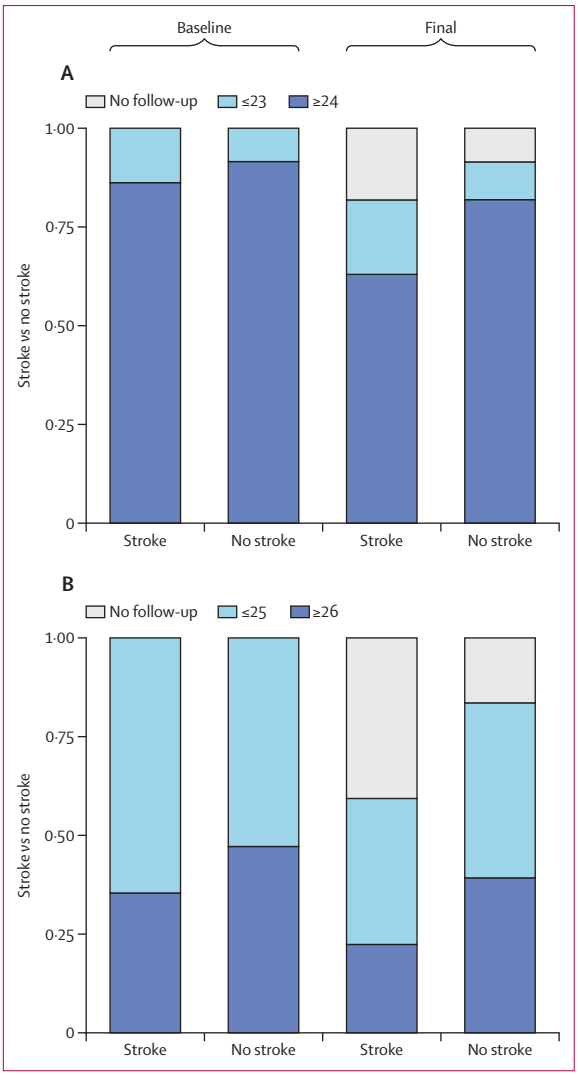

Figure 1: **Mini-Mental State Examination (A) and Montreal Cognitive Assessment (B) for participants with stroke versus no stroke, at baseline and follow-up assessments**
Cognitive scores of 23 or below (Mini-Mental State Examination score) and 25 or below (Montreal Cognitive Assessment) were predefined thresholds for cognitive impairment.

for non-disabling stroke, and –0·84 SD (–0·91 to –0·76; p<0·0001) for disabling stroke; levels of the modified Rankin Scale also showed a trend to greater Z score difference with greater stroke severity (p_{trend}<0·0001; figure 3). Compared with no stroke, the Z score difference was –0·75 SD (95% CI –0·95 to –0·55; p<0·0001) for haemorrhagic stroke and –0·42 SD (–0·48 to –0·36; p<0·0001) for ischaemic stroke. For both stroke types, this difference attenuated after adjusting for stroke severity (haemorrhagic –0·41; 95% CI –0·21 to –0·62 SD; ischaemic –0·11; –0·04 to –0·18 SD). The Z score difference for any stroke compared with no stroke was greatest in people with the lowest baseline cognition (those with a Montreal Cognitive Assessment <24 or Mini-Mental State Examination <26; ($p_{interaction}$<0·0001), although did not differ by age or sex (figure 3).

After adjustment for baseline cognition and other covariates, the Z score difference compared with no event was –0·08 (95% CI –0·01 to 0·16; p=0·021; I^2=0·0%) for transient ischaemic attack, corresponding to 3 years of cognitive ageing, 0·02 (–0·04 to 0·07; p=0·60; I^2=24·2%) for myocardial infarction, and –0·02 (–0·07 to 0·02; p=0·26; I^2=80·5%) for other hospitalisation (figure 2). In the sensitivity analyses, using a mixed effects regression model did not change our primary results. The OR for the association of events with end of trial cognitive impairment (Mini-Mental State Examination <24 or Montreal Cognitive Assessment <26) was 2·21 (95% CI 1·93 to 2·53; p<0·0001) for any stroke, 1·92 (95% CI 1·65 to 2·24; p<0·0001) for ischaemic stroke, 2·69 (95% CI 1·64 to 4·41; p<0·0001) for haemorrhagic stroke, 3·47 (95% CI 2·87 to 4·22; p<0·0001) for disabling stroke, 1·22 (95% CI 1·00 to 1·48; p=0·05) for non-disabling stroke, 1·12 (95% CI 0·89 to 1·41; p=0·33) for transient ischaemic attack, 1·01 (95% CI 0·87 to 1·18; p=0·85) for myocardial infarction, and 1·04 (95% CI 0·98 to 1·09; p=0·18) for hospitalisation. Duration of time between an event and measurement of cognition was not associated with the final cognitive performance. Estimates of cognitive ageing with the Medical Research Council Cognitive Function and Ageing Studies led to similar estimates of the years of cognitive ageing associated with stroke. Using country-standardised Z scores did not alter the results. Finally, adding treatment as a covariate to the event-cognition models did not lead to different results.

Discussion

In this individual-level meta-analysis of six randomised controlled trials of vascular risk interventions, participants with stroke during follow-up had significantly poorer cognitive performance than those who had a transient ischaemic attack, myocardial infarction, or hospitalisation. The effect of stroke was similar by age and sex, but greater in people with worse pre-stroke cognition or more severe or haemorrhagic stroke.

Few studies of post-stroke cognition[2–4,21] have controlled for pre-stroke cognitive performance. In four studies that controlled for pre-stroke cognitive performance, participants had poorer cognition post-stroke (appendix p 6).[22–25] None of these studies stratified results by stroke severity, and only the REGARDS study[22] reported data by stroke type (ischaemic or haemorrhagic). Similar to our findings, the ARIC study found increasing risk of dementia with increased stroke severity.[26] One previous study found that stroke led to 7 years of cognitive ageing, although the effect of age on cognitive performance in that study was larger than in the population based Medical Research Council Cognitive Function and Ageing Studies.[19] The differences could be explained by the distributions of stroke severities (or types) across studies, as we found that severity explained the heterogeneity in stroke estimates.

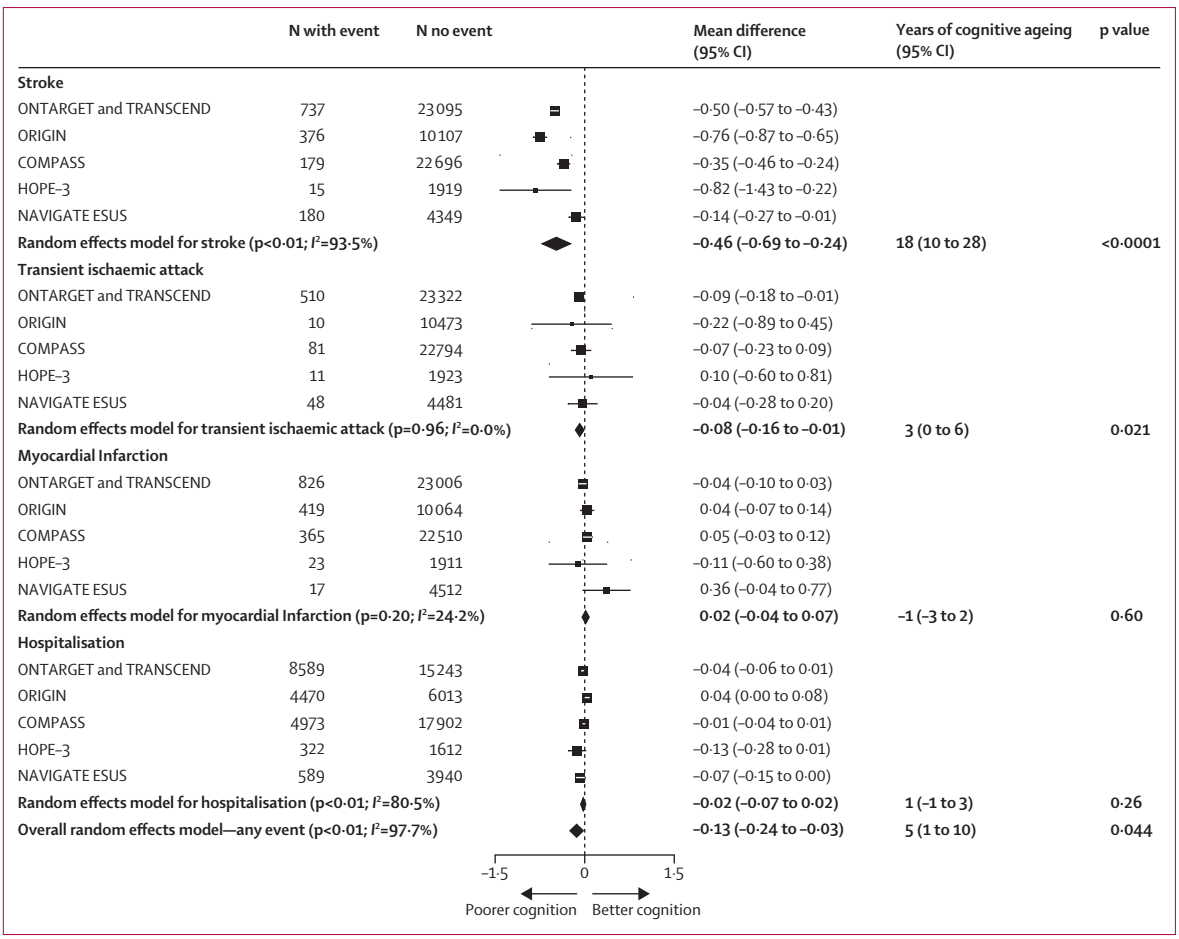

Figure 2: **Mean differences in cognitive Z scores by event type**

Zscores were adjusted for baseline cognition and covariates (age, sex, education, BMI, smoking status, hypertension, diabetes, previous stroke, myocardial infarction, and transient ischaemic attack). Z scores and associated years of cognitive ageing are presented for the events of stroke, transient ischaemic attack, myocardial infarction, and hospitalisation, across each of the six trials. COMPASS=Cardiovascular Outcomes for People Using Anticoagulation Strategies. HOPE–3=Heart Outcomes Prevention Evaluation-3. NAVIGATE ESUS=New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source. ONTARGET and TRANSCEND=Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. ORIGIN=Outcome Reduction With Initial Glargine Intervention.

Participants after haemorrhagic stroke had worse cognitive performance than participants after ischaemic stroke. This finding could be because haemorrhagic stroke is more disabling, although differences remained after adjustment for severity, or potentially due to shared pathologies (beyond the traditional cardiovascular risk factors shared by dementia and all stroke), which are associated with both lobar haemorrhage and dementia (eg, cerebral amyloid angiopathy).[27] In this study, the effect of stroke on cognition did not differ by sex or age of participants at baseline, although post-stroke dementia (which we did not assess) could differ by sex or age.[3,21] This difference could be because of selection bias associated with randomised controlled trial inclusion (selecting only the healthiest older people to take part), or the ability to adjust for pre-stroke cognition in this study (which could account for the effect of age in other studies).

The Oxford Vascular Study (OXVASC)[28] found that participants were more likely to have moderate to severe cognitive impairment after acute coronary syndrome than transient ischaemic attack at 1 year (OR 2·14, 95% CI 1·11–4·13), and after minor stroke than transient ischaemic attack at 1 year (1·48, 0·62–3·50). We similarly found that non-disabling stroke was associated with poorer cognition than transient ischaemic attack but conversely found that transient ischaemic attack had a greater effect than myocardial infarction. Our results were consistent with the Health Retirement Study,[23] which found that incident stroke was associated with greater odds of moderate to severe cognitive impairment (3·86, 2·10–7·11), whereas incident myocardial infarction was not associated with greater odds of cognitive impairment (1·68, 0·91–3·10).[23] In comparison, this study was larger and could adjust for pre-myocardial infarction cognition, although we might have selected

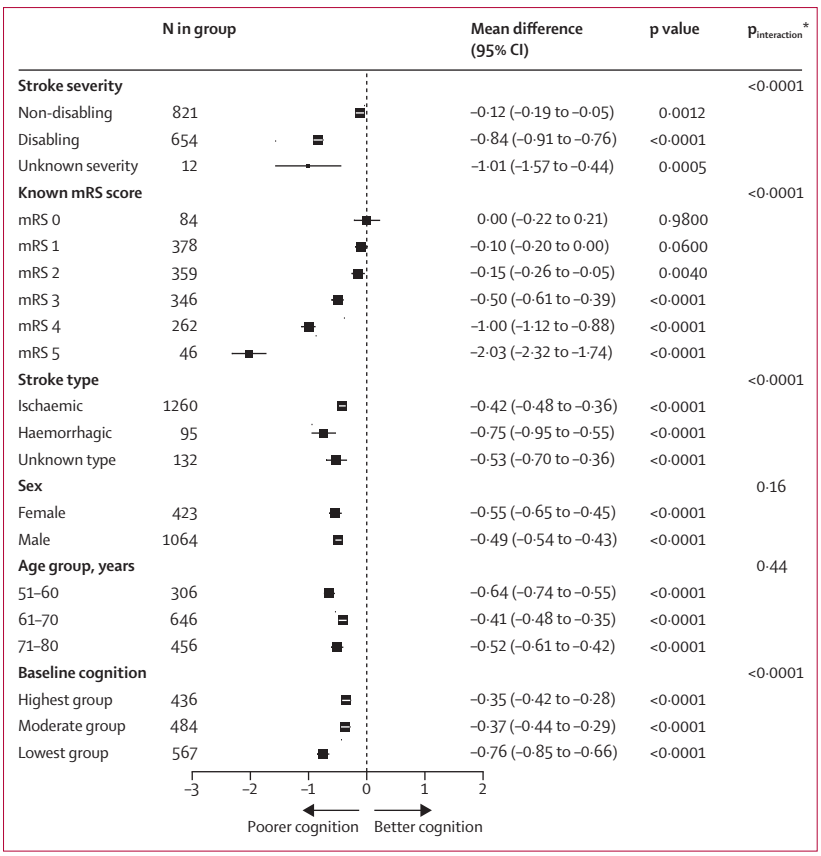

Figure 3: **Mean differences in cognitive Z scores for participants with stroke versus no stroke**
Z scores were adjusted for baseline cognition and covariates (age, sex, education, BMI, smoking status, hypertension, diabetes, previous stroke, myocardial infarction, and transient ischaemic attack). Z scores are presented for the subgroups; stroke severity, modified Rankin Scale (mRS) score, stroke type, sex, age, and baseline cognitive performance.

people who were younger and cognitively healthier before their myocardial infarction than those in the OXVASC study.

This study has several strengths: there were a large number of events reducing statistical uncertainty; event records were adjudicated centrally after report by the site investigator; we could account for pre-event cognitive scores; trials used trained investigators over multiple sites; and the study had excellent and complete recording of baseline characteristics, and previous health and adverse events. Data from 55 countries strengthened the generalisability of our results. For the sensitivity analysis, we standardised Z scores by country (using all scores for each country as a distribution) to account for differences in scores from administering the tests in different countries. This analysis did not change the magnitude or significance of any of the results presented.

Our study had some potential limitations. First, approximately 6% (5048 of 81777) of participants had died by trial end, and 16% (12623 of 76729) of survivors did not receive a final cognitive assessment (appendix p 5). Loss to follow-up is an inevitable consequence of the disabling (including dysphasia) and fatal effects of stroke, and is similar to the OXVASC study (16% loss to follow-up of survivors),[29] and Medical Research Council Cognitive Function and Ageing Studies study (21% loss to follow-up of survivors).[30] Individuals who did not have a cognitive assessment were probably unable to complete one and would have scored poorly had they been assessed and, similarly, had those who were deceased been alive and assessed, they probably would have performed poorly on the cognitive assessments; therefore, the effect of stroke on cognition might be underestimated. Second, because participants took part in randomised controlled trials, they were not representative of those in the wider population: the majority were men, there was a large number of participants with more than 12 years of education, there was a high prevalence of cardiovascular risk factors and disease, and all participants had consented to a randomised controlled trial. Third, there was no clinical diagnosis of mild cognitive impairment or dementia at study end. Fourth, duration of follow-up was short (median 4·4 years) in comparison with the long prodrome of dementia. Fifth, we were unable to control for stroke location, which could affect cognition. The region of the stroke could affect the ability to carry out cognitive assessment due to motor, language, and visual deficits, which can lead to poorer scores on cognitive assessment and could cause overestimation of cognitive impairment. Sixth, it is possible that different years of baseline assessment could have led to cohort effects, but the differences in start date are small and would not be anticipated to have a large effect in comparison with the effect of stroke. Seventh, the cognitive assessments used (Montreal Cognitive Assessment and Mini-Mental State Examination) are subject to practice effects, which could lead to improved cognitive scores with re-administration and, therefore, an underestimation of the effect of events on cognitive performance; however, the learning effects are likely to be small. Finally, the Montreal Cognitive Assessment and Mini-Mental State Examination are subject to ceiling effects.

Our study has focused on one of the primary concerns of stroke survivors and their carers, which is cognition post-stroke.[1] Our analyses suggest that the effect of stroke on cognition is substantial and is not primarily due to hospitalisation or acute illness, and could be similar at different ages. The effect of stroke on cognition was greatest in people with the poorest pre-stroke cognition, even when accounting for their pre-stroke cognitive abilities.

For researchers, this study shows that simple measures of cognition (Mini-Mental State Examination and Montreal Cognitive Assessment) could be effective for understanding the effect of stroke at a large scale. However, as discussed in the limitations, there could be disadvantages to using these assessments. The greatest issue for using these measures to assess the effects of

stroke is likely to be the heterogeneity in the effect of stroke depending on its location.

For practice, these findings should be useful to inform the counselling of survivors and their families. Improving access to treatments that reduce stroke severity might not only improve physical disabilities, but also cognition, and potentially the later clinical syndrome of dementia. Prevention of stroke in people with mild dementia could also reduce their cognitive decline due to stroke, although people with dementia are less likely to receive blood pressure and lipid lowering therapies.[31]

Contributors

LS, SFL, AHK, TC-Y, MC, RJ, MS, AS, HCG, MJO'D, GM-T, SY, JB, and WNW conceptualised the study and developed the methods. MJO'D, GM-T, SY, JB, and WNW supervised the study. SY, JB, and WNW acquired the funding for the study. LS and SFL had full access to and verified the data. LS conducted the formal analysis, created visualisations, and wrote the original draft. LS, SFL, AHK, TC-Y, MC, RJ, MS, AS, CB, HCG, MJO'D, GM-T, SY, JB, and WNW reviewed and edited the manuscript.

Declaration of interests

TC-Y has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, and educational events from Eli Lilly, Sanofi, Merck Sharp & Dohme, Novo Nordisk, Medtronic, Geffen Medical, AstraZeneca, and Boehringer Ingelheim. MS has done consultancy work for Bayer and Jassen, and is a member of the Board of Canadian Stroke Consortium. AS has done consultancy work for AstraZeneca, Takeda Pharmaceutical Company, Bioxodes, Bayer, Servier Canada, and Daiichi Sankyo; has done data safety monitoring for Bayer; and has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from AstraZeneca, Bayer, Daiichi Sankyo, and Servier Canada. HCG has done consultancy work for Abbott, AstraZeneca, Eli Lilly and Company, Novo Nordisk, Sanofi, Kowa, Pfizer, and Hanmi, and has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from AstraZeneca, Eli Lilly and Company, Jiangsu-Hanen, Carbon Brand, Novo Nordisk, Sanofi, and Boehringer Ingelheim. WNW has done consultancy work for Bayer; data safety monitoring for the Universities of Calgary, Manchester, Oxford, and Utrecht; has received compensation from UK Courts for expert witness services; and has received compensation from American Heart Association for other services. All other authors declare no competing interests.

Data sharing

Data can be shared as per the Public Health Research Institute Data Sharing Policy, which requires approval of the proposed use of the data by a review committee at the Public Health Research Institute. More detail is available at https://www.phri.ca/data-sharing.

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