COGNITIVE IMPAIRMENT IN STROKE AND MULTIPLE SCLEROSIS

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Abstract

Background: Due to the world's ever-growing and ageing population, dementia and cognitive impairments are major global health and socioeconomic burdens. Stroke is a leading cause of acquired cognitive impairment and dementia. Multiple sclerosis (MS) although less common than stroke, also causes cognitive impairment and in rare cases overt dementia. The risk factors for cognitive decline are still not fully understood and there is currently no recommended intervention for preventing cognitive decline. Therefore, we must determine which risk factors are associated with cognitive impairment and which interventions can help to delay or prevent the onset of cognitive impairment, to reduce the number of people who suffer from cognitive decline.

Methods and results: The clinical and radiological predictors of post-stroke cognitive impairment (PSCI), following an ischaemic stroke (IS) or transient ischaemic attack (TIA) in previously independent adults, were investigated using data from the international multicentre randomised control trials, ENOS and TARDIS. Together (Chapter 3), this dataset of 4798 participants, is one of the largest international hospital-based studies of PSCI to date. The predictors of post-stroke cognitive decline in this cohort were older age, greater stroke severity (National Institute of Health Stroke Scale (NIHSS)), pre-stroke disability (modified Rankin Scale (mRS)), non-UK participants, history of atrial fibrillation, lower systolic blood pressure, and higher heart rate.

The clinical and radiological predictors of PSCI, following an intracerebral haemorrhage (ICH) in previously independent adults, were investigated using data from the international multicentre randomised control trial,

TICH-2 (Chapter 4). This study involved 693 participants and is one of the largest cohorts of ICH survivors that focused on cognitive impairment. The predictors of long-term SCI were older age, non-Caucasian ethnicity, a greater level of deprivation (Index of Multiple Deprivations (IMD)), reduced level of consciousness (Glasgow coma scale (GCS)) and lobar ICH.

The effectiveness of intensive blood pressure and lipid-lowering on cognitive outcomes in patients with a recent stroke was investigated in the multicentre randomised trial, PODCAST (Chapter 5). Intensive BP and lipid-lowering did not alter cognition and did not have any long-lasting effects on cognition in participants approximately 5 years after stroke. Intensive lipid-lowering might still be partially effective at 33 months according to the global outcome and global cognition analysis.

The effectiveness of live hookworm infection on cognition in multiple sclerosis (MS) patients, as well as the clinical and radiological associations of cognitive function in MS patients, was investigated in the WIRMS trial (Chapter 6). We showed that there were no effects of hookworm infection on cognitive function, quality of life or fatigue over the 6 months of active treatment. We also showed there was no significant change in the cognition and functional outcomes over time in all participants and across both treatment groups. Worse cognitive function was associated with a greater number of T2 lesions and a poorer quality of life.

Discussion: The key predictors of cognitive impairment after IS and ICH were older age, a greater stroke severity, and non-UK/non-Caucasian

ethnicity. Blood pressure and heart rate were identified as potential therapeutic targets for the prevention of cognitive decline after IS. An important predictor of cognitive decline after ICH was a greater level of social deprivation. Blood pressure and lipid interventions in stroke patients, and parasitic infection in MS patients, did not affect cognitive function, however, they are still feasible and require further study. A major limitation of cognition studies is the loss of participants to follow up due to disease severity therefore informant-based cognition questionnaires are essential. Future research should consider accounting for a participant's level of education, ethnicity and other race-related factors, socioeconomic status, and should perform MRI scans and genetic analysis (AD biomarkers) where possible.

Conclusion: In conclusion, cognitive impairment due to stroke or multiple sclerosis is a socioeconomic burden that will continue to grow without further research into its risk factors and in turn potential interventions.

Declaration

I declare that this thesis is my work based on research that was undertaken at the Division of Stroke Medicine, School of Clinical Sciences, The University of Nottingham.

For the ENOS, TARDIS, TICH-2 and WIRMS trials, I retrospectively collated, analysed, interpreted, and managed the data and drafted the publications that arose from the work.

For the PODCAST extended follow study, I recruited participants, took consent, performed participant assessments, analysed, and managed the data, and drafted publications that arose from the work.

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Tables

Figures

Abbreviations

ACA	Anterior Cerebral Artery
ACE-R	Addenbrooke's Cognitive Examination-Revised
AD	Alzheimer's Disease
AF	Atrial Fibrillation
AUC	Area Under the Curve
BI	Barthel Index
BP	Blood Pressure
BPM	Beats Per Minute
CAA	Cerebral Amyloid Angiopathy
CI	Confidence Interval
CNS	Central Nervous System
CP	Cognitively Preserved
CT	Computerised Tomography
DBP	Diastolic Blood Pressure
DMTs	Disease-Modifying Therapies
EBV	Epstein-Barr Virus
EDSS	Expanded Disability Status Scale
ENOS	Efficacy of Nitric Oxide in Stroke
EQ-5D	EuroQOL 5 Descriptors
EQ-VAS	EuroQOL Visual Analogue Scale
FSS-5	Fatigue Severity Scale 5
GCS	Glasgow Coma Scale
Gd	Gadolinium
GTN	Glyceryl Trinitrate
HR	Heart Rate
HW	Hookworm
ICH	Intracerebral Haemorrhage
IHD	Ischaemic Heart Disease
IMD	Indices of Multiple Deprivation
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile Range
IS	Ischaemic Stroke

IVH	Intraventricular Haemorrhage
LACS	Lacunar Stroke
LDL	Low-Density Lipoprotein
MCA	Middle Cerebral Artery
MCI	Middle Cognitive Impairment
MD	Mean Difference
MMSE	Mini Mental State Examination
MMSE-M	Mini Mental State Examination-Modified
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSQOL-54	Multiple Sclerosis Quality of Life-54
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NIHSS	National Institutes of Health Stroke Scale
OCSP	Oxford Community Stroke Project
OR	Odds Ratios
PACS	Partial Anterior Circulation Stroke
PASAT	Paced Auditory Serial Addition Test
PBO	Placebo
PCA	Posterior Cerebral Artery
PICH	Primary Intracerebral Haemorrhage
POCS	Posterior Circulation Stroke
PODCAST	Prevention of Decline in Cognition After Stroke Trial
PPMS	Primary Progressive Multiple Sclerosis
PSCI	Post Stroke Cognitive Impairment
PSD	Post Stroke Dementia
QOL	Quality of Life
RCTs	Randomised Control Trials
ROC	Receiver Operating Characteristic
RRMS	Relapsing-Remitting Multiple Sclerosis
SAH	Subarachnoid Haemorrhage

SBP	Systolic Blood Pressure
SCI	Severe Cognitive Impairment
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
SPSS-24	Statistical Package for Social Sciences version-24
SVD	Small Vessel Disease
TACS	Total Anterior Circulation Stroke
TARDIS	Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke
TC	Total Cholesterol
TIA	Transient Ischaemic Attack
TICH-2	Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage-2
TICS-M	Telephone Interview for Cognitive Status-Modified
t-MMSE	telephone-Mini Mental State Examination
T-MoCA	Telephone Montreal Cognitive Assessment
TOAST	Trial of Org 10172 in Acute Stroke Treatment
Tregs	T regulatory cells
TTN	Time to Neuroimaging
UK	United Kingdom
UPW	Units Per Week
VaD	Vascular Dementia
VaMCI	Vascular Mild Cognitive Impairment
VCD	Vascular Cognitive Disorders
VCI	Vascular Cognitive Impairment
WIRMS	Worms for Immune Regulation of Multiple Sclerosis
WM	White Matter
WMH	White Matter Hyperintensities
WMLs	White Matter Lesions
ZDS	Zung Depression Scale

1 Introduction

1.1 Stroke

1.1.1 Definitions of Stroke and Transient ischaemic attack

The World Health Organisation defines stroke as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin' [1].

An updated definition of Stroke by the American Heart Association/American Stroke Association [2] states 'Stroke' is an umbrella term that encompasses the following:

- Central nervous system (CNS) infarction: 'CNS infarction is a brain, spinal cord, or retinal cell death attributable to ischaemia, based on 1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischaemic injury in a defined vascular distribution; or 2. Clinical evidence of cerebral, spinal cord, or retinal focal ischaemic injury based on symptoms persisting ≥24 hours or until death, and other aetiologies excluded'.
- Ischaemic stroke (IS): 'An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction'.
- Silent CNS infarction: 'Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion'.
- Intracerebral haemorrhage (ICH): 'Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of

blood within the brain parenchyma or ventricular system that is not caused by trauma'.

- Silent ICH: 'A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.
- Subarachnoid haemorrhage (SAH): 'Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma'.
- Stroke caused by cerebral venous thrombosis: 'Infarction or haemorrhage in the brain, spinal cord, or retina because of a thrombosis of a cerebral venous structure'.
- Unknown stroke: 'An episode of acute neurological dysfunction presumed to be caused by ischaemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above'.

The American Heart Association/American Stroke Association define a transient ischaemic attack (TIA) as 'A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction' [3].

The World Health Organisation, European Stroke Organisation and World Stroke Organisation do not include silent pathology in their definition of stroke and as such, there is no universal definition of stroke [4].

1.1.2 Epidemiology

According to the Global Burden of Disease Study 2016 [5], stroke was the second largest cause of death globally after ischaemic heart disease (IHD), with 5.5 million deaths, of which 2.9 million and 2.6 million were men and women, respectively. Ischaemic stroke (IS) and haemorrhagic stroke accounted for 2.7 million and 2.8 million deaths, respectively.

Stroke was also the second most common cause of global disability-adjusted life-years (116.4 million). Men (65.6 million) had more disability-adjusted life-years than women (50.8 million) and the number of disability-adjusted life-years due to haemorrhagic stroke (64.5 million) was higher than ischaemic stroke (51.9 million).

There were 80.1 million prevalent cases of stroke globally in 2016, of which 41.1 million were women and 39.0 million were men. IS accounted for 84.4% of all strokes. There were 13.7 million new strokes in 2016.

Stroke is a huge financial burden and costs the UK society an estimated £26 billion a year [6]. Due to the world's ever ageing population, the incidence of stroke and in turn the socioeconomic burden that it represents will continue to grow.

1.1.3 Aetiology

1.1.3.1 Ischaemic Stroke (IS)

Ischaemic stroke is defined as 'an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction' [2]. It is caused by ischaemia, an abrupt reduction in cerebral blood flow to a critical level that impairs neuronal structure, function and metabolism [7, 8]. This creates an ischaemic penumbra (viable yet dysfunctional tissue) that

progressively becomes permanently damaged tissue (infarction) known as the ischaemic core. The rate of infarction varies from person to person. Penumbral brain tissue can recover with rapid reperfusion [7-9]. A transient ischaemic attack (TIA) occurs when ischaemia is reversed rapidly, avoiding an infarction [10].

The aetiology of IS can be categorised by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification and includes five subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, a stroke of other determined aetiology and stroke of undetermined aetiology [11]. The ASCOD phenotyping system (A: atherosclerosis, S: small-vessel disease, C: cardiac pathology, O: other cause, D: dissection)[12] and the Causative Classification System [13] can also be used to classify aetiological subtypes of ischaemic stroke.

Atherosclerotic infarctions are twice as common in men as women and account for 14-25% of IS [10]. Atherosclerosis commonly affects large and medium-sized arteries and involves intimal proliferation and cholesterol deposition within the artery wall, resulting in the formation of an atheromatic plaque (atheroma). An IS can be caused when the atheroma forms a thrombus or an embolus that occludes an artery, resulting in infarction. The major risk factors for its development include hypertension, hyperlipidaemia, cigarette smoking and diabetes mellitus [14].

Lacunar strokes due to small vessel disease (SVD) account for 15-30% of IS. They are often caused by an occlusion of small penetrating arteries that supply deep brain regions, such as the thalamus and basal ganglia.

The major causative factors of SVD are chronic hypertension and diabetes. Lipohyalinosis or atherosclerosis of small penetrating arteries leads to increased rigidity and narrowing of blood vessels [10]. The subsequent restriction to blood flow is aggravated by the increase in tortuosity of cerebral arterioles associated with ageing [14]. SVD can also cause microinfarcts, haemorrhages, leukoaraiosis and microbleeds [15].

Cardioembolic stroke accounts for 15-30% of all IS [10] and occurs when an embolus from the heart migrates to cerebral blood vessels, restricting blood flow. Cardiac emboli develop in three distinct processes: thrombus in the left cardiac chamber, an embolus from abnormal heart valves, or paradoxical embolism. The major cause of cardioembolic stroke is atrial fibrillation (AF), a cardiac arrhythmia. Other high-risk causes include myocardial infarction, mechanical heart valve, mitral valve stenosis and dilated myocardiopathy. Emboli originating from the cardiac chambers are often large, therefore the resulting cardioembolic strokes are severe and are associated with greater disability and higher mortality rates [16].

Strokes of other determined aetiology include arterial dissection, cerebral vasculitis, reversible cerebral vasoconstriction syndrome and haematological disorders [8].

1.1.3.2 Intracerebral haemorrhage (ICH)

ICH is defined as 'a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma' [2]. ICH can be divided into two aetiological categories. Primary ICH (PICH) is caused by hypertension or cerebral amyloid angiopathy (CAA). Whereas secondary

ICH is caused by aneurysms, arteriovenous malformations, tumours or defective coagulation [17].

Subcortical haemorrhages in the basal ganglia, thalamus, cerebellum, and pons are associated with hypertension. The process of hypertensive arteriosclerosis involves smooth muscle cell necrosis and the deposition of collagen, which results in ectasia (dilation) or occlusion of the cerebral arterioles. Ectasia can lead to the formation of thinly walled micro-balloons (Charcot-Bouchart aneurysms) that may burst and lead to an ICH. CAA is associated with lobar haemorrhages and involves the deposition of the β-amyloid peptide (Aβ) into the wall of arteries, arterioles, and capillaries of the leptomeninges and cerebral cortex. This increases the risk of rupture in these vessels when exposed to high blood pressure or trauma. The risk of CAA increases with age and is associated with recurrent haemorrhages [18].

1.1.4 Diagnosis

The diagnosis of a stroke is made clinically based on patient history and physical examination. A Computerised Tomography (CT) scan is used to support the diagnosis by excluding mimics and differentiating between stroke types [10, 19].

The Oxfordshire Community Stroke Project (OSCP) [20] classified stroke into four clinical syndromes based on patients' symptoms:

- Total Anterior Circulation Stroke (TACS): Higher cerebral dysfunction (dysphasia, visuospatial disorder), homonymous hemianopia and unilateral weakness and or sensory deficit of the face, arm and leg.

- Partial Anterior Circulation Stroke (PACS): Two components of the TACS syndrome.
- Posterior Circulation Stroke (POCS): One of; loss of consciousness, isolated homonymous hemianopia or cerebellar or brainstem syndrome.
- Lacunar Stroke (LACS): One of; ataxic hemiparesis, pure sensory stroke, or unilateral weakness and or sensory deficit of the face, arm and leg or all three.

The gold standard for differentiating between IS and ICH is either CT or Magnetic Resonance Imaging (MRI) brain scans [19]. Current guidelines suggest suspected stroke patients must undergo brain imaging within 1 hour of admission to ensure maximum therapeutic benefits are gained from thrombolysis or ICH management [21].

CT and MRI scans can identify features of acute ischaemia such as hyperdense vessel/MCA sign, insular ribbon sign, and lentiform nucleus obscuration. CT angiography or MR angiography can be used to identify intracranial clots and can propose the use of intraarterial thrombolysis or mechanical thrombectomy [22].

1.1.5 Management

Stroke management is time-dependent and requires rapid and accurate recognition of a stroke. In the pre-hospital setting, the Face Arm Speech Test has improved the recognition of a stroke by the public and paramedics [23]. Unfortunately, no treatments are available before hospital attendance.

1.1.5.1 Hyperacute stroke management

Stroke units

Specialist stroke units provide an environment in which, stroke patients are managed by a multidisciplinary team in a dedicated ward, with access to a mobile stroke team or a disability service. A Cochrane review found that patients treated in a stroke unit were associated with reduced mortality, dependency and institutionalisation [24]. It is therefore recommended that patients with a suspected stroke are admitted directly to a hyperacute stroke unit immediately [21].

Thrombolysis and Thrombectomy

Intravenous thrombolysis in the form of alteplase, a recombinant tissue plasminogen activator (rtPA), is recommended to treat IS patients within 4.5 hours of onset [21]. Evidence has shown that treatment with alteplase improves outcome and the earlier treatment is associated with greater benefits. Alteplase carries an increased risk of death within the first 7 days after an ICH, therefore ICH must be ruled out before administration [25-27]. A meta-analysis of five randomised clinical trials showed that in patients with a proximal vessel occlusion, endovascular thrombectomy improved the functional outcome, with earlier treatment showing greater benefits [28]. If these patients have a significant neurological deficit, mechanical thrombectomy and intravenous thrombolysis is recommended within 5 hours of stroke onset [21]

Antihypertensive treatment

Antihypertensive treatment is recommended within 6 hours of stroke onset in ICH patients with systolic blood pressure (SBP) over 150mmHg, aiming to lower their SBP to 140 mmHg. Meanwhile, IS patients suitable

for intravenous thrombolysis should have their blood pressure reduced to 185/110 mmHg before treatment [21].

1.1.5.2 Acute stroke management

Antiplatelet therapy

Antiplatelet therapy (aspirin) should be given to presumed IS patients within 24 hours of a stroke [21] as it is associated with a reduced risk of early recurrent ischaemic stroke, improves long-term outcomes and carries no major risk of complications due to haemorrhage [29].

Decompressive hemicraniectomy

Life-threatening brain oedema can occur in patients with a middle cerebral artery (MCA) infarction, therefore, decompressive surgery should be performed within 48 hours of stroke onset [21], as it reduces mortality and disability [30, 31].

Intermittent pneumatic compression

Post-stroke immobility can often lead to deep vein thrombosis. Intermittent pneumatic compression increases venous blood flow in immobile stroke patients, reduces the risk of deep vein thrombosis, increases survival, but has no effect on functional recovery [32]. Clinical guidelines, therefore, suggest patients are offered intermittent pneumatic compression within 3 days of hospitalisation for 30 days or until the patient regains mobility [21].

1.1.5.3 Rehabilitation

Stroke deficits occur immediately following a stroke and can be transient, permanent, or even worsen over time. In-patients, therefore, require rehabilitation within a specialised stroke unit, and after discharge,

patients should continue to receive rehabilitation from a community-based specialist stroke team [21]. Stroke rehabilitation is associated with improved performance in activities of daily living [33] reduced dependency, institutionalisation and length of hospital stay [34].

1.1.5.4 Secondary Prevention

Stroke and TIA patients are at considerable risk of recurrent stroke, within the first 5 and 10 years (26% and 39% respectively) [35]. The highest risk of a further vascular event following an initial stroke or TIA is within the first 3 months, especially the first four days [36]. To reduce the risk of recurrent vascular events, secondary prevention should start immediately [21, 37].

Lifestyle interventions

Lifestyle factors such as exercise, diet, smoking, and alcohol intake increase the risk of first and recurrent stroke and are therefore important targets for secondary prevention. The modification of lifestyle factors is the patient's responsibility however, clinicians should advise and support patients in lifestyle adjustments [21].

Antiplatelet and Anticoagulation Therapy

In stroke or TIA patients, antiplatelet therapy can reduce the risk of recurrent events by 22% [38]. Clopidogrel and aspirin plus modified-release dipyridamole are equally effective and are more effective than aspirin monotherapy at preventing recurrent events [39-41]. The first-line treatment recommended for IS and TIA is clopidogrel monotherapy and aspirin plus modified-release dipyridamole, respectively [21].

Anticoagulation therapy (vitamin K antagonists e.g. warfarin) can increase the risk of bleeding and in non-cardioembolic stroke patients, are no more effective than antiplatelet therapy [42, 43]. However, it is the recommended treatment in patients with atrial fibrillation, as it has a superior reduction in recurrent stroke risk (versus antiplatelet therapy) that outweighs the bleeding risk [21]. Non-vitamin K oral anticoagulants are effective at preventing recurrent events in non-valvular AF and are associated with reduced mortality [44], and could, therefore, be used as an alternative to warfarin.

Blood pressure and lipid-lowering

Post-stroke blood pressure reduction prevents recurrent events [45], therefore, patients SBP should be reduced to below 130 mmHg with a dihydropyridine calcium channel. Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists should be added if blood pressure has not reached the set target [21].

Statins are an effective method of lipid-lowering and are associated with a reduced risk of recurrent events following a stroke [46]. However, statins carry a slight risk of intracerebral haemorrhage [47]. Patients with IS or TIA should be treated with a high-intensity statin such as, atorvastatin 20-80m daily, and aim to reduce non-high-density lipoprotein cholesterol by 40% [21].

Carotid endarterectomy

Carotid artery stenosis is associated with stroke, therefore, the risk of recurrent events can be reduced through carotid endarterectomy. This is the surgical removal of the atheroma and blood clots [21] and can

reduce the 5-year risk of IS by 16% and 4.6% in patients with 70-99% and 50-69% stenosis, respectively. However, there is no advantage for patients with stenosis below 50%, and in fact, surgery increased the risk of recurrence in patients below 30% stenosis [48]. Carotid endarterectomy is the recommended treatment for patients with symptomatic carotid stenosis and should be performed as early as possible or within 1 week of stroke onset [21].

1.1.6 Prognosis

Stroke is associated with an increased risk of mortality, disability, and institutionalisation. The risk of mortality within 7 days or 30 days post-stroke is 10% and 20%, respectively. Early death following a stroke, is often caused by brain damage due to cerebral oedema or haemorrhage. Later, complications of post-stroke immobility, such as pneumonia and pulmonary embolism, are common causes of death [19].

1.2 Multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic demyelinating inflammatory autoimmune disease of the CNS and is a major cause of non-traumatic disability in young adults [49, 50]. Historically, the pathological hallmark is demyelinating plaques in the CNS, due to inflammatory lesions, that damage the myelin sheath and inhibit axonal conduction [51, 52]. MS affects an estimated 2.3 million people worldwide [53, 54], and typically presents in young adults between 20-45 years of age, and is twice as common in women than men [55]. The economic burden of MS is huge and greatly affects patients and their families, as the onset of MS is often during the most productive years of their life [49, 56].

1.2.1 Epidemiology

The global prevalent cases of MS in 2016 was approximately 2.3 million (30.1 cases per 100,000). The age-standardised prevalence of MS across the globe was: North America and some northern European countries (120 per 100,00), Europe and Australasia (60-120 per 100,00) and the rest of the world (<60 per 100,000). Low prevalence regions often had sparse MS data [57]. MS displays a significant association between prevalence and latitude with a higher prevalence in populations further away from the equator [57]. The prevalence of MS is greater in women than in men (2:1 ratio). The prevalence of MS between boys and girls is similar during preteens and then starts to differ during adolescence [57]. There were approximately 18,000 deaths and 1.1 million disability-adjusted life-years due to MS globally in 2016 [57].

1.2.2 Aetiology

The aetiology of MS is believed to be a combination of genetic and environmental factors [58].

1.2.2.1 Environmental

Migrations studies have suggested that MS is secondary to environmental exposure [59]. Adult migrants from the low-risk regions to high-risk regions are at low risk of developing MS, whereas children migrants are at high risk [50]. Furthermore, the incidence of MS in the UK born offspring of immigrants from Asia and Africa was comparable to the high incidence of MS in England [60]. This suggests environmental factors are a major risk factor for MS.

Infectious agent

Further studies of migrant populations have shown that immigrants moving from areas of high MS rates to areas of low MS rates display a reduction in their risk of MS, whereas people moving in the opposite direction retain the risk of MS associated with their country of origin. It was proposed that the risk of MS is founded in the first two decades of life and implied that MS may be related to a delayed exposure to a common infectious agent [61].

Two general hypotheses were proposed for the infectious aetiology of MS. The poliomyelitis hypothesis was initially proposed by Leibowitz in 1966 [62] but has since become a hygiene hypothesis. It suggests that exposure to a causative agent during early childhood is protective against MS, and delayed exposure causes MS [58]. Whereas the prevalence hypothesis proposes that regions with high prevalence rates of MS are due to a pathogen that is highly prevalent in that region [63].

The hygiene hypothesis has two limitations that must be considered. First, it is unlikely that all infectious agents are equally involved in predisposing MS due to the variety of infectious agents and the diversity of host immune responses. The Epstein-Barr virus (EBV) paradox, is the second limitation, that is individuals who are seronegative for EBV have an extremely low risk of MS. These individuals that were not infected during childhood were more likely to have had a more 'hygienic' upbringing than individuals that are seropositive for EBV. This is supported by the positive correlation between age at infection with EBV and their socioeconomic status [64]. Per the hygiene hypothesis, these

individuals should have a high MS risk, however, their risk MS is many folds less than that of their EBV-positive peers [64-66].

EBV is a common and asymptomatic infection in young children. In adolescence, it presents as infectious mononucleosis that doubles the risk of MS [67]. EBV infection also follows a latitude gradient. For example, more young people are EBV seropositive in areas of low MS rates whereas in areas with a high prevalence of MS the levels of EBV seropositivity do not become high until after adolescence. This implies that early infection with EBV may be protective against MS. This may also explain the higher rates of MS observed in people with a high socioeconomic status [58]. The mechanism by which EBV increases MS risk is unclear, however, molecular mimicry and EBV-induced B-cell immortalisation and or transformation are involved [68, 69].

Sunlight and Vitamin D

Sunlight intensity and duration are strongly associated with latitude, and studies have identified a strong inverse correlation between sunlight duration and MS prevalence. Sunlight exposure is a major source of vitamin D, which is also associated with an inverse risk of MS [64, 70]. The latitudinal gradient of MS may be correlated to sunlight exposure and vitamin D intake. However, this is not clear as in Israeli-born offspring of African/Asian immigrants the rates of MS are higher compared with their forebears, despite both generations having similar sunlight exposure and vitamin D intake [71].

Sex differences and Smoking

In the early 1900s, the sex ratio in MS was considered to be equal and it wasn't until the 1950's that MS was considered to be more common in females [72]. Smoking has been shown to increase the risk of MS by approximately 50% and explains 40% of the increased incidence of MS in women. The increase in women smoking is parallel to the increase in MS incidence in women [73]. It has been suggested that organic solvent and smoked tobacco are associated with MS and may render the lungs proteins more immunogenic via post-translational modifications [74].

1.2.2.2 Genetics

The theory of genetic susceptibility is supported by the fact that Scandinavian and Scottish Caucasians are very susceptible to MS whereas, it is rarer in other ethnic groups [58]. Familial and twin studies also support this theory as the risk of MS is greater in first degree relatives, especially in twins [75, 76]. While this suggests MS is in part due to genetic susceptibility the specific genes involved are largely unknown. Genome-Wide Association Studies have identified over 100 loci associated with MS susceptibility, including the human leukocyte antigen allele DRB1*1501 which accounts for under 50% of the genetic basis of the disease [58, 77, 78]. Genetic differences between relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) have also been shown [79].

1.2.3 Diagnosis

The presenting symptoms of MS commonly include sensory symptoms of the arms and legs, optic neuritis, motor deficits, diplopia and gait ataxia and incoordination. Particularly characteristic symptoms of MS include

Lhermitte's sign, which is an electrical sensation down the back when flexing the neck, and Uhthoff's phenomenon, a worsening of symptoms due to higher-than-normal levels of heat. MS can also affect bladder, bowel and sexual function, and cause fatigue, depression and cognitive difficulties [10, 80].

Unfortunately, there is no definitive diagnostic test for MS and as there are many MS mimics an extensive knowledge of the clinical presentations of MS is essential to ensure an accurate diagnosis. Blood testing can also be used to exclude MS mimics [81, 82]. According to the National Institute for Health and Care Excellence (NICE) clinical guidelines [82] a consultant neurologist should make the diagnosis of MS based on the revised McDonald criteria [83], which requires the fulfilment of two criteria:

- Dissemination in space: 'at least one T2 lesion in at least two out of four MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)'.
- Dissemination in time: 'the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time or a new T2 and/or gadolinium-enhancing lesion on follow-up MRI, irrespective of its timing regarding a baseline scan'.

The diagnosis of MS cannot be determined by MRI alone and is used in conjunction with the clinical assessment [81]. MRI is an essential tool in the diagnosis of MS [84] and lesions associated with MS appear as T2/fluid-attenuated inversion recovery white-matter hyper intensities. Other supporting investigations for the diagnosis of MS include sensory

evoked potential tests and lumbar puncture. Visual evoked potentials can be used to support the diagnosis of MS as they can provide evidence of lesions on the optic nerve when they may not be present on the MRI scan [80]. A lumbar puncture can also be used to support the diagnosis of MS as 85-90% of patients have elevated immunoglobulin G levels or the presence of oligoclonal bands in the cerebrospinal fluid [10].

1.2.4 Disease Course

MS can be classified by disease modifier phenotypes [85]:

- Clinically isolated syndrome; is the first clinical signs of inflammatory demyelination that could be due to MS but has not fulfilled the dissemination of time criteria.
- Relapsing-remitting MS (RRMS); affects 85% of MS patients and is the most common. It is characterised by relapses of symptoms followed by periods of remission in which, symptoms can improve or disappear.

These can be further divided into active or not active states. Activity is identified from clinical relapses assessed annually and/or MRI activity.

Progressive disease courses include:

- Primary progressive MS (PPMS); affects 10% of MS patients and is characterised by continually worsening symptoms from disease onset, with no relapses or remissions but a plateau of symptoms may occur.
- Secondary progressive MS (SPMS); can develop in patients with RRMS and is characterised by a continual worsening of symptoms without periods of remission.

These can be further divided into active and with progression, active but without progression, not active but with progression, and not active and without progression. Progression is measured by annual clinical evaluation.

1.2.5 Management

1.2.5.1 Symptomatic relief

According to NICE the following pharmacological treatment for the symptoms of MS are recommended [82]. The first-line treatment of spasticity, a disorder of involuntary movement (stiffness and muscle spasms) that affects mobility, is either baclofen or gabapentin. Gabapentin is also recommended to treat nystagmus, an abnormal movement of the eye (nystagmus) that can affect a patients' vision. Amitriptyline is recommended to treat emotional lability, uncontrollable laughter or crying without an apparent trigger. Amantadine is recommended for fatigue.

1.2.5.2 Acute relapses

Corticosteroids are used to relieve the symptoms of an acute relapse and oral methylprednisolone 0.5g daily for 5 days is recommended [82]. Following an acute relapse, methylprednisolone has been shown to reduce the duration of relapses and improve recovery time, however, future relapses and disease progression are not prevented by corticosteroids [86].

1.2.5.3 Disease-Modifying Therapies (DMTs)

There is no cure for MS, therefore, DMTs are used to modulate the immune response, prevent the formation of inflammatory lesions, reduce

the duration and frequency of relapses, relieve symptoms, and slow the accumulation of disability. The use of DMTs can be individually tailored to the patient based on factors such as disease severity, side effects and long-term safety. The DMT chosen will depend on several factors including disease activity/type, side effect profile/tolerability, patient preference regarding oral vs intravenous route, age, sex, and current or future plans of pregnancy. The treatment can also be escalated to second or third line DMTs if there are concerns regarding disease activity. Other factors such as cognition, fatigue, depression, and quality of life are also considered when choosing or switching DMT [87].

1.2.6 Prognosis

Patients with MS have a reduced life expectancy by 5-10 years but typically live with the disease for 20 to 45 years. Mortality in MS is due to the accumulation of disability, ageing, and concurrent disease [55].

1.3 Cognitive Impairment in Stroke

Stroke is a leading cause of acquired cognitive impairment and dementia in the elderly, second only to Alzheimer's disease (AD) [88]. Dementia is considered a continuous decline of mental capacity that interferes with daily and independent living [89]. Many different terminologies have been used to describe cognitive impairment following a stroke including multi-infarct dementia, post-stroke cognitive impairment (PSCI), post-stroke dementia (PSD) and vascular dementia (VaD). The term vascular cognitive impairment (VCI) is now used and refers to a syndrome that includes all disorders of cognition associated with vascular disease. This spectrum covers cognitive impairments ranging from mild (Vascular mild cognitive impairment (VaMCI)) to severe (VaD). In summary, VCI

includes all severities of cognitive impairment and all forms of stroke aetiology [90].

1.3.1 Prevalence of VCI

As different terminologies have been used to describe cognitive impairment estimation of the prevalence of VCI varies. Rates also vary considerably depending on clinical characteristics and stroke severity [91]. For instance, dementia after stroke is common, with 1 in 10 patients developing dementia in the first year after their first-ever stroke with lower risks thereafter [92]. For example, a study using the South London Stroke Register found the overall prevalence of cognitive impairment using the Mini-Mental State Examination (MMSE) or the Abbreviated Mental Test was 22% at 3 months and 5 years, and 21% at 14 years post-stroke [93]. This is supported by a study of stroke patients from 10 countries, which found almost 30% of stroke survivors developed cognitive impairment [94]. On the other hand, other studies have reported higher prevalence rates of cognitive impairment, for example, 57% at 1 year [95], 47.3% at 3 months [96], and 50-58% at 3 months [97, 98].

The Framingham study found 19.3% of stroke patients were demented 10 years after stroke [99], whereas in a Singaporean study, 6 months after a stroke cognition was preserved in 56%, impaired in 40% and demented in 4%. However, at 1 year 31% of the cognitively impaired patients recovered but 10% of the cognitively preserved group became cognitively impaired and 11% of the cognitively impaired group progressed to dementia [100].

Unfortunately, longitudinal studies investigating the natural history of cognitive impairment suffer for several reasons. As they often do not exclude patients with pre-existing cognitive deficits, are limited by their sensitivity to different cognitive domains on cognitive assessments, and to the loss of patients to follow up. Patient withdrawal results in bias as these patients are usually more severe and are more likely to drop out due to inability to attend or death [14]. In summary, VCI affects a significant amount of stroke patients and may be underestimated, therefore accurate recognition of VCI is essential.

1.3.2 The Pattern of Cognitive Impairments after Stroke

The cognitive domains affected in VCI is variable and depends on the stroke type, severity, and lesion; volume, number, and location [101]. A variety of cognitive domains can be affected including; memory, language, orientation, attention, and executive function [14]. Even though any cognitive domain can be affected, VCI is commonly associated with disturbances in executive function [102], the ability to perform a complex goal-orientated behaviour and to adapt to environmental changes. Executive dysfunction includes deficits in information processing speed, task shifting, working memory, initiation, planning, decision making, hypothesis generation, cognitive flexibility and judgement [89]. These impairments are associated with lesions of the frontal lobe, cortical, subcortical and infratentorial areas [103].

Other common VCI deficits include attention/orientation, memory, and language. Attention is the ability to select and filter information and underpins many other cognitive functions. It is impaired in 46-92% of stroke patient's [104] and is often associated with right hemispheric

temporoparietal lobe lesions [14]. Orientation is a part of attention and is impaired in 22% of patients at 3 months [105]. Memory involves the encoding, storing, and retrieving of information and is divided into short term memory (working memory) and long-term memory. Working memory is the most affected aspect of memory in VCI however, other aspects of memory are also affected. The most common language deficit in stroke patients is dysphasia, more specifically expressive (production) and receptive (comprehension) dysphasia. Language deficits are associated with left hemispheric lesions, with expressive dysphasia associated with lesions in the inferior frontal gyrus (Broca's area) whereas receptive dysphasia is associated with lesions in the superior temporal gyrus (Wernicke's area) [14].

1.3.3 Cognitive Assessments in Stroke

The NICE guidelines recommend screening for cognitive impairment in stroke patients using a validated tool [106]. The most commonly used screening tools for cognitive impairment after a stroke are the MMSE [107] and the Montreal Cognitive Assessment (MoCA)[108].

The MMSE is a short and easy to administer dementia screening tool that covers orientation, memory, attention, language, and visuospatial assessment. It has high sensitivity and specificity for dementia when using a cutoff score <24 [107], however, it does not have specified cut-offs for MCI and it does not assess executive function, which is the most commonly affected domain in VCI. Current guidelines, however, recommend using the MoCA [21] as it is more effective in stroke patients than the MMSE [108-112]. For example, in patients with normal cognitive scores on the MMSE, the MoCA recognised 67% and 48% of stroke and

TIA patients with CI, respectively. Unfortunately, in stroke patients without memory deficits, the MoCA loses accuracy [113]. The Addenbrooke's Cognitive Examination-Revised (ACE-R) is another cognition screen that was designed to detect dementia [114] and was subsequently compared to the MMSE and MoCA. The study found that both the MoCA and the ACE-R could detect VCI with good specificity and sensitivity [113].

Telephone-based cognitive assessments in stroke are attractive as; they will be cheaper, may be tolerated better by patients and could, therefore, allow for continued follow-ups in longitudinal studies in patients that lack motivation or with physical limitations [115]. The Telephone Interview for Cognitive Status-Modified (TICS-M) [116] and the Telephone MoCA (T-MOCA) [117], are brief cognitive screens that do not require the use of a pencil and paper or visual stimulus. A study of community-dwelling patients one year post-stroke or TIA found that both the TICS-M and T-MOCA were valid tests of cognition that had good sensitivity and specificity for VaMCI [117], therefore telephone cognitive assessments provide an alternative strategy to in-person assessments. There is also interest in computerised neuropsychological assessment devices, however, further psychometric data regarding their use is required [118].

1.3.4 Risk Factors of VCI

VCI could potentially be prevented as many of its risk factors are modifiable [90], therefore the identification of predictors of cognitive impairment and in turn patients at risk may help prevent or delay the onset of vascular cognitive impairment.

1.3.4.1 Non-Modifiable risk factors

Age is an important risk factor for both stroke and VCI, and as age increases so does the prevalence and incidence of VCI [90]. This is supported by the fact that the risk of dementia doubles every 5 years after the age of 65 and continues to increase after the age of 90 [119]. Studies evaluating the differences in the incidence of VCI between genders have been contradictory. For example, the Rotterdam study [120] found the incidence of VaD was lower in women whereas the EURODEM studies showed no difference [121]. In terms of race, black patients appear to have a higher incidence of VaD than white patients [122] however, this might be due to a higher incidence of vascular risk factors in black people [90]. AD is associated with the apolipoprotein E4 allele [90], however, no association with VCI has been reported [123, 124].

1.3.4.2 Modifiable Risk Factors

Lifestyle factors

The association between diet and VCI is under-researched, and interpretation is difficult [90]. Antioxidants and cognitive function showed no association [125, 126] and studies investigating the association between vitamin D, B6, B12, folic acid, homocysteine, and VCI produced inconsistent results [90, 127, 128]. Long term physical activity has been associated with better cognitive functioning and less cognitive decline and VaD [129-132]. Heavy alcohol consumption has been associated with VCI however, moderate drinking has been associated with superior cognitive function when compared with little or no alcohol consumption [133-136]. Heavy midlife smoking was associated with a greater long-

term risk of VaD in later life [137] but further studies are required to determine whether smoking cessation prevents dementia [90]. Lastly, a higher risk of VCI is associated with a lower educational status [130].

Physiological risk factors

Midlife hypertension is associated with cognitive decline, MCI and VaD [138-141]. A review of hypertension and cognition showed high blood pressure and cognitive decline demonstrate a J or U-shaped relationship [142]. Therefore, it has been theorised that chronic hypertension impairs vasomotor reactivity and autoregulation, resulting in a higher minimum blood pressure needed to achieve sufficient cerebral perfusion [143]. Randomised control trials (RCT's) investigating the effectiveness of antihypertensive treatment in preventing cognitive impairment have produced inconsistent results [144].

Recent studies have suggested the inability to provide and regulate fuel supply to aged brains is associated with cognitive decline, therefore both hyperglycaemia and hypoglycaemia are associated with cognitive impairment [145, 146]. Chronic hyperglycaemia also causes impaired autoregulation and neuronal damage, which is associated with cognitive function [90]. There is also an association between the duration of diabetes and cognitive function, therefore VCI due to hyperglycaemia may depend on disease duration [147]. However, there is no evidence that intensive treatment of diabetes protects against cognitive impairment [148].

The relationship between total cholesterol (TC) and VCI are controversial. The CAIDE study [149] suggested that the relationship is bidirectional,

with high TC during midlife and low TC after midlife associated with cognitive impairment. Other studies have produced conflicting results with hyperlipidaemia associated with lower and higher risks of VaD [150, 151]. There is contradictory evidence for the use of statins to prevent cognitive impairment particularly as the PROSPER study found statins did not prevent cognitive decline and suggesting their use in the elderly is futile [152].

Atrial fibrillation, if not treated, is a risk factor for stroke [153] and is associated with VCI [154, 155]. People with atrial fibrillation are at a greater risk of cognitive impairment and dementia, regardless of whether they have had a stroke [156].

Several studies have shown severe carotid stenosis is associated with VCI [157] including symptomatic and asymptomatic carotid stenosis, and carotid intima-media thickness [158, 159]. Severe carotid stenosis was also associated with VCI at 1-year post-stroke and suggests patients with carotid stenosis >70% are at a high risk of VCI [157].

1.3.5 Radiological Predictors of VCI

Stroke is believed to cause cognitive impairment based on the volume of infarcted brain tissue, the number of infarcts/lesions, strategic neuroanatomical involvement, location and severity of white matter disease (leukoaraiosis) and coexistence of other pathologies such as AD [160].

1.3.5.1 Cerebral infarcts

Initially, it was proposed that there was an association between the volume or strategic location of cerebral infarct and CI [161]. Over 100 ml

of infarcted tissue was associated with dementia however, dementia did occur in volumes greater than 50 ml. Further studies have identified an association between larger volumes and a greater number of cerebral infarcts and dementia [162]. Unfortunately, the association between the volume and number of infarcts and cognitive impairment has been inconsistent [163, 164]. Therefore, identifying the exact volume or number of infarcts required to produce VCI or dementia is challenging and currently there are no definitive neuropathological criteria for the diagnosis of VCI [90]. Total lesion volume cannot explain all the variability of cognitive impairment and supports the idea that strategic neuroanatomical lesions play a key role in the development of cognitive impairment and its severity [165]. Key strategic locations associated with cognitive impairment include; dominant thalamus and angular gyrus, medial temporal lobe/hippocampus, deep frontal areas, and the left hemisphere [166, 167]. Cerebral infarcts that have not been linked to a neurological deficit are termed silent infarcts. Silent infarcts have also been suggested as a predictor of PSD, especially when the time since the stroke is greater [168].

1.3.5.2 White matter lesions (WMLs)

White matter lesions (leukoaraiosis) are common radiological manifestations of an ischaemic stroke and appear as white matter hyperintensities on T2 MRI. Lacunar stroke due to SVD is commonly associated with WML's and has been associated with cognitive impairment [169]. A study on nondemented elderly patients found that cognitive impairment was correlated with WML's and cerebral atrophy [170]. This is further supported by branch studies of the Leukoaraiosis

And Disability Study (LADIS) [171]. One study found lacunar infarcts in the thalamus were associated with worse cognitive performance, whereas further branch studies found WML's and lacunar infarcts resulted in cognitive impairment and mainly affected psychomotor speed, executive function and global cognition [172, 173]. Another LADIS study showed WML's and brain atrophy were independently associated with VCI and brain atrophy could aggravate the effect of WML's on VCI [174].

1.3.5.3 Cerebral Atrophy

Both global cerebral atrophy and medial temporal lobe atrophy are associated with PSD [168]. Medial temporal lobe atrophy was also associated with a reduced time to dementia [175] and in comparison, to WML's, demonstrates a stronger association with cognitive decline [176]. Atrophy of the left and right hippocampus were associated with verbal episodic long-term memory impairment and nonverbal episodic long-term memory impairments, respectively [177]. Medial temporal lobe atrophy was predictive of patients with and without dementia in the Lille study [178] and could therefore potentially distinguish between patients with and without dementia after a stroke [179].

In conclusion, VCI has been associated with stroke-related features such as volume, number and location of cerebral infarcts and chronic brain changes such as white matter lesions and cerebral atrophy. These features, therefore, present an opportunity for earlier recognition and prevention of VCI, however further research is required to fully determine their predictive power.

1.4 Cognitive Impairment in Multiple sclerosis

Cognitive deficits are common in MS and can affect 43-70% of patients [180, 181], and can occur early during the disease and may be a presenting symptom [182]. Severe dementia is rare and occurs in 20-30% of cognitively impaired MS patients, mainly in the end stages of the disease [183]. However, cognitive impairment in MS can result in; higher rates of unemployment, reduced social and vocational activity, increased difficulty performing activities of daily living, as well as greater susceptibility to psychiatric illness, leading to a negative impact on a patients' quality of life [184, 185].

1.4.1 The Pattern of Cognitive Impairment in MS

The pattern of cognitive impairment varies among patients; however a characteristic pattern has emerged and includes deficits in; memory, information processing efficiency, executive functioning, attention, and processing speed [180].

Slowed information processing speed is a hallmark cognitive deficit in MS and is often seen in conjunction with deficits in working memory, long-term memory and executive function [186-190]. Long-term memory is commonly impaired in MS occurring in 40-65% of patients [183]. It was initially thought that memory problems were due to deficits in the retrieval of long-term memories however, it has since been shown that MS patients struggle to acquire new information but their recall and recognition are comparable to healthy controls [191]. Working memory impairments have been observed in MS but are less common than processing speed deficits [186]. Attention is associated with processing speed and working memory, and deficits in sustained and divided

attention have been observed in MS [192]. Executive dysfunction occurs less commonly than memory and processing speed deficits, however, it still occurs in up to 17% of MS patients [193]. Visual perception is the ability to recognise visual stimuli and later perceive that stimulus accurately. There have been fewer studies on visual perception dysfunction in MS when compared with the other cognitive domains, however, it may occur in up to a quarter of MS patients [51]. Although understudied, the language domain was initially thought to be unaffected [194], however, a recent study has shown that language deficits occur in 20% and 58% in RRMS and SPMS, respectively [195]. Social cognition, which is how people process, store, and apply information about other people and social situations, is also affected in MS patients [196].

1.4.2 Cognitive Assessment in MS

The most commonly used neuropsychological assessments in MS are the Brief Repeatable Battery of Neuropsychological tests [197] and the Minimal Assessment of Cognitive Function in MS [198]. The Brief Repeatable Battery of Neuropsychological tests can be administered in 20-30 minutes and includes selective reminding test, 10/36 spatial recall test, symbol digit modalities test, paced auditory serial addition test (PASAT), and word fluency. The Minimal Assessment of Cognitive Function in MS is a 90-minute neuropsychological battery composed of PASAT, SDMT, California Verbal Learning Test-II, Brief Visuospatial Memory Test-Revised, D-KEFS Sorting Test, Judgement of Line Orientation Test and Controlled Oral Word Association Test. A comparative study found the sensitivity of the batteries were similar [199].

However, both batteries require time-consuming evaluation by an expert, therefore, the Brief International Cognitive Assessment for Multiple sclerosis was recently recommended as a brief cognitive assessment [200]. It consists of the SDMT, the first five recall trials of the California Verbal Learning Test-II and the first three recall trials of Brief Visuospatial Memory Test-Revised. If only 5 minutes are available, the SDMT should be done but if a further 10 minutes are available the California Verbal Learning Test-II and Brief Visuospatial Memory Test-Revised should be done.

1.4.3 Factors Affecting Cognition

1.4.3.1 Disease course and duration

Disease duration seems to not affect cognitive impairment [201] but is influenced by disease course, for example, progressive MS is associated with severe cognitive impairment [202, 203]. The true effect of disease course on cognitive impairment is therefore mystified by disease duration as patients with SPMS have a greater disease duration and degree of disability [204]. Several studies have distinguished between PPMS and SPMS and found that SPMS was associated with worse cognitive function [187, 205, 206].

1.4.3.2 Depression and Anxiety

Depression is common in MS and can affect a patients cognitive function [51], however, the link between depression and cognition is not fully understood. Previous studies were inconsistent, however positive associations were found in studies with adequate power and a representative sample of MS patients [207]. A wide variety of cognitive domains can be affected by depression including working memory,

processing speed, abstract reasoning, memory, learning, and executive function [205, 208-210].

Depression occurs in up to 60% of MS patients and determining the source of depression has proved a challenge [211]. MS patients with mainly spinal cord lesions were less likely to suffer from depression, which suggests brain involvement is associated with depression [212]. Further studies have shown a relationship between demyelination and depression, for example, cortical-subcortical disconnection of regions involved in limbic function could play a role in depression [213]. This is supported by the fact that disconnection due to frontoparietal white matter lesions and atrophy was also associated with depression [214]. Increased lesion number in the temporal lobe has also been linked with depression [215]. Anxiety is also common in MS patients [216], however, it is understudied and its association with cognitive performance is unclear [217, 218].

1.4.3.3 Fatigue

The most commonly reported symptom in MS is fatigue [10]. Fatigue can be separated into physical and cognitive but evaluating cognitive fatigue is difficult and is hindering our understanding of the association between cognitive fatigue and cognitive function [219]. Cognitive impairment has not been associated with subjective cognitive fatigue; however, a decline in performance on tasks of sustained mental effort over time has been observed and suggests fatigue may be affecting cognition [219, 220]

1.4.4 Radiological Predictors of Cognitive Impairment in MS

Structural MRI is essential for the diagnosis and monitoring of MS [221]. It has been used extensively to determine the radiological correlates of cognitive impairment in MS and can identify features such as global cerebral atrophy, cortical atrophy, and lesion volume [180, 222, 223]

1.4.4.1 Lesion volume and location

Numerous studies have identified an association between T2 and T1 white matter lesion volume and cognitive performance [224]. Longitudinal studies have shown in patients with clinically isolated syndrome T1 lesion volume at baseline and new T2 lesions at 3-month follow up predicted executive deficits and decreased processing speed at 7 years, respectively [225]. In patients with RRMS T1 lesions were correlated with attention deficits at 5 years, whereas T2 lesion volumes were not associated with cognitive decline [225, 226]. On the other hand, cognitive dysfunction in PPMS patients at 5 years was correlated with T2 lesions [227]. Lesion location has also been associated with cognition and supports the idea of disconnection syndrome. It proposes cognitive deficits are caused by lesions in strategic white matter tracts [224]. Unfortunately, several studies have shown white matter lesions are a minor player in the process of cognitive dysfunction in MS in comparison to normal-appearing white matter or gray matter [228-230].

1.4.4.2 Cerebral atrophy

Global cerebral atrophy including both white and gray matter atrophy has been associated with cognitive impairment [231, 232]. Gray matter atrophy has been identified in the early stages of MS and progresses quicker than white matter atrophy [233, 234]. In a group of RRMS

patients, there was an observable difference in gray matter volume in cognitively impaired patients and those that were cognitively preserved whereas no difference was seen in white matter volume [235]. On the other hand, another study found both white matter and gray matter atrophy were associated with cognitive impairment but affected different cognitive domains. White matter atrophy affected processing speed and working memory whereas verbal memory was impaired by gray matter atrophy [232]. A study of RRMS patients found neocortical atrophy was associated with deficits in verbal memory, verbal fluency, and attention [236]. This supports a study of RRMS and SPMS patients that also found neocortical atrophy was associated with cognitive impairment [237]. The width of the third ventricle, which represents atrophy of the thalamus has been associated with cognitive function and is predictive for cognitive impairment, especially memory and processing speed [237-240]. Temporal lobe atrophy observed in RRMS and SPMS patients predicted worse memory function whereas central atrophy was associated with processing speed [241]. A study of hippocampal atrophy found it was linked with memory-encoding [242]. Overall atrophy is a strong predictor of cognitive performance and longitudinal studies have suggested early atrophy can predict cognitive impairment 5 years later [225].

Cognitive impairment is common in both stroke and multiple sclerosis and is a growing global socioeconomic burden. The early recognition and prevention of cognitive impairment are therefore essential. Identifying clinical and radiological factors associated with cognitive impairment could present an opportunity for earlier recognition and potential avenues for prevention.

2 General Methods

The cognitive and functional assessments that were used throughout this thesis are described in detail below.

2.1 Cognitive Assessments

There are a plethora of telephone cognitive assessments available [243]. The cognition assessments used in the clinical trials and described below were selected considering a variety of factors, such as availability (free to use), ease and experience of administration of the test, time to administer, and assessment of cognitive domains commonly affected in the disease group.

2.1.1 Mini Mental State Examination (MMSE)

The MMSE is a validated global cognition screening tool used to identify cognitive impairment and dementia in stroke. It covers spatial and temporal orientation, memory, attention, language and visuospatial evaluation but does not cover executive function. It has a total score of 30 with a cutoff score of <24 as a reliable diagnosis of dementia with high specificity and sensitivity [107].

The MMSE-M is a modified telephone version of the MMSE that was initially developed for the Efficacy of Nitric Oxide in Stroke (ENOS) trial and was subsequently used in the following trials. It consists of place orientation, attention, subtraction, and memory recall and has a total score of 18 with a cutoff score of <14 for cognitive impairment (equivalent to <24 on the MMSE).

2.1.2 Telephone Instrument for Cognitive Status-Modified (TICS-M)

TICS-M is a validated global cognition measure and has been used as a screening test for dementia and cognitive impairment in stroke patients [116]. It covers place orientation, attention, memory and language assessments. It has a total score of 37 and a cutoff score of <20 for cognitive impairment was used (equivalent to <21 on the TICS-M score with 39 points) [244].

2.1.3 Animal Naming (Verbal Fluency)

Animal naming is a verbal fluency test and involves patients naming as many animals as possible in 1 minute. Patient performances are determined by the number of correct answers without repetition. A cut off score of <10 is used for cognitive impairment [245].

Table 2.1: Mini Mental State Examination – Modified (MMSE-M)

MMSE-M	Score
Place Orientation: Floor, building, city, county, country	5
Attention: Spell "WORLD" backwards Serial 7 subtractions (93, 86, 79, 72, 65)	5 5
Delayed Recall: Repeat the following 3 words	3
Total	18

Table 2.2: Telephone Instrument for Cognitive Status – Modified (TICS-M).

TICS-M	Score
Time Orientation: What is the day, date, month, season, and year? How old are you?	6
Registration: Recall the following 10 words: Cabin, Pipe, Elephant, Chest, Silk, Theatre, Watch, Whip, Pillow, Giant	10
Attention/Calculation: Serial 7 subtractions (93, 86, 79, 72,65) Count backwards from 20 to 1	6
Comprehension/ Semantic and Recent Memory: What do people usually use to cut paper? What is the prickly green plant found in the desert? Who is the head of state now? What is the opposite direction to east?	4
Language/Repetition: Repeat "No ifs ands or buts"	1
Delayed Recall: Repeat the 10 words from earlier	10
Total	37

2.1.4 Addenbrooke's Cognitive Examination-Revised (ACE-R)

ACE-R is a global cognition measure used to detect dementia. It has a total score of 100 and covers attention, orientation, memory, fluency, language, and visuospatial assessments. A cut off score of <82 is used for dementia [114].

2.1.5 Montreal Cognitive Assessment (MoCA)

The MoCA is a brief cognitive screening test used in stroke patients and covers visuospatial/executive function, verbal fluency, memory, attention, language, orientation, and abstraction assessments. It has a total score of 30 and a cutoff score of <25 is used for cognitive impairment [108].

2.1.6 Paced Auditory Serial Addition Task (PASAT)

The PASAT is a neuropsychological test used to assess sustained and divided attention, concentration, and information processing speed in patients with MS. The total score is 60 and cognitive impairment is determined by comparison with normative data that considers years of education. For PASAT, cut off scores of less than 32 and 35 respectively, for less than 12 and more than 12 years of education, were considered cognitively impaired [246].

2.2 Functional Assessments

2.2.1 National Institute of Health Stroke Scale (NIHSS)

NIHSS is a 7-minute stroke severity scale with higher scores associated with greater severity [247]. It has a max score of 42 and covers several neurological domains including cognition, and accounts for untestable components. It is a valid reliable assessment of stroke severity in clinics and research [248].

Table 2.3: National Institutes of Health Stroke Scale (NIHSS).

Domain	Description	Score
Consciousness	Alert, keenly responsive	0
	Not alert, responds to minor stimuli	1
	Not alert, requires repeated stimuli	2
	Unresponsive or only reflex effects	3
LOC questions	Answers both correctly	0
(month and age)	Answers one correctly	1
	Answers neither correctly	2
LOC Commands	Performs both correctly	0
(open and close eyes)	Performs one correctly	1
(grip and release)	Performs neither correctly	2
Best gaze	Normal	0
	Partial gaze palsy	1
	Forced deviation	2
Visual field	No visual loss	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
Motor arm	No drift, limb holds for 10 seconds	0
	Limb holds but drifts before 10 seconds	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Motor leg	No drift, limb holds for 5 seconds	0
	Limb holds but drifts before 5 seconds	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Facial palsy	Normal	0
	Minor paralysis	1
	Partial paralysis	2
	Complete paralysis	3
Sensory	Normal	0
	Mild to moderate sensory loss	1
	Severe loss	2
Limb ataxia	Absent	1
	Present in one limb	1
	Present in two limbs	2
Best language	No dysphasia	0
	Mild to moderate dysphasia	1

	Severe dysphasia	2
	Aphasia	3
Dysarthria	None	0
	Mild to moderate	1
	Severe	2
Inattention	None	0
	Inattention in one modality	1
	Inattention in more than one modality	2

2.2.2 Modified Rankin Scale (mRS)

The mRS is a stroke outcome measure that assesses patient dependency. The score ranges from no symptoms (0) to severe disability (5) and includes death (6) [249].

2.2.3 Barthel Index (BI)

BI is used to evaluate patient disability and covers different aspects of activities of daily living. These include mobility, use of stairs, transfer, feeding, dressing, grooming, toilet use, bathing, bowel and bladder control. The score ranges from 0-100 with lower scores associated with greater disability and dependency [249].

2.2.4 Zung Depression Scale (ZDS)

The ZDS [250] is a valid assessment of mood and depression. The score ranges from 0-100, with 70 and higher considered severely depressed. The short form of the test was used (score 0-40) and was then converted to match the full score (Score*100/40).

2.2.5 EuroQOL-5 Dimensions and Visual Analogue Scale (EQ-5D-VAS)

The EUROQOL assesses the quality of life using 5 descriptors and a visual analogue scale [251]. The EQ-5D descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The EQ-5D health state is converted into an index score using a formula, which can be compared with general population scores. The EuroQol-VAS is a subjective health state questionnaire scored from 0-100. Patients are asked to rate their health

state on the day of the question, with 100 being the best health imaginable and 0 being the worst health possible.

Table 2.4: Modified Rankin Scale (mRS)

Functional status	Score
No symptoms at all	0
No significant disability despite symptoms; able to carry out usual duties	1
Slight disability but able to look after own affairs without assistance	2
Moderate disability: requires some help, but walks without assistance	3
Moderately severe disability and unable to walk without assistance	4
Severe disability; bedridden, incontinent, and constant nursing care	5
Dead	6

Table 2.5: Barthel Index (BI)

Activity of Daily Living	Criteria	Score
Bowels	Incontinent	0
	Occasional accident (once per week)	5
	Continent	10
Bladder	Incontinent, or catheterised	0
	Occasional accident (max once/24 hrs)	5
	Continent	10
Grooming	Needs help with personal care	0
	Independent face/hair/teeth/shaving	5
Toilet use	Dependent	0
	Needs some help	5
	Independent	10
Feeding	Unable	0
	Needs help	5
	Independent	10
Transfer	Unable, no sitting balance	0
(bed to chair)	Major help (one or two people)	5
	Minor help (verbal or physical)	10
	Independent	15
Mobility	Immobile	0
	Wheelchair independent	5
	Walks with help of one person	10
	Independent	15
Dressing	Dependent	0
	Needs help but can do about half	5
	Independent	10
Stairs	Unable	0
	Needs help	5
	Independent	10
Bathing	Dependent	0
	Independent	5

Table 2.6: Zung Depression Scale (ZDS)

Question	Seldom/ Never	Some time	Good part of the time	Most of the time
I feel downhearted and blue	1	2	3	4
Morning is when I feel best	4	3	2	1
I have trouble sleeping at night	1	2	3	4
I eat as much as I used to	4	3	2	4
I get tired for no reason	1	2	3	4
I feel hopeful about the future	4	3	2	1
I find it easy to make decisions	1	2	3	4
I feel that I am useful/needed	4	3	2	1
My life is somewhat empty	1	2	3	4
I still enjoy the things I used	4	3	2	1

Table 2.7: EUROQOL-5D (EQ-5D)

Function	Description	Score
Mobility	I have no problems in walking about	1
	I have some problems in walking about	2
	I am confined to bed	3
Self-care	I have no problems with self-care	1
	I have some problems with washing or dressing	2
	I am unable to wash or dress myself	3
Usual activities	I have no problems performing my usual activities	1
	I have some problems performing usual activities	2
	I am unable to perform my usual activities	3
Pain/discomfort	I have no pain or discomfort	1
	I have moderate pain or discomfort	2
	I have extreme pain or discomfort	3
Anxiety/Depression	I am not anxious or depressed	1
	I am moderately anxious or depressed	2
	I am extremely anxious or depressed	3

2.2.6 Multiple Sclerosis Functional Composite (MSFC)

The MSFC comprises quantitative functional measures of three key clinical dimensions of MS: leg function/ambulation, arm/hand function and cognitive function. Scores on component measures are converted to standard scores (Z-scores), which are averaged to form a single MSFC score. The MSFC consists of the Timed 25-Foot Walk, 9-Hole Peg Test and the PASAT. The Timed 25-foot walk measures lower extremity function, and the patient is directed to walk 25 feet as quick as possible, the time limit is 3 minutes, and the task is immediately repeated. The 9-Hole Peg Test is a measure of upper extremity function and tests both hands twice, with a time limit of 5 minutes. The PASAT measures cognition as described previously [252].

2.2.7 Multiple Sclerosis Impact Scale

The Multiple Sclerosis Impact Scale is a 29-item scale measuring the physical (20 items) and psychological (9 items) impact of multiple sclerosis on the patient daily lives for the last two weeks. The score ranges from 1 (Not at all) to 5 (extremely), with lower scores representing less impact on activities of daily living [253].

2.2.8 Multiple Sclerosis Quality of Life-54 (MSQOL-54)

The MSQOL-54 assesses the quality of life and consists of generic components (Short Form-36) and 18 MS-specific components. These 54 items cover 12 components and include physical function, the role of limitations (physical and mental), pain, emotional health, energy, the perception of health, social function, cognitive function, health distress, the overall quality of life, and sexual function. It generates two scores for physical and mental function [254].

2.2.9 Health Status Questionnaire Short Form-36

The Health Status Questionnaire Short Form-36 [255] assesses health-related quality of life and can be used in MS patients. It has two separate scores for physical and mental function, which is produced by assessing 8 components. They include physical function, role limitation due to physical difficulties, role limitation due to emotional difficulties, pain, the perception of general health, vitality, social functioning, and mental health. A higher score represents better health, and scores can then be combined to make a raw score ranging from 0-100.

2.2.10 Fatigue Severity Scale 5 (FSS)

The FSS is a brief 9-item questionnaire assessing the severity of fatigue and activities of daily living. The scores range from 9 to 63 using a 7-point scale represented by 1 (strongly disagree) and 7 (strongly agree). Greater fatigue severity is represented by higher scores. A cut off score of >36 is indicative of severe fatigue in patients with MS [256].

2.2.11 Expanded Disability Status Scale (EDSS)

The EDSS measures the disability of patients with MS and monitors changes in the level of disability over time. The EDSS scale ranges from 0-10 in 0.5unit increments that represent higher levels of disability with 1 (no disability) to 10 (death). EDSS steps 1.0 to 4.0 refer to people with MS who can walk without any aid and is based on measures of impairment in eight functional systems: pyramidal (weakness or difficulty moving limbs), cerebellar (ataxia, loss of coordination or tremor), brain stem (problems with speech, swallowing and nystagmus), sensory (numbness or loss of sensations), bowel and bladder function, visual

function, cerebral functions and other. EDSS steps 5.0 to 9.5 are defined by the impairment of walking [257].

3 Clinical and Radiological Predictors of Cognitive Impairment after Ischaemic Stroke or Transient Ischaemic Attack: Data from the Randomised Clinical Trials ENOS and TARDIS

3.1 Abstract

3.1.1 Importance

Post-stroke cognitive impairment (PSCI) is common and associated with poor recovery. Previous studies investigating predictors of PSCI reflect restricted populations.

3.1.2 Objective

To determine the baseline clinical and radiological predictors of PSCI at 3 months.

3.1.3 Design and Setting

ENOS was an international multicentre single-blind randomised controlled trial that investigated blood pressure management between July 20, 2001, and Oct 14, 2013, with a follow-up duration of 3 months. Participants were recruited within 48 hours of stroke and randomised to 7 days of treatment with transdermal glyceryl trinitrate, and a subset was randomised for continuing or stopping their pre-stroke antihypertensive drugs for 7 days. TARDIS was an international and multicentre prospective randomised open-label blinded endpoint trial that investigated the safety and efficacy of triple antiplatelet therapy between April 7, 2009, and March 18, 2016, with a follow-up duration of 3 months. Participants were recruited within 48 hours of transient ischaemic attack (TIA) or ischaemic stroke (IS) and randomised to triple antiplatelet therapy or guideline therapy for 30 days.

3.1.4 Participants

Participants were previously independent adults with an acute ischaemic stroke or transient ischaemic attack that were recruited into the Efficacy of Nitric Oxide in Stroke (ENOS) or Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trials. Functionally dependent participants (mRS >2) before their stroke were excluded. 7107 participants were enrolled in the ENOS (n=4011) and TARDIS (n=3096) trials. 6395 participants had an IS or TIA and were independent before their stroke.

3.1.5 Main Outcome and Measure

Cognitive function was assessed at 90 days post-stroke using the Telephone Interview for Cognitive Status-Modified (TICS-M), Mini-Mental State Examination-Modified (MMSE-M), and animal naming (verbal fluency test). A hierarchical approach was used to determine PSCI: the primary determinant was a TICS-M score ≤19 (equivalent to ≤20 on the TICS-M /39); if the TICS-M was unavailable, an MMSE-M (/18) score of <14 (equivalent to <24 on the MMSE) was used and if both were unavailable, a verbal fluency score of <10 was used as the final determiner. Adjusted binary logistic regression was used to identify predictors of PSCI. A p-value <0.01 was used to account for multiple testing.

3.1.6 Results

Of the 4798/6395 participants with cognition data, 1639 (34.2%) had PSCI (TICS-M score ≤19) and 451 had died (9.4%) by 90 days. Independent baseline predictors of PSCI were increasing age (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.04-1.05; p $\leq$0.001), pre-

stroke disability (mRS >0) (OR 1.28, 95% CI 1.08-1.51; p 0.003), non-UK participants (OR 1.40, 95% CI 1.18-1.66; p ≤0.001), atrial fibrillation (OR 1.53, 95% CI 1.14-2.06; p 0.004), low systolic blood pressure (OR 0.93, 95% CI 0.90-0.96; p ≤0.001), heart rate (OR 1.12, 95% CI 1.06-1.17; p ≤0.001) and stroke severity (OR 1.12, 95% CI 1.10-1.13; p ≤0.001).

3.1.7 Conclusion and Relevance

PSCI was common and independently associated with older age, pre-stroke disability, non-UK participants, atrial fibrillation, lower systolic BP, higher heart rate and stroke severity.

3.2 Introduction

Stroke is a leading cause of death and disability worldwide [258] and a major risk factor for dementia, with a doubling in risk in individuals younger than 85 years old [99]. First-ever and recurrent strokes are associated with new-onset dementia in one-tenth and over a third of participants, respectively [92]. Post-stroke cognitive impairment (PSCI), which includes lesser degrees of cognitive impairment as well as dementia, is even more common after stroke [92, 93] and can negatively impact a participant's independence and quality of life. PSCI is also associated with an increased risk of depression, institutionalisation and mortality [92, 259-262].

Previous studies investigating clinical and radiological predictors of PSCI have consistently shown that older age and low levels of education are major predictors of poor cognitive outcome following a stroke [263-265]. Meanwhile, studies investigating the association between cognition and vascular risk factors, pre-existing brain imaging signs, and stroke characteristics were unclear and require further exploration whilst accounting for the independence of variables and reflect a range of stroke severities [91, 92].

Here, we determined baseline clinical and radiological predictors of PSCI in a large cohort of previously independent adults with an acute ischaemic stroke (IS) or transient ischaemic attack (TIA), enrolled into either the Efficacy of Nitric Oxide in Stroke (ENOS) trial [266] or the Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial [267].

3.3 Methods

3.3.1 Studies and participants

Eligible participants were previously independent (modified Rankin Score (mRS) ≤2) adults (≥18 y), with an acute IS or TIA that was recruited into the ENOS or TARDIS trials. ENOS was an international multicentre single-blind randomised controlled trial that investigated blood pressure management in acute stroke (ISRCTN99414122). In brief, participants were recruited within 48 hours of stroke and randomised to 7 days of treatment with transdermal glyceryl trinitrate, and a subset was randomised for continuing or stopping their pre-stroke antihypertensive drugs for 7 days [266, 268-270]. TARDIS was an international multicentre prospective randomised open-label blinded endpoint trial that investigated the safety and efficacy of triple antiplatelet therapy (ISRCTN47823388). Briefly, participants were recruited within 48 hours of transient ischaemic attack (TIA) or ischaemic stroke and randomised to triple antiplatelet therapy (aspirin/clopidogrel/dipyridamole) or guideline therapy (clopidogrel monotherapy, or dual antiplatelet therapy with aspirin and dipyridamole) for 30 days [267, 271-273]. Participants and carers provided written informed consent, and the trials were approved by national or local ethics committees in each participating country and site and were adopted by the Australian, Canadian and UK National Institute of Health Research Stroke Research Network. National competent authorities (or equivalent) gave approvals for this study.

3.3.2 Clinical assessment and neuroimaging

At baseline, we collected participant demographics, medical history and stroke: severity (National Institute of Health Stroke Scale, NIHSS) [247],

subtype (Oxfordshire Stroke Community Project (OCSP) classification) [20], and aetiology (Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria) [11]. Functionally dependent participants (mRS >2) before their stroke were excluded [249].

Participants underwent a CT or MRI scan at baseline depending on the availability of neuroimaging at the time of admission. Scans were sent for central rating using validated scales by blinded expert raters. Raters scored early ischaemic signs (infarct location, size and swelling) and pre-existing cerebral structural signs (old vascular lesions, leukoaraiosis and cerebral atrophy) using validated scores [274]. Lesion location was categorised into 1) middle cerebral artery (MCA), anterior cerebral artery (ACA) or borderzone, 2) posterior (posterior cerebral artery (PCA), cerebellum, or brainstem), and 3) lacunar [274]. Infarct size was categorised into small, medium and large using the International Stroke Trial-3 method [274, 275]. Old vascular lesion location was defined as either: cortical, striatocapsular, borderzone, lacunar or brainstem [275]. Cortical and subcortical atrophy were classified as either: none (0), moderate (1), or severe (2), using a standard example for comparison. A global cerebral atrophy severity score (total 4) was calculated from the combined severity of cortical and subcortical atrophy. Severe atrophy was defined as a score of 2 on either cortical or subcortical atrophy.

The presence and severity of leukoaraiosis or white matter hyperintensities (WMH) were identified on CT [276] or MRI [277]. On CT, the anterior and posterior WMH were each classified using the van Swieten score as either: none (0), lucency restricted to the region adjoining the ventricles (1), or lucency covering the entire region from

lateral ventricle to cortex (2) [276]. On MRI, periventricular and deep WMH were classified using the Fazekas score. Periventricular WMH were classified as either: absent (0), caps or pencil-thin lining (1), and smooth halo or irregular periventricular signal extending into deep white matter (2). Deep WMH were classified as either: absent (0), punctate foci (1), and beginning confluence or large confluent areas (2) [277]. A leukoaraiosis severity score (total 4) was calculated from the combined severity of anterior and posterior WMH (total 4) or the combined severity of periventricular and deep WMH (total 4). Severe leukoaraiosis was defined as a score of ≥2 on either anterior, posterior, periventricular, or deep WMH. A small vessel disease (SVD) score (total 3) was summed from the presence of any severe leukoaraiosis (≥2), any severe atrophy (>1) and any old lacunar infarct (1), omitting perivascular spaces from any MR scans [278, 279]. A brain frailty score (/3) was summed from the presence of an old vascular lesion (1), any leukoaraiosis (1), and any cerebral atrophy (1)[274].

3.3.3 Cognitive impairment and functional assessments

Cognitive status and functional outcomes were assessed at 90 days via telephone in the country of recruitments national language. Cognitive impairment was screened for using the Telephone Interview for Cognitive Status-Modified (TICS-M) [280], the Mini-Mental State Examination-Modified (MMSE-M) [281] and a verbal fluency test (animal naming) [282]. To allow for international use, two questions were excluded from the TICS-M resulting in a total score of 37. [116, 283]. A hierarchical approach was used to determine PSCI: the primary determinant was a TICS-M score ≤19 (equivalent to ≤20 on the TICS-M /39); if the TICS-M

was unavailable, an MMSE-M (/18) score of <14 (equivalent to <24 on the MMSE) was used;[281, 284, 285] and if both were unavailable, a verbal fluency score of <10 was used as the final determiner [282]. Incomplete cognitive assessments were not included. PSCI does not include focal cognitive deficits such as aphasia and neglect. Cognitive sub-domains were determined from the components of the cognition assessments: 1) Episodic memory (/28) using orientation in place and delayed recall (MMSE-M) and immediate and delayed recall from (TICS-M); 2) Attention and working memory (/7) using serial sevens subtraction (MMSE-M/TICS-M), the spelling of 'WORLD' backwards (MMSE-M) and language repetition of "No ifs, ands or buts" (TICS-M); 3) Language using comprehension, semantic and recent memory (TICS-M) and verbal fluency (animal naming) [286]. Participant dependence, disability, quality of life and mood were assessed by the mRS [249], Barthel Index (BI) [249], EuroQol health utility status (EQ-HUS) and visual analogue scale (EQ-VAS) [287], and Zung depression scale (ZDS), respectively [288]. A score for death was included for each functional scale: mRS 6, BI -5, ZDS 102.5, EQ-HUS 0, EQ-VAS -1 [266, 267]. Dementia is a fatal disease and as such participants that died were given a score of -1 for each cognition measure [266, 267].

3.3.4 Statistical Methods

Independent-Samples T-Test (continuous variable), Chi-Square test for homogeneity (binary variable) and Mann-Whitney U (ordinal variable) were used to compare the differences between two independent groups. One-way ANOVA (continuous variable), or Chi-square test (binary variable) (multiple comparisons and Bonferroni adjustment for P values)

or Kruskal-Wallis (ordinal variable) were used to compare differences between three independent groups. Homogeneity of variance was determined using Levene's Test for Equality of Variances. If the assumption of homogeneity of variances is violated, Welch's ANOVA is used instead of the One-Way ANOVA. One-Way ANOVA Post-hoc tests were Tukey-Kramer and Games-Howell depending on whether homogeneity of variances was not or was violated, respectively. Unadjusted and adjusted backward binary logistic regression was used to identify predictors of cognitive impairment. The receiver operating characteristic (ROC) area under the curve (AUC) was used to determine the models' level of discrimination. All statistical analysis was performed using the Statistical Package for Social Sciences version-24 (SPSS-24). Standard deviation (SD), interquartile range [IQR], odds ratios [OR] and 95% confidence intervals (CI) were calculated, and significance was set at $p < 0.05$ or $p < 0.01$ if accounting for multiple testing.

3.4 Results

Participant recruitment, exclusion and cognitive ability are shown in Figure 3.1. On day 90, 4798 (67.5%) participants completed the cognition assessment (n=4347) or had documentation of the participants death (n=451) and 1597 (22.5%) participants did not complete the cognition assessment (Figure 3.1). Participants without cognition data (Table 3.1) were more likely to be older, female, have a pre-stroke disability, have higher systolic blood pressure (SBP) and heart rate (HR), or have greater severity of left-hemisphere stroke. A history of hypertension, atrial fibrillation (AF), prior stroke or TIA or ischaemic heart disease (IHD) were also more prevalent. They were also more likely on neuroimaging to have old vascular lesions or have greater severity of cerebral atrophy, leukoaraiosis, brain frailty and small vessel disease features (Table 3.2). These participants were also more likely to be dependent, disabled, have a poorer quality of life, and be depressed at 90 days (Supplementary Table I).

Of 4798 participants, PSCI was present in 1639 (34.2%) participants and a further 451 (9.4%) participants died by day 90 (Figure 3.1). Participants with PSCI or that died were more likely to be older, female, recruited outside the UK, and to have a pre-stroke disability, a history of hypertension, AF, IHD, or a higher SBP and HR, or greater stroke severity when compared to patients with preserved cognition (Table 3.1). Participants with PSCI were more likely to have a left-hemisphere stroke as compared to participants with preserved cognition (Table 3.1). Participants that died were more likely to have a history of prior stroke or TIA, a shorter time to randomisation, or a higher diastolic BP (DBP) in

comparison to participants with preserved cognition (Table 3.1). Participants with PSCI or that died were also more likely to have a large lesion, infarct swelling, old vascular lesions, and greater severity of cerebral atrophy, leukoaraiosis, brain frailty and SVD features in comparison to cognitively preserved patients (Table 3.2). Participants that died were also more likely to have a lesion affecting the MCA, ACA or borderzone territories in comparison to both participants with PSCI and participants with preserved cognition (Table 3.2). Participants with PSCI were more likely at three months to be dependent, disabled, depressed and to have a worse quality of life (Table 3.3).

Participants with higher baseline SBP after stroke had greater severity of the stroke, had a higher SVD score and performed significantly worse on all cognitive and functional assessments (Supplementary Table II, Supplementary Table III, Supplementary Table IV). Participants recruited outside the UK were more likely to have clinical factors and radiological features associated with greater stroke severity, however, they did not differ from UK participants concerning brain frailty features (Supplementary Table V, Supplementary Table VI). Participants recruited outside the UK performed significantly worse on all cognition and functional outcomes, especially on the subdomains of attention and working memory and language (Supplementary Table VII).

The unadjusted predictors of PSCI were age, female sex, pre-stroke disability, recruitment outside the UK, a history of hypertension, AF, previous stroke, or TIA, higher SBP and HR, greater severity of the stroke and higher SVD and brain frailty scores (Supplementary Table VIII). The independent predictors of PSCI were age, pre-stroke disability,

recruitment outside the UK, AF, lower SBP, higher HR, and greater severity of the stroke (Table 3.4, n = 4564, R^2 = 0.237, AUC = 0.735, 95% CI, 0.721 to 0.750). This model was statistically significant (p <0.001) and showed an acceptable level of discrimination. All independent predictors, apart from AF, remained significant after excluding participants that died, whereas a higher SVD score became significant (Supplementary Table IX, n = 4125, R^2 = 0.134, AUC = 0.683, 95% CI, 0.666 to 0.700). This model was statistically significant (p <0.001) and showed a poor to an acceptable level of discrimination.

3.5 Discussion

This is the largest international hospital-based study of PSCI to date. Of 4798 participants, PSCI was present in 34.2% of participants and a further 9.4% of participants had died by 90 days. Independent predictors of PSCI were older age, greater stroke severity, pre-stroke disability, non-UK participants, a history of AF, lower SBP, and a higher HR. A higher SVD score was an independent predictor of PSCI after excluding patients that died.

Our results suggest that PSCI is common after stroke especially in older participants with SVD features. As previously reported, pre-stroke disability (mRS >0) was a significant predictor of PSCI despite the exclusion of pre-stroke dependence [92, 289]. This suggests cognitive changes, potentially due to underlying neurodegenerative pathology, may have been present in independent participants before their stroke. This may be related to the theory that a combination of neurodegenerative and vascular pathologies exacerbate the risk of PSCI [290]. Although non-UK participants were significantly more likely to develop PSCI, the effect of sample size and confounding factors such as healthcare access, socioeconomic status, language, cultural interpretation, participant mood and delivery of assessments must be considered [260, 291-294].

The association between AF and PSCI has been inconsistently reported [92, 295-298] although population-based studies in persons with AF and without clinical stroke suggest a positive association [299]. Our results suggest that the influence of AF on cognitive function was dependent on patient mortality and in turn stroke severity. We found no consistent

association between baseline BP after stroke and cognition. similar to previous studies [300, 301]. Our results suggest a higher baseline SBP after stroke influences cognitive function through factors related to stroke severity and brain frailty. However, our results also suggest a lower baseline SBP after stroke also influences cognitive function, independent of stroke severity, perhaps through a reduction in cerebral blood flow and brain tissue metabolism. Previous studies have suggested a U-shaped relationship between BP and cognitive function [302-307], with a recent study showing low SBP and high SBP were associated with PSCI at 3 months [308].

Since an increased baseline HR was also an independent predictor of PSCI, our findings support the theory that HR is associated with cognition [309-311] perhaps through reduced variability reflecting vagal dysfunction. A greater degree of brain frailty, which we define as a sum score of old vascular lesions, WMH and cerebral atrophy, was not an independent predictor of PSCI after accounting for multiple testing. However, a higher SVD score, which we define as the presence of an old lacunar infarct, severe WMH and severe cerebral atrophy, was an independent predictor of PSCI after excluding patients that died. These factors constitute a spectrum for SVD, which increases brain damage and worsens cognitive function [92, 312-316].

This analysis has several strengths including its inclusion of two large clinical trials of prospective design with a standardised and detailed collection of information on cognition, large size, international multicentre recruitment, follow-up by telephone (which results in more participants providing data, that might have been unable to if otherwise

done in-person), and inclusion of both IS and TIA. However, the study has several limitations. Information on the level of education and participant ethnicity, as shown previously to be associated with PSCI [92] were not collected. Neither premorbid nor baseline cognition could be assessed and so participants with pre-stroke cognitive impairment may have been included. Although this may have led to an overestimation of the prevalence of PSCI, this effect was minimised by excluding participants with pre-stroke dependency. As participants with severe strokes were less likely to complete the cognitive assessment, they will not have been fully represented in the cohort. Although this may cause an underestimation of factors associated with stroke severity, participants that died following very severe strokes were included, reducing this bias. The PSCI was assessed at 3 months after stroke, a relatively early stage and may not reflect long term PSCI risk. For non-UK sites, the English validated versions of the cognition and functional assessments were translated by the assessor into the country of recruitments national language. Lastly, the cognition assessment was not an extensive neuropsychological examination and as such, it did not assess executive and visuospatial function.

In conclusion, this large analysis of prospectively collected data indicates that older age, pre-stroke disability, greater stroke severity, lower SBP and higher HR were predictors of PSCI. A higher SVD score (older lacunar infarct, severe WMH and severe atrophy) was predictive of PSCI when excluding patients that died. The pattern of risk factors was similar for the UK and non-UK participants although non-UK participants appeared to have a higher risk of PSCI, this may reflect technical or cultural

differences and requires further evaluation. Further investigation in a similarly large cohort in other countries and regions with adjustment for pre-stroke cognition, level of education, and participant ethnicity is required to confirm these associations. Also, these further investigations should focus on cerebral haemorrhage cohorts to determine whether these associations also apply to different stroke types.

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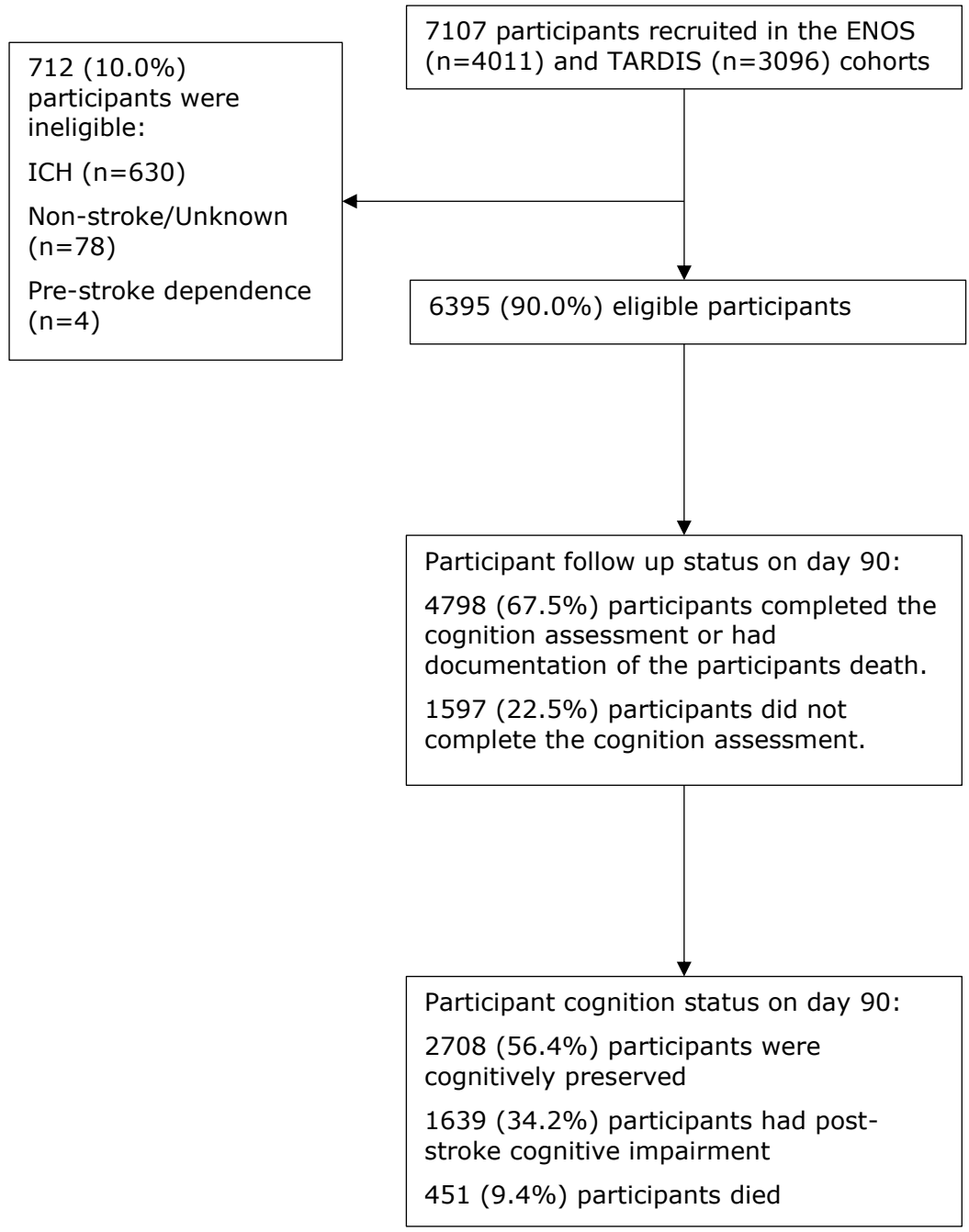

Figure 3.1 Participant flow chart

Table 3.1. Baseline clinical characteristics of participants with or without cognition data and participants with or without post-stroke cognitive impairment (PSCI) at 3 months.

	All	**No cognition data**	**With cognition data**	**P**	**No PSCI**	**PSCI**	**Died**	**P**
No. of participants (%)	6395	1597 (25.0)	4798 (75.0)		2708 (56.4)	1639 (34.2)	451 (9.4)	
Demographics								
Age (years)	70.0 (11.1)	72.4 (11.0)	69.3 (11.1)	<0.001	66.7 (10.3)	71.3 (10.9)	77.3 (11.1)	<0.001
Female (%)	2608 (40.8)	701 (43.9)	1907 (39.7)	0.003	988 (36.5)	688 (42.0)	231 (51.2)	<0.001
Pre-morbid mRS >0 (%)	1341 (21.0)	390 (24.4)	951 (19.8)	<0.001	414 (15.3)	378 (23.1)	159 (35.3)	<0.001
Recruited in the UK (%)	5090 (79.6)	1265 (79.2)	3825 (79.7)	0.66	2247 (83.0)	1246 (76.0)	332 (73.6)	<0.001
Time to randomisation [h]	27.8 [18.7-38.5]	28.5 [18.5-38.7]	27.7 [18.7-38.4]	0.23	27.9 [19.0-38.5]	28.1 [18.8-38.8]	25.1 [16.3-35.5]	<0.001
Medical history (%)								
Hypertension	3982 (62.3)	1101 (68.9)	2881 (60.0)	<0.001	1526 (56.4)	1039 (63.4)	316 (70.1)	<0.001
Diabetes	1190 (18.6)	320 (20.0)	870 (18.1)	0.090	468 (17.3)	321 (19.6)	81 (18.0)	0.16
Atrial fibrillation	531 (8.3)	201 (12.6)	330 (6.9)	<0.001	78 (2.9)	130 (7.9)	122 (27.1)	<0.001

Stroke/TIA	1457 (22.8)	403 (25.2)	1054 (22.0)	0.007	563 (20.8)	365 (22.3)	126 (27.9)	0.003
Hyperlipidaemia (n=5884)	2269 (38.6)	553 (38.0)	1716 (38.8)	0.58	1011 (39.9)	574 (38.3)	131 (33.0)	0.027
Ischaemic heart disease	1001 (15.8)	286 (18.1)	715 (15.1)	0.005	327 (12.2)	268 (16.6)	120 (27.1)	<0.001
Haemodynamics								
Systolic blood pressure (mm Hg)	155.6 (21.7)	158.2 (21.7)	154.7 (21.6)	<0.001	152.9 (21.4)	155.2 (21.8)	163.5 (20.0)	<0.001
Diastolic blood pressure (mm Hg)	84.4 (13.1)	84.9 (13.0)	84.2 (13.1)	0.052	84.2 (13.0)	83.4 (12.8)	86.8 (14.1)	<0.001
Heart rate (bpm) (n=6391)	75.3 (13.9)	76.2 (14.4)	75.0 (13.8)	0.003	73.6 (13.0)	75.5 (13.9)	81.6 (16.0)	<0.001
Index event								
Ischaemic stroke (%)	5558 (86.9)	1461 (91.5)	4097 (85.4)	<0.001	2220 (82.0)	1433 (87.4)	444 (98.4)	<0.001
Transient ischaemic attack (%)	837 (13.1)	136 (8.5)	701 (14.6)	<0.001	488 (18.0)	206 (12.6)	7 (1.6)	
NIHSS (/42)	7.1 (6.3)	9.4 (6.9)	6.3 (5.9)	<0.001	4.6 (4.4)	6.6 (5.6)	15.4 (6.5)	<0.001
Left hemisphere stroke (%) (n=6187)	2969 (48.0)	825 (52.6)	2144 (46.4)	<0.001	1136 (43.8)	793 (50.2)	215 (48.0)	<0.001
Stroke subtype (%) (n=6393)								<0.001
Total anterior	1167 (18.3)	460 (28.8)	707 (14.7)	<0.001	190 (7.0)	251 (15.3)	266 (59.0)	
Partial anterior	2425 (37.9)	606 (37.9)	1819 (37.9)	0.98	1080 (39.9)	630 (38.5)	109 (24.2)	

Posterior	347 (5.4)	51 (3.2)	296 (6.2)	<0.001	198 (7.3)	89 (5.4)	9 (2.0)	
Lacunar	2454 (38.4)	480 (30.1)	1974 (41.2)	<0.001	1239 (45.8)	668 (40.8)	67 (14.9)	
Ischaemic cause (%)								
Cardioembolic	769 (12.0)	278 (17.4)	491 (10.2)	<0.001	163 (6.0)	173 (10.6)	155 (34.4)	<0.001
Large vessel	1153 (18.0)	353 (22.1)	800 (16.7)	<0.001	388 (14.3)	303 (18.5)	109 (24.2)	<0.001
Small vessel	2414 (37.7)	491 (30.7)	1923 (40.1)	<0.001	1213 (44.8)	654 (39.9)	56 (12.4)	<0.001
Mixed	128 (2.0)	27 (1.7)	101 (2.1)	0.30	45 (1.7)	40 (2.4)	16 (3.5)	0.018
Not determined	1931 (30.2)	448 (28.1)	1483 (30.9)	0.031	899 (33.2)	469 (28.6)	115 (25.5)	<0.001

Data are n (%), mean (SD) or median [IQR]. mRS = modified Rankin Scale. BPM = beats per minute. NIHSS = National Institute of Health Stroke Scale.

Table 3.2: Baseline radiological characteristics of participants with or without cognition data and participants with or without post-stroke cognitive impairment (PSCI) at 3 months.

	All	**No cognition data**	**With cognition data**	**P**	**No PSCI**	**PSCI**	**Died**	**P**
No. of participants (%)	6118	1544 (25.2)	4574 (74.8)		2571 (56.2)	1633 (34.2)	440 (9.6)	
Lesion territory (%)								
MCA, ACA, or borderzone	2584 (42.2)	750 (48.6)	1834 (40.1)	<0.001	935 (36.4)	617 (39.5)	282 (64.1)	<0.001
Posterior	204 (3.3)	35 (2.3)	169 (3.7)	0.007	94 (3.7)	54 (3.5)	21 (4.8)	0.43
Lacunar	419 (6.8)	71 (4.6)	348 (7.6)	<0.001	213 (8.3)	123 (7.9)	12 (2.7)	<0.001
Indeterminate	2911 (47.6)	688 (44.6)	2223 (48.6)	0.006	1329 (51.7)	769 (49.2)	125 (28.4)	<0.001
Lesion size (%) (n=6108)				<0.001				<0.001
Nonvisible	2911 (47.7)	688 (44.6)	2223 (48.7)		1329 (51.8)	769 (49.3)	125 (28.5)	
Small	2006 (32.8)	445 (28.9)	1561 (34.2)		922 (35.9)	522 (33.5)	117 (26.7)	
Medium	615 (10.1)	193(12.5)	422 (9.2)		213 (8.3)	148 (9.5)	61 (13.9)	
Large	576 (9.4)	216 (14.0)	360 (7.9)		103 (4.0)	121 (7.8)	136 (31.0)	
Presence of swelling	1711 (28.0)	544 (35.2)	1167 (25.5)	<0.001	526 (20.5)	398 (25.5)	243 (55.2)	<0.001
Pre-existing structural signs								

Presence of atrophy (%)	5387 (88.1)	1398 (90.5)	3989 (87.2)	<0.001	2157 (83.9)	1409 (90.1)	423 (96.1)	<0.001
Cerebral atrophy severity (/4)	1.81 (1.13)	2.01 (1.15)	1.74 (1.11)	<0.001	1.53 (1.04)	1.91 (1.14)	2.33 (1.09)	<0.001
Presence of leukoaraiosis (%)	2427 (39.7)	665 (43.1)	1762 (38.5)	0.002	895 (34.8)	656 (42.0)	211 (48.0)	<0.001
Leukoaraiosis severity (/4) (n=6106)	0.85 (1.23)	0.94 (1.28)	0.82 (1.21)	0.001	0.73 (1.17)	0.90 (1.25)	1.03 (1.29)	<0.001
Presence of old lesions (%)	3709 (60.6)	1004 (65.0)	2705 (59.1)	<0.001	1398 (54.4)	999 (63.9)	308 (70.0)	<0.001
Small vessel disease score (/3) (n=6106)	0.86 (0.81)	0.97 (0.82)	0.83 (0.80)	<0.001	0.70 (0.77)	0.94 (0.82)	1.1 (0.84)	<0.001
Brain frailty score (/3)	1.88 (0.88)	1.99 (0.85)	1.85 (0.88)	<0.001	1.73 (0.89)	1.96 (0.86)	2.14 (0.79)	<0.001

Data are n (%) or mean (SD). MCA=Middle cerebral artery. ACA=Anterior cerebral artery.

Table 3.3: Cognition and functional outcomes of participants with and without PSCI at 3 months.

	All	**No PSCI**	**PSCI**	**P**
No. of participants (%)	4798	2708 (56.4)	2090 (43.6)	
Cognition outcome				
TICS-M	18.5 (8.9)	24.3 (3.6)	10.8 (7.9)	<0.001
MMSE-M	12.9 (5.9)	16.2 (1.9)	8.4 (6.4)	<0.001
Verbal fluency	13.6 (8.6)	17.8 (6.9)	8.2 (7.4)	<0.001
Episodic memory	11.9 (6.3)	15.8 (3.6)	6.7 (5.3)	<0.001
Attention and working memory	7.4 (4.1)	9.7 (1.7)	4.2 (4.2)	<0.001
Language	16.8 (9.5)	21.6 (7.0)	10.5 (8.7)	<0.001
Functional outcome				
modified Rankin scale	2.0 [1.0-3.0]	1.0 [1.0-2.0]	3.0 [1.0-4.0]	<0.001
Barthel index	81.9 (32.6)	94.1 (13.1)	66.1 (42.2)	<0.001
Zung depression scale	52.3 (22.3)	44.6 (14.6)	62.5 (26.3)	<0.001
Euroqol-health utility status	0.65 (0.36)	0.77 (0.27)	0.51 (0.40)	<0.001
Euroqol-visual analogue scale	65.2 (28.7)	74.9 (18.4)	52.3 (34.2)	<0.001

N: varied between 4040 and 4798. Data are mean (SD) or median [IQR]. PSCI = Post Stroke Cognitive Impairment. TICS-M = Telephone Interview for Cognitive Status-Modified. MMSE-M = Mini-Mental State Examination-Modified.

Table 3.4: Multiple variable predictors of PSCI at 3 months using backward binary logistic regression

Risk factors	**All, adjusted OR (95% CI) ***	**P**
Age	1.046 (1.039-1.054)	<0.001
Pre-morbid mRS >0	1.284 (1.089-1.514)	0.003
Recruited outside the UK	1.401 (1.181-1.662)	<0.001
Atrial fibrillation	1.537 (1.143-2.066)	0.004
Systolic blood pressure	0.936 (0.906-0.968)	<0.001
Heart rate	1.120 (1.067-1.176)	<0.001
Stroke severity (NIHSS)	1.122 (1.106-1.137)	<0.001
Brain frailty	1.104 (1.006-1.212)	0.038
Small vessel disease	1.097 (0.994-1.210)	0.065

Shown are odds ratios (OR) and 95% confidence intervals (CI) with p-values. mRS = modified Rankin Scale. NIHSS = National Institute of Health Stroke Scale. * Adjusted for all factors included in the univariable analysis.

3.6 Supplemental Material

Supplementary Table I: Functional outcomes of participants with vs without cognition data 3 months after their index event.

	All	**No cognition data**	**With Cognition Data**	**P**
No. of Participants (%)	6359	1561 (24.5)	4798 (75.5)	
Functional outcome				
modified Rankin scale	2.0 [1.0-4.0]	3.0 [2.0-4.0]	2.0 [1.0-3.0]	<0.001
Barthel index	78.0 (34.1)	65.3 (35.6)	81.9 (32.6)	<0.001
Zung depression scale	52.5 (21.9)	54.1 (17.5)	52.3 (22.3)	0.034
Euroqol-health utility status	0.60 (0.39)	0.42 (0.42)	0.65 (0.36)	<0.001
Euroqol-visual analogue scale	64.4 (28.1)	60.5 (24.4)	65.2 (28.7)	<0.001

N varied between 5175 and 6359. Data are mean (SD) or median [IQR].

Supplementary Table II: Baseline clinical characteristics of participants by their baseline systolic blood pressure after stroke, including patients that died.

	All	**Normal (SBP <120)**	**Elevated (SBP 120-129)**	**Stage 1 (SBP 130 to 139)**	**Stage 2 (SBP 140 to 179)**	**Hypertensive crisis (SBP ≥180)**	**P**
No. of participants (%)	4798	226 (4.7)	365 (7.6)	549 (11.4)	3080 (64.2)	578 (12.1)	
Demographics							
Age (years)	69.2 (11.0)	66.4 (9.2)	67.7 (10.6)	69.2 (11.0)	69.4 (11.0)	70.3 (11.6)	<0.001
Female (%)	1907 (39.7)	93 (41.2)	138 (37.8)	219 (39.9)	1192 (38.7)	265 (45.8)	0.025
Pre-morbid mRS >0 (%)	951 (19.8)	37 (16.4)	64 (17.5)	103 (18.8)	603 (19.6)	144 (24.9)	0.012
Recruited in the UK (%)	3825 (79.7)	224 (99.1)	352 (96.4)	489 (89.1)	2384 (77.4)	376 (65.1)	<0.001
Time to randomisation [h]	27.7 [18.7-38.4]	32.5 [25.2-41.1]	29.1 [22.6-39.8]	28.7 [20.6-39.0]	27.2 [18.0-37.7]	26.0 [15.5-36.7]	<0.001
Medical history (%)							
Hypertension	2881 (60.0)	102 (45.1)	203 (55.6)	309 (56.3)	1891 (61.4)	376 (65.1)	<0.001
Diabetes	870 (18.1)	31 (13.7)	66 (18.1)	107 (19.5)	560 (18.2)	106 (18.3)	0.45
Atrial fibrillation	330 (6.9)	0 (0.0)	0 (0.0)	16 (2.9)	253 (8.2)	61 (10.6)	<0.001
Stroke/TIA	1054 (22.0)	45 (19.9)	88 (24.1)	113 (20.6)	660 (21.4)	148 (25.6)	0.12
Hyperlipidaemia (n=5884)	1716 (38.8)	105 (48.2)	161 (46.9)	217 (41.4)	1080 (38.2)	153 (29.9)	<0.001
Ischaemic heart disease	715 (15.1)	36 (15.9)	60 (16.5)	79 (14.4)	431 (14.2)	109 (19.3)	0.031
Haemodynamics							
Diastolic blood pressure (mm Hg)	84.1 (13.0)	67.6 (8.1)	72.5 (8.5)	76.2 (9.5)	85.7 (11.0)	96.8 (13.4)	<0.001
Heart rate (bpm) (n=6391)	75.0 (13.7)	71.9 (11.9)	72.2 (12.1)	73.9 (13.6)	75.5 (14.0)	76.3 (13.7)	<0.001

Index event							
Ischaemic stroke (%)	4097 (85.4)	164 (72.6)	276 (75.6)	422 (76.9)	2669 (86.7)	566 (97.9)	<0.001
Transient ischaemic attack (%)	701 (14.6)	62 (27.4)	89 (24.4)	127 (23.1)	411 (13.3)	12 (2.1)	
NIHSS (/42)	6.2 (5.9)	2.4 (2.8)	2.6 (3.7)	3.8 (4.8)	6.7 (5.9)	9.8 (5.5)	<0.001
Left hemisphere stroke (%) (n=6187)	2144 (46.4)	87 (40.8)	159 (46.8)	250 (48.0)	1393 (46.9)	255 (44.3)	0.33
Stroke subtype (%) (n=6393)							0.007
Total anterior	707 (14.7)	14 (6.2)	25 (6.8)	43 (7.8)	492 (16.0)	133 (23.1)	
Partial anterior	1819 (37.9)	112 (49.6)	153 (41.9)	247 (45.0)	1136 (36.9)	171 (29.6)	
Posterior	296 (6.2)	17 (7.5)	22 (6.0)	36 (6.6)	186 (6.0)	35 (6.1)	
Lacunar	1974 (41.2)	83 (36.7)	165 (45.2)	223 (40.6)	1265 (41.1)	238 (41.2)	
Ischaemic cause (%)							
Cardioembolic	491 (10.2)	13 (5.8)	17 (4.7)	30 (5.5)	356 (11.6)	75 (13.0)	<0.001
Large vessel	800 (16.7)	31 (13.7)	51 (14.0)	82 (14.9)	533 (17.3)	103 (17.8)	0.20
Small vessel	1923 (40.1)	88 (38.9)	150 (41.1)	237 (43.2)	1208 (39.2)	240 (41.5)	0.41
Mixed	101 (2.1)	1 (0.4)	3 (0.8)	6 (1.1)	71 (2.3)	20 (3.5)	0.006
Not determined	1483 (30.9)	93 (41.2)	144 (39.5)	194 (35.3)	912 (29.6)	140 (24.2)	<0.001

Data are n (%), mean (SD) or median [IQR]. mRS = modified Rankin Scale. BPM = beats per minute. NIHSS = National Institute of Health Stroke Scale.

Supplementary Table III: Baseline radiological features of participants by their baseline systolic blood pressure after stroke, including patients that died.

	All	**Normal (SBP <120)**	**Elevated (SBP 120-129)**	**Stage 1 (SBP 130 to 139)**	**Stage 2 (SBP 140 to 179)**	**Hypertensive crisis (SBP ≥180)**	**P**
No. of participants (%)	4574	213 (4.7)	344 (7.5)	513 (11.2)	2952 (64.5)	552 (12.1)	
Lesion territory (%)							
MCA, ACA, or borderzone	1834 (40.1)	72 (33.8)	109 (31.7)	168 (32.7)	1211 (41.0)	274 (49.6)	<0.001
Posterior	169 (3.7)	8 (3.8)	11 (3.2)	18 (3.5)	107 (3.6)	25 (4.5)	0.84
Lacunar	348 (7.6)	11 (5.2)	21 (6.1)	32 (6.2)	228 (7.7)	56 (10.1)	0.05
Indeterminate	2223 (48.6)	122 (57.3)	203 (59.0)	295 (57.5)	1406 (47.6)	197 (35.7)	<0.001
Lesion size (%) (n=4566)							<0.001
None-visible	2223 (48.7)	122 (57.3)	203 (59.0)	295 (57.5)	1406 (47.6)	197 (35.7)	
Small	1561 (34.2)	11 (5.2)	21 (6.1)	32 (6.2)	228 (7.7)	56 (10.1)	
Medium	422 (9.2)	8 (3.8)	11 (3.2)	18 (3.5)	107 (3.6)	25 (4.5)	
Large	360 (7.9)	72 (33.8)	109 (31.7)	168 (32.7)	1211 (41.0)	274 (49.6)	
Presence of swelling	1167 (25.5)	47 (22.1)	63 (18.3)	108 (21.1)	765 (25.9)	184 (33.3)	<0.001
Pre-existing structural signs							

Presence of atrophy (%)	3989 (87.2)	180 (84.5)	303 (88.1)	463 (90.3)	2570 (87.1)	473 (85.7)	0.13
Cerebral atrophy severity (/4)	2.0 [1.0-2.0]	1.3 (1.0)	1.4 (0.9)	1.7 (1.0)	1.7 (1.1)	1.8 (1.1)	<0.001
Presence of leukoaraiosis (%)	1762 (38.5)	60 (28.2)	140 (40.7)	188 (36.6)	1134 (38.4)	240 (43.5)	0.002
Leukoaraiosis severity (/4) (n=4564)	0.0 [0.0-2.0]	0.5 (1.0)	0.8 (1.1)	0.7 (1.1)	0.8 (1.2)	0.9 (1.2)	<0.001
Presence of old lesions (%)	2705 (59.1)	97 (45.5)	188 (54.7)	289 (56.3)	1790 (60.6)	341 (61.8)	<0.001
Small vessel disease score (/3) (n=4564)	1.0 [0.0-1.0]	0.4 (0.6)	0.5 (0.7)	0.7 (0.7)	0.8 (0.8)	0.9 (0.8)	<0.001
Brain frailty score (/3)	2.0 [1.0-3.0]	1.5 (0.8)	1.8 (0.8)	1.8 (0.8)	1.8 (0.8)	1.9 (0.9)	<0.001

Data are n (%), mean (SD) or median [IQR]. MCA=Middle cerebral artery. ACA=Anterior cerebral artery.

Supplementary Table IV: Day 90 cognition and functional outcomes of participants by their baseline systolic blood pressure after stroke, including participants that died.

	All	**Normal (SBP <120)**	**Elevated (SBP 120-129)**	**Stage 1 (SBP 130 to 139)**	**Stage 2 (SBP 140 to 179)**	**Hypertensive crisis (SBP ≥180)**	**P**
Participants	4798	226 (4.7)	365 (7.6)	549 (11.4)	3080 (64.2)	578 (12.1)	
Died	451 (9.4)	2 (0.9)	8 (2.2)	29 (5.3)	314 (10.2)	98 (17.0)	<0.001
Cognition outcome							
TICS-M	18.5 (8.8)	21.7 (6.1)	20.4 (6.7)	20.0 (7.6)	18.2 (9.0)	14.8 (10.6)	<0.001
<20	1741 (43.1)	68 (30.8)	143 (40.6)	189 (37.0)	1112 (43.5)	229 (57.7)	<0.001
MMSE-M	12.8 (5.8)	14.8 (3.6)	14.2 (4.3)	14.0 (4.9)	12.6 (6.0)	10.7 (6.9)	<0.001
<14	1679 (37.2)	57 (25.4)	111 (30.6)	153 (28.5)	1106 (38.3)	252 (50.2)	<0.001
Verbal fluency	13.6 (8.5)	17.5 (7.0)	17.0 (7.8)	15.8 (8.2)	13.1 (8.4)	9.6 (8.2)	<0.001
<10	1306 (30.1)	28 (12.7)	48 (13.5)	111 (21.1)	880 (31.8)	239 (50.5)	<0.001
PSCI	2090 (43.6)	70 (31.0)	148 (40.5)	202 (36.8)	1352 (43.9)	318 (55.0)	<0.001
Episodic memory	13.5 (4.6)	14.1 (4.7)	13.4 (4.7)	13.6 (4.5)	13.4 (4.6)	13.1 (4.7)	0.19
Attention and working memory	8.3 (2.9)	8.8 (2.6)	8.4 (2.8)	8.7 (2.7)	8.3 (2.9)	7.6 (3.5)	<0.001
Language	18.8 (7.7)	21.3 (7.2)	21.0 (7.8)	20.3 (7.8)	18.4 (7.6)	15.8 (7.3)	<0.001
Functional outcome							
Modified Rankin scale	2.0 [1.0-3.0]	1.0 [0.0-2.0]	1.0 [0.5-2.0]	1.0 [0.5-2.0]	2.0 [1.03.0]	3.0 [1.0-4.0]	<0.001
Barthel index	81.9 (32.6)	96.3 (11.5)	93.4 (18.3)	90.3 (25.1)	80.4 (33.6)	68.8 (39.2)	<0.001
Zung depression scale	52.3 (22.3)	47.5 (17.2)	47.8 (18.2)	48.1 (19.3)	52.7 (22.7)	58.8 (24.8)	<0.001

Euroqol-health utility status	0.6 (0.3)	0.7 (0.2)	0.7 (0.3)	0.7 (0.3)	0.6 (0.3)	0.5 (0.3)	<0.001
Euroqol-visual analogue scale	65.1 (28.7)	73.7 (21.3)	71.1 (23.4)	70.9 (24.5)	64.5 (29.1)	55.7 (32.3)	<0.001

N varied between 4040 and 4798. Data are n (%), mean (SD) or median [IQR]. TICS-M = Telephone Interview for Cognitive Status-Modified. MMSE-M = Mini-Mental State Examination-Modified.

Supplementary Table V: Baseline clinical characteristics of participants by their region of recruitment, including patients that died.

	All	Asia	Europe	Other	Non-UK	UK	P
No. of participants (%)	4798	301 (6.3)	469 (9.8)	203 (4.2)	973 (20.3)	3825 (79.7)	
Demographics							
Age (years)	69.2 (11.0)	62.2 (11.0)	69.1 (10.2)	65.6 (13.4)	66.2 (11.5)	70.0 (10.8)	<0.001
Female (%)	1907 (39.7)	97 (32.2)	195 (41.6)	86 (42.4)	378 (38.8)	1529 (40.0)	0.52
Pre-morbid mRS >0 (%)	951 (19.8)	37 (12.3)	114 (24.3)	48 (23.6)	199 (20.5)	752 (19.7)	0.58
Time to randomisation [h]	27.7 [18.7-38.4]	32.5 [24.0-40.9]	24.8 [15.2-33.9]	16.4 [8.4-26.7]	26.0 [15.1-36.4]	28.1 [19.5-38.6]	<0.001
Medical history (%)							
Hypertension	2881 (60.0)	194 (64.5)	364 (77.6)	128 (63.1)	686 (70.5)	2195 (57.4)	<0.001
Diabetes	870 (18.1)	106 (35.2)	79 (16.8)	59 (29.1)	244 (25.1)	626 (16.4)	<0.001
Atrial fibrillation	330 (6.9)	14 (4.7)	53 (11.3)	23 (11.3)	90 (9.2)	240 (6.3)	0.001
Stroke/TIA	1054 (22.0)	59 (19.6)	128 (27.3)	80 (39.4)	267 (27.4)	787 (20.6)	<0.001
Hyperlipidaemia (n=5884)	1716 (38.8)	64 (27.7)	92 (22.1)	54 (34.4)	210 (26.1)	1506 (41.6)	<0.001
Ischaemic heart disease	715 (15.1)	31 (10.8)	125 (27.0)	41 (20.6)	197 (20.8)	518 (13.6)	<0.001
Haemodynamics							
Systolic blood pressure (mm Hg)	154.6 (21.6)	168.4 (19.2)	162.2 (19.0)	163.8 (20.9)	164.5 (19.6)	152.1 (21.3)	<0.001
Diastolic blood pressure (mm Hg)	84.1 (13.0)	92.5 (12.7)	87.6 (11.8)	87.7 (13.1)	89.2 (12.6)	82.8 (12.8)	<0.001

Heart rate (bpm) (n=6391)	75.0 (13.7)	74.8 (14.0)	77.1 (13.6)	79.4 (14.8)	76.8 (14.0)	74.5 (13.6)	<0.001
Index event							
Ischaemic stroke (%)	4097 (85.4)	301 (100.0)	445 (94.9)	199 (98.0)	945 (97.1)	3152 (82.4)	<0.001
Transient ischaemic attack (%)	701 (14.6)	0 (0.0)	24 (5.1)	4 (2.0)	28 (2.9)	673 (17.6)	
NIHSS (/42)	6.2 (5.9)	8.7 (5.1)	8.4 (6.1)	11.1 (5.9)	9.1 (5.8)	5.5 (5.6)	<0.001
Left hemisphere stroke (%) (n=6187)	2144 (46.4)	145 (48.2)	239 (51.6)	83 (40.9)	467 (48.3)	1677 (45.9)	0.18
Stroke subtype (%) (n=6393)							0.049
Total anterior	707 (14.7)	40 (13.3)	79 (16.8)	52 (25.6)	171 (17.6)	536 (14.0)	
Partial anterior	1819 (37.9)	63 (20.9)	152 (32.4)	71 (35.0)	286 (29.4)	1533 (40.1)	
Posterior	296 (6.2)	22 (7.3)	33 (7.0)	19 (9.4)	74 (7.6)	222 (5.8)	
Lacunar	1974 (41.2)	176 (58.5)	205 (43.7)	61 (30.0)	442 (45.4)	1532 (40.1)	
Ischaemic cause (%)							
Cardioembolic	491 (10.2)	19 (6.3)	77 (16.4)	24 (11.8)	120 (12.3)	371 (9.7)	0.016
Large vessel	800 (16.7)	29 (9.6)	113 (24.1)	43 (21.2)	185 (19.0)	615 (16.1)	0.028
Small vessel	1923 (40.1)	224 (74.4)	181 (38.6)	68 (33.5)	473 (48.6)	1450 (37.9)	<0.001
Mixed	101 (2.1)	15 (5.0)	7 (1.5)	18 (8.9)	40 (4.1)	61 (1.6)	<0.001
Not determined	1483 (30.9)	14 (4.7)	91 (19.4)	50 (24.6)	155 (15.9)	1328 (34.7)	<0.001

Data are n (%), mean (SD) or median [IQR]. mRS = modified Rankin Scale. BPM = beats per minute. NIHSS = National Institute of Health Stroke Scale.

Supplementary Table VI: Baseline radiological features of participants by their region of recruitment, including patients that died.

	All	**Asia**	**Europe**	**Other**	**Non-UK**	**UK**	**P**
No. of participants (%)	4574	286 (6.2)	439 (9.6)	192 (4.2)	917 (20.0)	3657 (80.0)	
Lesion territory (%)							
MCA, ACA, or borderzone	1834 (40.1)	123 (43.0)	189 (43.1)	95 (49.5)	407 (44.4)	1427 (39.0)	0.003
Posterior	169 (3.7)	20 (7.0)	22 (5.0)	9 (4.7)	51 (5.6)	118 (3.2)	0.001
Lacunar	348 (7.6)	65 (22.7)	36 (8.2)	14 (7.3)	115 (12.5)	233 (6.4)	<0.001
Indeterminate	2223 (48.6)	78 (27.3)	192 (43.7)	74 (38.5)	344 (37.5)	1879 (51.4)	<0.001
Lesion size (%) (n=4566)							<0.001
None-visible	2223 (48.7)	78 (27.8)	192 (43.7)	74 (38.5)	344 (37.7)	1879 (51.4)	
Small	1561 (34.2)	169 (60.1)	155 (35.3)	69 (35.9)	393 (43.1)	1168 (32.0)	
Medium	422 (9.2)	17 (6.0)	53 (12.1)	23 (12.0)	93 (10.2)	329 (9.0)	
Large	360 (7.9)	17 (6.0)	39 (8.9)	26 (13.5)	82 (9.0)	278 (7.6)	
Presence of swelling	1167 (25.5)	67 (23.4)	129 (29.4)	62 (32.3)	258 (28.1)	909 (24.9)	0.042
Pre-existing structural signs							
Presence of atrophy (%)	3989 (87.2)	208 (72.7)	387 (88.2)	159 (82.8)	754 (82.2)	3235 (88.5)	<0.001
Cerebral atrophy severity (/4)	2.0 [1.0-2.0]	2.0 [0.0-2.0]	2.0 [1.0-3.0]	2.0 [1.0-3.0]	2.0 [1.0-3.0]	2.0 [1.0-2.0]	0.003
Presence of leukoaraiosis (%)	1762 (38.5)	119 (41.6)	168 (38.3)	68 (35.4)	355 (38.7)	1407 (38.5)	0.89
Leukoaraiosis severity (/4) (n=4564)	0.0 [0.0-2.0]	0.0 [0.0-2.0]	0.0 [0.0-2.0]	0.0 [0.0-2.0]	0.0 [0.0-2.0]	0.0 [0.0-2.0]	0.78
Presence of old lesions (%)	2705 (59.1)	156 (54.5)	287 (65.4)	128 (66.7)	571 (62.3)	2134 (58.4)	0.031

Small vessel disease score (/3) (n=4564)	1.0 [0.0-1.0]	1.0 [0.0-1.0]	1.0 [0.0-2.0]	1.0 [0.0-2.0]	1.0 [0.0-1.0]	1.0 [0.0-1.0]	<0.001
Brain frailty score (/3)	2.0 [1.0-3.0]	2.0 [1.0-2.0]	2.0 [1.0-3.0]	2.0 [1.0-3.0]	2.0 [1.0-3.0]	2.0 [1.0-2.0]	0.52

Data are n (%), mean (SD) or median [IQR]. MCA=Middle cerebral artery. ACA=Anterior cerebral artery.

Supplementary Table VII: Day 90 cognition and functional outcomes of participants by their region of recruitment, including participants that died.

	All	Asia	EU	Other	Non-UK	UK	P
Participants	4798	301 (6.3)	469 (9.8)	203 (4.2)	973 (20.3)	3825 (79.7)	
Died	451 (9.4)	21 (7.0)	69 (14.7)	29 (14.3)	119 (12.2)	332 (8.7)	0.001
Cognition outcome							
TICS-M	18.5 (8.8)	16.0 (10.2)	15.7 (9.3)	19.0 (12.4)	16.4 (10.2)	18.9 (8.5)	<0.001
<20	1741 (43.1)	74 (52.9)	235 (58.9)	54 (40.6)	363 (54.0)	1378 (40.9)	<0.001
MMSE-M	12.8 (5.8)	11.6 (6.1)	10.5 (6.1)	11.8 (7.0)	11.1 (6.3)	13.2 (5.6)	<0.001
<14	1679 (37.2)	137 (51.3)	271 (59.2)	70 (41.2)	478 (53.4)	1201 (33.2)	<0.001
Verbal fluency	13.6 (8.5)	7.2 (5.2)	9.4 (7.8)	8.6 (6.4)	8.7 (7.0)	14.6 (8.4)	<0.001
<10	1306 (30.1)	116 (67.1)	222 (54.3)	88 (52.1)	426 (56.7)	880 (24.5)	<0.001
PSCI	2090 (43.6)	153 (50.8)	277 (59.1)	82 (40.4)	512 (52.6)	1578 (41.3)	<0.001
Episodic memory	13.5 (4.6)	13.1 (5.5)	12.5 (4.5)	17.1 (6.1)	13.6 (5.4)	13.4 (4.4)	0.59
Attention and working memory	8.3 (2.9)	6.7 (3.7)	6.9 (3.2)	8.8 (3.1)	7.2 (3.4)	8.5 (2.8)	<0.001
Language	18.8 (7.7)	11.4 (5.3)	14.7 (7.4)	13.9 (5.8)	13.7 (6.7)	19.8 (7.5)	<0.001
Functional outcome							
Modified Rankin scale	2.0 [1.0-3.0]	2.0 [1.0-3.0]	2.0 [1.0-3.0]	2.0 [1.0-4.0]	2.0 [1.0-3.0]	2.0 [1.0-3.0]	<0.001
Barthel index	81.9 (32.6)	78.7 (32.5)	74.6 (37.5)	71.4 (38.8)	75.2 (36.4)	83.6 (31.3)	<0.001
Zung depression scale	52.3 (22.3)	49.6 (21.2)	56.2 (24.4)	53.5 (25.3)	53.6 (23.8)	51.9 (21.8)	0.045
Euroqol-health utility status	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.5 (0.4)	0.6 (0.3)	0.6 (0.3)	<0.001

Euroqol-visual analogue scale	65.1 (28.7)	63.8 (26.7)	61.2 (32.1)	60.7 (30.8)	61.9 (30.3)	65.9 (28.2)	<0.001

N varied between 4040 and 4798. Data are n (%), mean (SD) or median [IQR]. TICS-M = Telephone Interview for Cognitive Status-Modified. MMSE-M = Mini-Mental State Examination-Modified.

Supplementary Table VIII: Univariable predictors of PSCI at 3 months

Risk factors	All, unadjusted OR (95% CI)	P
Age	1.054 (1.048-1.060)	<0.001
Female	1.366 (1.216-1.535)	<0.001
Pre-morbid mRS >0	1.916 (1.660-2.212)	<0.001
Recruited outside the UK	1.581 (1.373-1.822)	<0.001
Time to randomisation	0.997 (0.992-1.001)	0.16
Hypertension	1.428 (1.270-1.606)	<0.001
Diabetes	1.140 (0.984-1.321)	0.082
Atrial fibrillation	4.623 (3.561-6.001)	<0.001
Previous stroke or TIA	1.170 (1.020-1.342)	0.025
Systolic blood pressure (10mmHg)	1.092 (1.063-1.121)	<0.001
Heart rate (10bpm)	1.185 (1.136-1.235)	<0.001
Stroke severity (NIHSS)	1.133 (1.120-1.145)	<0.001
Brain frailty score	1.424 (1.330-1.525)	<0.001
Small vessel disease score	1.560 (1.448-1.681)	<0.001

Shown are odds ratios (OR) and 95% confidence intervals (CI) with p-values. mRS = modified Rankin Scale. NIHSS = National Institute of Health Stroke Scale.

Supplementary Table IX: Independent predictors of cognitive impairment 3 months after the index event, excluding participants that died.

Risk Factors	**All, OR (95% CI)**	**P**
Age	1.043 (1.036-1.051)	<0.001
Pre-morbid mRS >0	1.267 (1.069-1.502)	0.006
Recruited outside the UK	1.488 (1.248-1.775)	<0.001
Atrial fibrillation	1.375 (1.002-1.887)	0.048
Systolic blood pressure	0.942 (0.911-0.975)	0.001
Heart rate	1.093 (1.039-1.150)	0.001
Stroke severity (NIHSS)	1.082 (1.066-1.098)	<0.001
Small vessel disease	1.162 (1.063-1.269)	0.001

N = 4125/4347. Shown are the odds ratios (OR) and 95% confidence intervals (CI) with p-values. mRS = modified Rankin Scale. NIHSS = National Institute of Health Stroke Scale.

4 Clinical and Radiological Associations with Cognitive Impairment after Intracerebral Haemorrhage: Data from the Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2) trial

4.1 Abstract

4.1.1 Background

Cognitive impairment is common after intracerebral haemorrhage (ICH), but its clinical and radiological associations are uncertain.

4.1.2 Methods

Participants with ICH in the TICH-2 trial (ISRCTN93732214) underwent the Telephone Interview for Cognitive Status-Modified (TICS-M) if they survived on days 90 and 365 after ICH. Severe cognitive impairment (SCI, TICS-M <21) was the primary outcome at both time points. We used an adjusted backward binary logistic regression using backward stepwise selection to determine independent associations with cognitive impairment on days 90 and 365.

4.1.3 Results

On day 90, 693/2118 (32·7%) participants had completed the cognition assessment, of these 182 (26·3%) had SCI. Independent associations with SCI on day 90 were non-Caucasian ethnicity (odds ratio [OR] 4·84, 95% confidence interval [CI] 2·59-9·06, p<0·001), left hemisphere ICH (OR 2·25, 95% CI 1·53-3·31, p<0·001), lobar ICH (OR 2·18, 95% CI 1·36-3·50, p 0·001), intraventricular haemorrhage (OR 2·05, 95% CI 1·27-3·31, p 0·003), stroke severity (National Institute of Health Stroke Scale) (OR 1·07, 95% CI 1·03-1·11, p<0·001) and age (OR 1·06, 95% CI 1·04-1·08, p<0·001). On day 365, 496/2218 (23·4%) participants completed the cognition assessment, of these 129 (26·0%) had SCI. Independent associations of SCI on day 365 were non-Caucasian ethnicity (OR 17·92, 95% CI 7·78-41·27, p<0·001), lobar ICH (OR

1·91, 95% CI 1·11-3·29, p 0·018), age (OR 1·09, 95% CI 1·06-1·12, p<0·001), Glasgow Coma Scale at randomisation (OR 0·69, 95% CI 0·56-0·84, p<0·001), level of socioeconomic deprivation (OR 0·88, 95% CI 0·81-0·96, p 0·007).

4.1.4 Conclusion

Early and long-term SCI were common and associated with non-Caucasian ethnicity, lobar ICH, greater stroke severity (baseline NIHSS/GCS) and older age. A greater level of socioeconomic deprivation was associated only with long-term SCI. Informant-based cognition assessments may improve data completion in future trials.

4.2 Introduction

Ten per cent of first-ever stroke patients and 30% of recurrent stroke patients develop new-onset dementia [92]. Studies that have included mixed populations of participants with ischaemic and haemorrhagic stroke have been limited by small numbers of intracerebral haemorrhage (ICH) patients [92]. ICH has a relatively low prevalence yet high mortality rate in comparison to ischaemic stroke, which might have contributed to the lack of studies focused on cognitive decline in ICH patients [317, 318]. Previous studies have reported high rates of dementia after ICH with prevalence rates ranging from 5-44% [319]. Two cross-sectional studies, of 78 and 50 participants with ICH, investigating long-term cognition after ICH found cognitive impairment was very common and was associated with Rankin score>1 at discharge and haemorrhage volume or age and lobar ICH, respectively [320, 321]. The severity of cortical atrophy was associated with cognitive decline in a prospective cohort of 167 participants with ICH, of whom 37% had cognitive decline [322]. In a subsequent prospective observational cohort study of 218 participants with ICH at 4 years, post-ICH new-onset dementia occurred in over a quarter of participants and was associated with age, cortical atrophy, cerebral microbleeds and disseminated superficial siderosis [323]. A recent longitudinal study of 738 participants with ICH found early and delayed dementia were prevalent in 19% and 32% of participants, respectively. Also, education level, mood and leukoaraiosis were associated with delayed dementia whereas, ICH characteristics were associated with early dementia [324]. The factors associated with dementia after ICH thus require further elucidation due to the small sample size and scarcity of previous studies [92, 320-324]. We therefore aimed to determine the factors associated

with mild and severe cognitive impairment following ICH within an international multi-centre randomised controlled trial.

4.3 Research in context

4.3.1 Evidence before this study

Moulin, Labreuche and colleagues previously published a summary of data in dedicated intracerebral haemorrhage (ICH) cohorts. They identified four studies that focused on cognitive impairment and or dementia. To update the summary, we used the same search criteria and MeSH terms. We searched Ovid Medline, Embase, and Cochrane Library for articles published between Jan 1, 1995, and April 1, 2019, using an electronic search strategy for titles and abstracts with the MeSH terms "cerebral haemorrhage", or "intracerebral haemorrhage", or "cerebral haematoma", or "brain haemorrhage", or "haemorrhagic stroke" AND "dementia", or "cognitive decline", or "cognitive impairment", or "cognitive dysfunction" or "cognition". In line with the prior summary, studies were reviewed if participants had imaging or autopsy evidence of ICH, at least 30 adult participants were recruited, with at least one cognition assessment at 3 months after stroke.

We identified five studies, including Moulin, Labreuche, reporting cognitive data in dedicated ICH cohorts additional to those previously summarised. A single-centre cross-sectional study of 78 participants with ICH showed that dementia and cognitive impairment without dementia was observed in 23% (18/78) and 77% (37/48) of participants at 40 months post-stroke, respectively. Factors that predicted long-term dementia were a Rankin score>1 at discharge and haemorrhage volume. Another single-centre cross-sectional study of 50 participants with ICH found 54% (27/50) had cognitive impairment, which was independently associated with age and lobar ICH. A prospective cohort of 167 participants with ICH found 37% (62/167) had cognitive decline over 4 years. The severity of cortical atrophy was the only prognostic factor for cognitive

decline after excluding pre-existing cognitive impairment. A prospective observational cohort study of 218 participants with ICH was the first study that focused on dementia using a prospective and rigorous design. This study showed a new-onset dementia incidence rate of 14·2% and 28·3% at 1 and 4 years after ICH, respectively. The incidence of new-onset dementia in participants with lobar ICH was twice that of participants with non-lobar ICH. Risk factors for new-onset dementia were disseminated superficial siderosis, cortical atrophy score, a higher number of cerebral microbleeds and older age. A larger single-centre longitudinal cohort study of 738 participants with ICH investigated early and delayed dementia. They showed 19% of participants developed dementia within 6 months of the ICH and 32% of participants during the whole trial. This study suggested early dementia was associated with ICH characteristics whereas delayed dementia was associated with education level, incident mood, and white matter disease. These studies were often limited by small sample size, single centre setting or selection bias.

4.3.2 Added-value of this study

This study is a large international multi-centre cohort of ICH survivors reporting mild and severe cognitive impairment using a prospective design. We studied CT data to clarify the influence of ICH characteristics and pre-existing structural changes on early and long-term cognitive impairment. We show that both mild and severe cognitive impairment was highly prevalent in a large cohort of international participants. We showed that the severity of early and long-term cognitive impairment was associated with lobar haematomas, whereas the risk of early cognitive impairment was associated with ICH volume. Additionally, we have shown that non-Caucasian ethnicity and a greater level of socioeconomic deprivation are risk factors for cognitive impairment in ICH survivors.

4.3.3 Implications of all the available evidence

Our results suggest that ICH in an ageing brain was sufficient to cause long term cognitive impairment. However, the location of the haematoma (lobar) seems to be of greater importance in predicting the severity of cognitive impairment, which in turn may be related to underlying cerebral amyloid angiopathy. This suggests there is an underlying cognitive decline that is exacerbated by ICH. Due to the severity of ICH, a large proportion of participants were unable to complete the cognition assessment, therefore future studies should include an informant-based cognition assessment. Future research should be performed in a similarly large multi-centre international cohort with greater ethnic diversity and data on participant education, socioeconomic status, complimented by brain MRI or head CT with Apolipoprotein E genotype analyses to classify the presence of cerebral amyloid angiopathy.

4.4 Methods

4.4.1 Study design and participants

The Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2) trial was an international, double-blind, randomised, placebo-controlled, parallel-group, phase 3 trial. Participants were adults that were admitted to the hospital within 8 hours of an acute ICH. Key exclusion criteria of the TICH-2 trial were participants with a secondary ICH, a contraindication to tranexamic acid, severe disability (modified Rankin Scale (mRS) >4), severe brain injury (Glasgow Coma Scale (GCS) <5), or a life expectancy of <3 months. The ethical approval for the study was obtained and approved at each recruitment centre and country before the commencement of the study. In the UK, the trial was approved and registered with the National Institute of Health Research (NIHR) Clinical Research Network (ISRCTN93732214). Written informed consent was obtained from each participant. If the participant did not have the capacity to provide consent, a relative or representative gave proxy consent and sought consent once the participant regained capacity. The TICH-2 protocol, statistical plan, and results have been published [325, 326].

4.4.2 Clinical assessment and neuroimaging

Participant demographics, medical history, and stroke lateralisation and severity (National Institute of Health Stroke Scale, NIHHS) [247] were collected at baseline. Participants' Indices of Multiple Deprivation (IMD), which is a unique measure of relative deprivation at a small local area level, was determined and used as a surrogate marker for socioeconomic status in UK participants only. IMD ranks every small area in England from 1 (most deprived area) to 32·844 (least deprived area). IMD includes seven domains of deprivation indices for income (22·5%), employment (22·5%), education, skills, and training (13·5%),

health and disability (13·5%), crime (9·3%), barriers to housing (9·3%), and services and living environment (9·3%). All participants underwent a CT scan at baseline. Participants with a final diagnosis other than an ICH or who had a confirmed secondary ICH on adjudicated neuroimaging were excluded from the study. Semi-automated segmentation of the ICH was performed on Digital Imaging and Communications in Medicine-compliant images by one of three assessors to give ICH volumes. The user-guided three-dimensional active contour tool [327] in the ITK-SNAP software (version 3·6) was used to perform the segmentation with additional manual editing if required. Central independent expert assessors, who were blinded to treatment allocation and outcome, assessed CT scans using a web-based adjudication system. Lesion location was categorised as either frontal, parietal, occipital, temporal, basal ganglia, midbrain, pontine or cerebellar and was then further classified into either lobar, deep or infratentorial. Cerebral amyloid angiopathy (CAA) was classified using the Boston criteria [328]. Suspected CAA includes both probable and possible categories of CAA diagnosis from the Boston criteria. Old vascular lesion location was defined as either: cortical, striatocapsular, borderzone, lacunar or brainstem [275]. The presence of intraventricular haemorrhage (IVH) was recorded. Cortical and subcortical atrophy were classified as either: none (0), moderate (1), or severe (2), when compared against a validated collection of standard templates that were collected from ageing studies [329]. A global cerebral atrophy severity score (/4) was calculated from the combined severity of cortical and subcortical atrophy [274]. The presence and severity of leukoaraiosis or white matter hyperintensities (WMH) were identified on CT using the van Swieten score [276]. The anterior and posterior WMH were each classified as none (0); lucency restricted to the region adjoining the ventricles (1); or lucency

covering the entire region from lateral ventricle to cortex (2). A leukoaraiosis severity score (/4) was calculated from the combined severity of anterior and posterior WMH [276, 277].

4.4.3 Cognitive impairment and functional assessments

Cognitive status and functional outcomes were assessed via telephone in the national language of the recruiting country at 3 months in all participants and additionally at 1-year in UK participants only. Cognitive impairment was screened for using the Telephone Interview for Cognitive Status-Modified (TICS-M). The cut-off thresholds for mild cognitive impairment (MCI) and severe cognitive impairment (SCI) were <25 and <21 [116, 283]. Post-stroke cognitive impairment (PSCI) is an umbrella term that encompasses both mild and severe cognitive impairment, however, it does not include focal cognitive deficits such as aphasia or neglect. Cognitive sub-domains were determined from the components of the TICS-M on day 90 and day 365: verbal memory (/20, immediate and delayed recall), orientation and mental tracking (/8, time orientation and counting backwards), language and reasoning (/5, comprehension), and attention and working memory (/6, serial 7's and repetition) [286]. Participant independence, disability, quality of life and mood were assessed by the mRS [249], Barthel Index [249], EuroQol health utility status and visual analogue scale [287], and Zung depression scale, respectively [288]. The primary outcome was severe cognitive impairment (SCI) at both time points. Secondary outcomes were PSCI and functional outcomes.

4.4.4 Statistical Methods

Independent-Samples T-Test (continuous variable), Chi-Square test for homogeneity (binary variable) and Mann-Whitney U (ordinal variable) were used to compare the differences between two independent groups. One-way ANOVA

(continuous variable), or Chi-square test with multiple comparisons and Bonferroni adjustment for P values (binary variable) or Kruskal-Wallis (ordinal variable) was used to compare differences between three independent groups. Homogeneity of variance was determined using Levene's Test for Equality of Variances. If the assumption of homogeneity of variances is violated, Welch's ANOVA is used instead of the One-Way ANOVA. One-Way ANOVA Post-hoc tests were Games-Howell and Tukey-Kramer depending on whether homogeneity of variances was or was not violated, respectively. Unadjusted and adjusted binary logistic regression using backward stepwise selection was used to identify the factors associated with early (day 90) and long-term (day 365) cognitive impairment and its severity. The receiver operating characteristic (ROC) area under the curve (AUC) was used to determine the model's level of discrimination.

All statistical analysis was performed using the Statistical Package for Social Sciences version-24 (SPSS-24, IBM, Armonk, NY). Standard deviation (SD), interquartile range [IQR], odds ratios [OR] and 95% confidence intervals (CI) were calculated, and significance was set at $p < 0{\cdot}05$.

4.5 Results

2325 participants were enrolled in the TICH-2 trial (Figure 4.1), of whom, 2118 (96·5%) participants had a spontaneous ICH. On day 90, 693 (32·7%) participants completed the cognition assessment, of these 304 (43·9%) participants were cognitively preserved (CP), 207 (29·9%) participants had mild cognitive impairment (MCI) and 182 (26·3%) participants had severe cognitive impairment (SCI). 967 (45·7%) participants did not complete the cognition assessment and 458 (21·6%) participants had died within 3 months. On day 365, 496 (23·4%) participants completed the cognition assessment, of these 227 (45·8%) participants were CP, 140 (28·2%) had MCI and 129 (26·0%) had SCI. 1066 (50·3%) participants did not complete cognition assessment, of whom 304 (28·6% of 1066 or 14·3% of 2118) were non-UK participants that did not complete the day 365 assessment due to the study design, and 556 (26·3%) participants had died within 1 year.

The baseline clinical (Supplementary Table X) and neuroimaging (Supplementary Table XI) characteristics of participants with and without cognition data on day 90 and day 365 were compared. At both timepoints participants without cognition data were older, aphasic, non-Caucasian participants, with a pre-stroke disability, a history of previous stroke or TIA, worse level of consciousness (GCS), a greater stroke severity (NIHSS), and lived in an area of greater deprivation (Supplementary Table X). They also had a greater haematoma volume, a higher prevalence of IVH, suspected CAA, and old vascular lesions, and greater severity of global atrophy and leukoaraiosis (Supplementary Table XI).

Table 4.1 shows the participants baseline clinical features by their cognition status on day 90 and day 365. When compared with CP participants, participants

with SCI on day 90, were more likely to be older, non-Caucasian, aphasic, have a pre-stroke disability, a history of previous stroke or TIA, a lower diastolic blood pressure, a greater severity (NIHSS) of left hemisphere stroke, and live in an area of greater deprivation. Participants with MCI on day 90, when compared with CP participants, were more likely to be older, aphasic, have a greater alcohol intake, have a left hemisphere stroke, and live in an area of greater deprivation. Between, participants with MCI and SCI on day 90, the latter were more likely to be non-Caucasian, aphasic, have a history of previous stroke or TIA, have lower diastolic blood pressure, have a left hemisphere stroke, and consume less alcohol. Further, participants with SCI on day 365, when compared with CP participants, were older, non-Caucasian, aphasic, consumed less alcohol, had lower diastolic blood pressure, had a worse level of consciousness (GCS), and lived in an area of greater deprivation. Participants with MCI and CP on day 365 showed no baseline clinical difference. Meanwhile, participants with SCI on day 365 were more likely to be older, non-Caucasian, aphasic and have a lower alcohol intake than participants with MCI. A supplementary analysis compared non-Caucasian and Caucasian participants (Supplementary Table XII*,* Supplementary Table XIII*,* Supplementary Table XIV). Non-Caucasian participants were significantly more likely to be from an area of greater deprivation and performed worse on the language/reasoning and attention/working memory components of the TICS-M at both timepoints.

Table 4.2 displays the participants' baseline neuroimaging features related to their cognition status on day 90 and day 365. Participants with SCI on day 90, when compared with CP participants, were more likely to have IVH, a lobar haematoma, suspected CAA, and greater severity of global leukoaraiosis. Meanwhile, participants with MCI on day 90, when compared with CP

participants, were more likely to have old vascular lesions, particularly cortical lesions, and greater severity of global leukoaraiosis. Comparison of participants with MCI and SCI on day 90 shows the latter were more likely to have multiple haematomas and have an IVH. In participants with SCI on day 365, the presence of suspected CAA and anterior leukoaraiosis was significantly higher when compared with CP participants. Whereas, a significantly higher prevalence of old vascular lesions, especially cortical lesions, was observed in participants with MCI on day 365 when compared with CP participants. Lastly, MCI and SCI participants on day 365 showed no difference in neuroimaging features.

Table 4.3 compares the cognition and functional outcomes of participants by their cognition status on day 90 and day 365. At both time points, participants with SCI performed significantly worse on all functional outcomes in comparison to CP participants. In comparison to CP participants, MCI participants performed significantly worse on all functional outcomes at both time points, except the Zung Depression Scale (ZDS) on day 90 and the Barthel Index (BI) and EuroQol-Visual Analogue Scale (EQ-VAS) on day 365. Participants with SCI and MCI at both timepoints differed significantly on their degree of disability and dependence concerning their activities of daily living (mRS and BI). However, the groups did not differ on their level of mood disturbances (ZDS) or objective quality of life (EQ-5-Dimensions) at both time points. The participant's subjective quality of life (EQ-VAS) was only significantly different between participants with SCI and MCI on day 365. Participants without cognition data performed significantly worse on all functional outcomes at both time points (Supplementary Table XV*).*

Baseline factors that had significant unadjusted binary logistic regression associations with either PSCI or SCI on day 90 or day 365 (Table 4.4) were

included in an adjusted binary logistic regression using backward stepwise selection (Table 4.5). On day 90, the independent associations of Post-Stroke Cognitive Impairment (PSCI) (Model A; n = 662, R^2 = 0·19, AUC = 0·724, 95% CI, 0·686 to 0·763) were older, of non-Caucasian ethnicity, and had a left-hemisphere stroke, increasing ICH volume, and a greater degree of leukoaraiosis. The independent associations of SCI (Model B; n=662, R^2 = 0·23, AUC = 0·757, 95% CI, 0·715 to 0·799) that differed from PSCI were an increasing NIHSS score, the presence of an IVH and lobar haematoma, however, ICH volume and the degree of leukoaraiosis were no longer significant. On day 365, the independent associations of PSCI (Model C; n = 464, R^2 = 0·17, AUC = 0·709,95% CI, 0·663 to 0·755) were older age, non-Caucasian ethnicity, greater deprivation, and a decreasing Glasgow coma scale (GCS) score. The independent associations of SCI (Model D; n = 464, R^2 = 0·29, AUC = 0·796, 95% CI, 0·751 to 0·841) that differed from PSCI was the presence of a lobar haematoma. Supplementary tables Supplementary Table XVI and Supplementary Table XVII show the unadjusted and adjusted binary logistic regression with the inclusion of participants that died. Adjusted associations that included participants that died showed factors related to stroke severity such as ICH volume, and NIHSS and GCS scores became significant associations for both time points, whereas lobar haematoma was no longer significant. All models of the adjusted binary logistic regression using backward stepwise selection was statistically significant ($p<0·001$) and showed an acceptable to an excellent level of discrimination using ROC under the AUC.

4.6 Discussion

In this cohort, we showed that over half of the participants had early and long-term PSCI, with a quarter of participants suffering from severe cognitive deficits. We showed that the independent associations of early SCI were older age, non-Caucasian ethnicity, a left hemisphere stroke, greater stroke severity (NIHSS), lobar ICH and IVH. Meanwhile, in addition to the above factors, early PSCI was independently associated with a greater ICH volume and a greater degree of leukoaraiosis, but not associated with lobar ICH, IVH and stroke severity (NIHSS). Furthermore, the long-term associations of PSCI were older age, non-Caucasian ethnicity, reduced level of consciousness (GCS), and greater deprivation, however, the severity of long-term cognitive impairment was associated with a lobar haematoma. This suggests an ICH in a biologically ageing brain is sufficient to cause cognitive impairment. However, participants suffering from a lobar ICH are more likely to have greater severity of early and long-term cognitive impairment. This proposes that underlying cerebral amyloid angiopathy may also be contributing to cognitive decline in these participants.

Older age and haematoma size, which often reflects stroke severity, are well-defined predictors of cognitive decline [320-324]. Our results are in accordance and also showed that a participant's level of consciousness (GCS) after stroke is associated with long-term SCI.

In mixed stroke cohorts, non-Caucasian participants, including both Black and Hispanic ethnic groups, have been shown to have a higher prevalence of PSCI [93]. However, the association between PSCI and ethnicity is unclear [92]. In a cohort of 738 ICH survivors, African American ethnicity was an independent association of dementia 6 months after ICH, however, it was not associated with dementia within 6 months of the ICH [324]. Here, we have shown that non-

Caucasian ethnicity is strongly associated with both early and long-term PSCI and its severity. Due to the small number of non-Caucasian participants in this cohort, it is difficult to conclude which of the myriad of ethnicity related factors affecting cognitive impairment are of importance, however, non-Caucasian participants were more likely to be from an area of greater deprivation and as such may reflect healthcare and educational access. Socioeconomic status has previously been associated with a higher prevalence of PSCI [93], however, subsequent studies on cognitive decline in pure ICH cohorts have accounted for the level of education but not socioeconomic status. We found that a greater level of deprivation was predictive of long-term cognitive impairment in UK participants, however, this needs to be validated in non-UK populations.

We have suggested that the volume of the ICH itself is sufficient to cause early cognitive impairment with greater severity if located in a lobar region. This is supported by the fact that cortical functions and in turn cognition are more likely to be affected in a lobar ICH [323]. The influence a lobar ICH has on long term severe cognitive impairment may in part be related to underlying cerebral amyloid angiopathy and its associations with global cognitive decline and Alzheimer's disease [330]. Unfortunately, it is not possible to determine whether Alzheimer's disease biomarkers were present as there was no magnetic resonance imaging (MRI) or Apolipoprotein E genotype analysis. This supports the hypothesis that an ongoing process of cognitive decline due to vascular or degenerative pathologies are exacerbated by ICH and further supports an association between lobar haemorrhages and an AD-like degenerative process [323, 331].

This analysis has several strengths. This is a large cohort of ICH survivors that focused on mild and severe cognitive impairment using a prospective design.

The TICH-2 trial recruited a large sample size from multiple international hospital centres with detailed and standardised data collection. The cognition assessment was a practical and validated telephone-based cognition screen that allowed for an increased number of participants to complete the follow up in comparison to an in-clinic assessment. The cognition assessment was performed on day 90 and day 365 after stroke to allow for the investigation of both early and long-term cognitive impairment. Baseline CT scans were available for 98.5% of participants with cognitive data. Death is common in ICH cohorts, but it is also the endpoint of dementia, therefore we included participants that died in a supplementary sensitivity analysis, a novel approach in ICH cognition studies.

This analysis has some limitations. Due to the nature of acute stroke trials, we did not perform pre-morbid cognitive testing and therefore we could not adjust for participants with pre-existing dementia. However, participants with pre-existing severe disability (mRS >4), which would include participants with significant dementia, were excluded from trial participation. Also, the most severely affected stroke patients who did not meet the trial inclusion criteria, have the highest risk of cognitive impairment. We did not collect the participants' level of education, which has been previously associated with PSCI [92]. Due to the inherent severity and mortality associated with an ICH, a large number of participants were unable to complete the cognition assessment. Future trials should endeavour to include an informant-based cognition questionnaire such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [332]. The English validated version of the TICS-M was translated by the assessor into the country of recruitments' national language and we must also consider the effect of language and cultural confounders. The cognition assessment was not an extensive neuropsychological examination and

as such, it did not assess executive and visuospatial function. Lastly, the lack of MRI limits our ability to diagnose probable CAA, which is the highest level of diagnostic certainty without a brain biopsy, as without MRI we are unable to detect cerebral microbleeds or cortical superficial siderosis.

In conclusion, there is a high prevalence of cognitive impairment in spontaneous ICH survivors. Our findings will allow for the dissemination of information regarding the risk of cognitive impairment after ICH to patients and carers. This may benefit the management and prognosis of ICH survivors by identifying those at the greatest risk of cognitive impairment. Our results suggest that an ICH is sufficient to cause early cognitive impairment, whereas long-term cognitive impairment may be due to the ICH exacerbating an underlying degenerative process of pre-existing cognitive decline. Three months after ICH may therefore be too early to measure the long-term effects of the ICH on cognition and should be measured at 1-year post-ICH. Furthermore, a participant's ethnicity and socioeconomic status may also impact their cognition after ICH. It is unclear, however, whether this is related to socioeconomic factors, such as access to greater and better levels of healthcare and education, or one or many of the myriad of race-related factors. Also, monitoring cognitive function for several years after ICH is required to further elucidate the long-term effects. Future research should be performed in large multi-centre international cohorts with greater ethnic diversity, informant-based questionnaires and the impact of participant education, socioeconomic status and MRI brain imaging should be explored.

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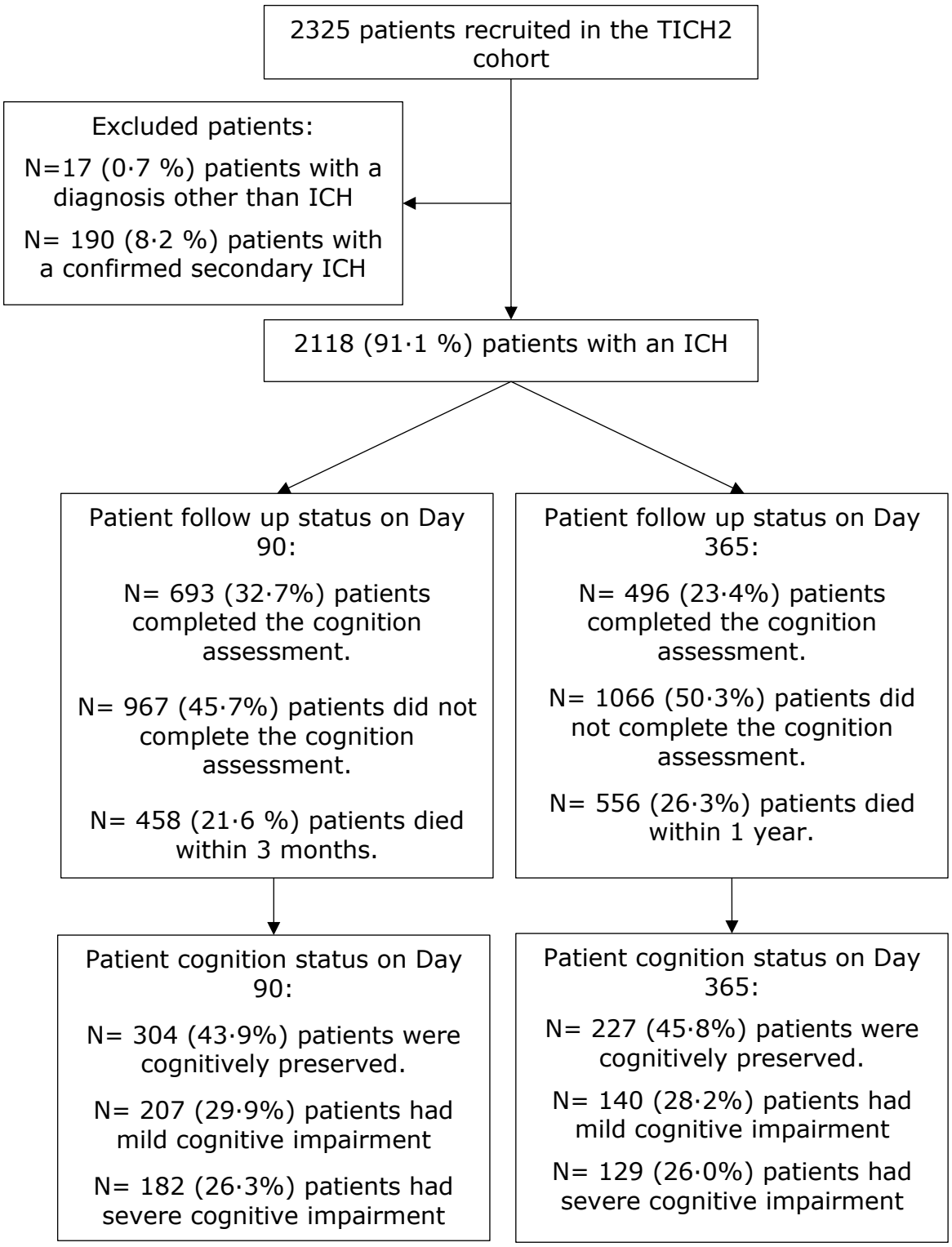

Figure 4.1 Participant flow chart.

Cognition after intracerebral haemorrhage (ICH) was measured by the Telephone Interview for Cognitive Status-Modified (TICS-M). The cut-off thresholds for mild cognitive impairment and severe cognitive impairment were <25 and <21, respectively. ICH = Intracerebral haemorrhage.

Table 4.1: Baseline clinical features of participants by their cognition status on Day 90 and Day 365.

Baseline clinical features	**Day 90**					**Day 365**				
	All	**CP**	**MCI**	**SCI**	**P**	**All**	**CP**	**MCI**	**SCI**	**P**
Participants (%)	693	304 (43·9)	207 (29·9)	182 (26·2)		496	227 (45·8)	140 (28·2)	129 (26·0)	
Demographics										
Age (years)	63·2 (12·4)	**59·5** (11·4)	64·8 (11·9)	67·7 (12·7)	<0·001	64·5 (12·3)	62·1 (11·4)	64·5 (12·0)	68·5 (12·9)	<0·001
Female (%)	250 (36·1)	112 (36·8)	67 (32·4)	71 (39·0)	0·36	186 (37·5)	90 (39·6)	41 (29·3)	55 (42·6)	0·05
Treatment (%)	341 (49·2)	157 (51·6)	103 (49·8)	81 (44·5)	0·30	251 (50·6)	113 (49·8)	76 (54·3)	62 (48·1)	0·56
Recruited in the UK (%)	499 (72·2)	208 (68·9)	152 (73·4)	139 (76·4)	0·18	496 (100·0)	227 (100·0)	140 (100·0)	129 (100·0)	-
TTN [hours]	1 [1-2]	1 [1-2]	1 [1-2]	2 [1-3]	0·42	1 [1-2]	1 [1-2]	1 [1-3]	2 [1-2]	0·52
IMD [decile]	6 [4-9]	7 [5-9]	6 [3-8]	6 [3-8·5]	0·021	6 [4-8]	7 [4-9]	6 [4-8]	6 [3-8]	0·049
Caucasian (%)	619 (89·3)	276 (90·8)	190 (91·8)	153 (84·1)	0·026	447 (90·1)	217 (95·6)	130 (92·9)	100 (77·5)	<0·001
mRS >0 (%)	97 (14·0)	31 (10·2)	28 (13·5)	38 (20·9)	0·004	74 (14·9)	30 (13·2)	20 (14·3)	24 (18·6)	0·37
Medical history (%)										
Stroke or TIA	82 (11·8)	30 (9·9)	21 (10·1)	31 (17·0)	0·041	35 (7·1)	13 (5·8)	8 (5·8)	14 (10·9)	0·25
Hypertension	433 (62·8)	183 (60·4)	141 (68·1)	109 (60·6)	0·16	269 (54·3)	114 (50·4)	83 (59·3)	72 (55·8)	0·23
Hyperlipidaemia	151 (21·8)	58 (19·1)	53 (25·6)	40 (22·1)	0·21	109 (22·0)	49 (21·6)	30 (21·4)	30 (23·3)	0·92
Diabetes	86 (12·4)	35 (11·5)	24 (11·6)	27 (14·9)	0·49	61 (12·3)	26 (11·5)	15 (10·7)	20 (15·5)	0·42

AF	18 (2·6)	6 (2·0)	5 (2·4)	7 (3·9)	0·43	12 (2·4)	5 (2·2)	2 (1·4)	5 (3·9)	0·40
Smoking- ever	354 (52·2)	142 (48·0)	114 (55·9)	98 (55·1)	0·14	233 (48·2)	100 (44·6)	68 (51·1)	65 (51·6)	0·33
Alcohol intake [UPW]	2·0 [0·0-12·0]	2·0 [0·0-12·0]	5·0 [0·0-14·0]	1·0 [0·0-8·0]	0·008	2·0 [0·0-13·0]	3·5 [0·0-14·0]	3·0 [0·0-20·0]	1·0 [0·0-7·5]	0.013
Blood pressure (mmHg)										
Systolic	172·4 (26·3)	173·9 (27·3)	173·6 (25·7)	168·5 (24·9)	0·06	172·8 (26·7)	174·9 (27·5)	171·3 (25·6)	170·5 (26·5)	0·24
Diastolic	96·1 (18·0)	98·2 (17·6)	96·3 (18·4)	92·3 (17·5)	0·002	94·9 (18·3)	97·2 (18·3)	94·0 (18·2)	92·0 (17·9)	0·028
Index event										
Left hemisphere (%)	330 (49·4)	119 (41·0)	101 (51·0)	110 (61·1)	<0·001	227 (47·6)	99 (45·0)	64 (48·1)	64 (51·6)	0·49
NIHSS (/42)	9·3 (5·6)	8·8 (5·4)	8·9 (5·3)	10·4 (6·2)	0·006	9·0 (5·9)	8·4 (5·6)	9·1 (6·1)	9·9 (6·1)	0·06
Aphasic (%)	170 (24·5)	52 (17·1)	52 (25·1)	66 (36·3)	<0·001	125 (25·2)	44 (19·4)	34 (24·3)	47 (36·4)	0·002
GCS (/15)	14·4 (1·3)	14·5 (1·1)	14·4 (1·2)	14·1 (1·5)	0·004	14·5 (1·2)	14·7 (0·8)	14·5 (1·2)	14·2 (1·6)	0·002

Data are n (%), mean (SD) or median [IQR]. CP = Cognitively preserved. MCI = Mild cognitive impairment. SCI = Severe cognitive impairment. TTN = Time to neuroimaging. IMD = Indices of multiple deprivation. mRS = modified Rankin Scale. TIA = Transient ischaemic attack. AF = Atrial fibrillation. UPW = units per week. NIHSS = National Institute of Health Stroke Scale. GCS = Glasgow coma scale. Day 90 missing data: UK (n=2), IMD (n=203), Hypertension (n=3), Hyperlipidaemia (n=1), Diabetes (n=1), AF (n=1), Smoking (n=15), Alcohol intake (n=54), Left hemisphere stroke (n=25). Day 365 missing data: IMD (n=9), Previous stroke or TIA (n=2), Hypertension (n=1), Smoking (n=13), Alcohol intake (n=48), left hemisphere stroke (n=19).

Table 4.2: Baseline neuroimaging features of participants by their cognition status on Day 90 and Day 365.

Baseline neuroimaging features	**Day 90**					**Day 365**				
	All	**CP**	**MCI**	**SCI**	**P**	**All**	**CP**	**MCI**	**SCI**	**P**
Participants (%)	684	298 (43·6)	204 (29·8)	182 (26·6)		491	224 (45·6)	138 (28·1)	129 (26·3)	
ICH features										
Volume (mL)	11·3 (12·4)	10·3 (11·1)	11·1 (12·3)	13·1 (14·2)	0·06	13·0 (14·5)	11·9 (13·4)	13·6 (14·0)	14·3 (16·7)	0·27
Multiple (%)	22 (3·2)	11 (3·7)	1 (0·5)	10 (5·5)	0·018	15 (3·1)	4 (1·8)	3 (2·2)	8 (6·2)	0·05
Presence of IVH (%)	112 (16·4)	42 (14·1)	24 (11·8)	46 (25·3)	0·001	88 (18·0)	34 (15·2)	25 (18·2)	29 (22·5)	0·22
Location (%)										
Lobar	129 (18·9)	39 (13·1)	39 (19·3)	51 (28·0)	<0·001	99 (20·2)	41 (18·3)	23 (16·8)	35 (27·1)	0·06
Deep	535 (78·6)	249 (83·8)	159 (78·7)	127 (69·8)	0·001	381 (77·8)	177 (79·0)	111 (81·0)	93 (72·1)	0·17
Infratentorial	17 (2·5)	9 (3·0)	4 (2·0)	4 (2·2)	0·72	10 (2·0)	6 (2·7)	3 (2·2)	1 (0·8)	0·47
Cerebral amyloid angiopathy (%) (n=452)	109 (24·1)	31 (16·9)	33 (23·4)	45 (35·2)	0·001	88 (25·8)	31 (20·5)	23 (22·8)	34 (38·2)	0·007
Pre-existing structural signs										
Cortical atrophy (%)	607 (88·7)	259 (86·9)	182 (89·2)	166 (91·2)	0·34	432 (88·0)	196 (87·5)	122 (88·4)	114 (88·4)	0·95
Subcortical atrophy (%)	160 (23·4)	61 (20·5)	50 (24·5)	49 (26·9)	0·24	96 (19·6)	42 (18·8)	24 (17·4)	30 (23·3)	0·44
Atrophy severity (/4)	1·0 [1·0-2·0]	1·0 [1·0-1·0]	1·0 [1·0-2·0]	1·0 [1·0-2·0]	0·37	1·0 [1·0-1·0]	1·0 [1·0-1·0]	1·0 [1·0-1·0]	1·0 [1·0-2·0]	0·34

Anterior WMH (%)	189 (27·6)	57 (19·1)	69 (33·8)	63 (34·6)	<0·001	131 (26·7)	49 (21·9)	38 (27·5)	44 (34·1)	0·042
Posterior WMH (%)	195 (28·5)	59 (19·8)	70 (34·3)	66 (36·3)	<0·001	124 (25·3)	50 (22·3)	37 (26·8)	37 (28·7)	0·36
WMH severity (/4)	0·0 [0·0-1·0]	0·0 [0·0-0·0]	0·0 [0·0-2·0]	0·0 [0·0-2·0]	<0·001	0·0 [0·0-1·0]	0·0 [0·0-1·0]	0·0 [0·0-1·0]	0·0 [0·0-2·0]	0·06
Old lesions (%)	386 (56·4)	152 (51·0)	129 (63·2)	105 (57·7)	0·023	263 (53·6)	109 (48·7)	88 (63·8)	66 (51·2)	0·016
Cortical	323 (47·2)	123 (41·3)	108 (52·9)	92 (50·5)	0·021	216 (44·0)	86 (38·4)	74 (53·6)	56 (43·4)	0·018
Lacunar	178 (26·0)	67 (22·5)	58 (28·4)	53 (29·1)	0·17	117 (23·8)	47 (21·0)	38 (27·5)	32 (24·8)	0·34

Data are n (%), mean (SD) or median [IQR]. Cerebral amyloid angiopathy (CAA) was adjudicated by neuroradiologists according to the Boston criteria. CP = cognitively preserved. MCI = Mild cognitive impairment. ICH = Intracerebral haemorrhage. IVH = Intraventricular haemorrhage. WMH = White matter hyperintensities. Day 90 missing data: ICH volume (n=16), ICH multiple (n=12), presence of IVH (n=10), ICH location (n=12), Cerebral amyloid angiopathy (n=241), pre-existing structural signs (n=9). Day 365 missing data: ICH volume (n=10), ICH multiple (n=6), presence of IVH (n=6), ICH location (n=6), CAA (n=155), pre-existing structural signs (n=5).

Table 4.3: Cognition and functional outcomes of participants by cognition status on Day 90 and Day 365.

	Day 90					Day 365				
	All	**CP**	**MCI**	**SCI**	**P**	**All**	**CP**	**MCI**	**SCI**	**P**
Participants (%)	693	304 (43·9)	207 (29·9)	182 (26·2)		496	227 (45·8)	140 (28·2)	129 (26·0)	
Cognition outcome										
TICS-M	23·4 (5·4)	28·0 (2·9)	22·7 (1·1)	16·5 (3·3)	<0·001	23·4 (5·8)	28·2 (2·8)	22·6 (1·1)	15·8 (3·8)	<0·001
Domains										
Verbal memory	7·2 (3·6)	10·2 (2·9)	6·1 (1·7)	3·6 (2·0)	<0·001	7·1 (3·7)	10·2 (2·8)	5·9 (1·5)	3·0 (1·5)	<0·001
Orientation and mental tracking	7·1 (1·2)	7·7 (0·5)	7·3 (0·9)	6·0 (1·5)	<0·001	7·1 (1·2)	7·6 (0·5)	7·3 (0·7)	5·9 (1·8)	<0·001
Language and reasoning	4·4 (0·8)	4·8 (0·4)	4·5 (0·6)	3·7 (1·0)	<0·001	4·5 (0·7)	4·8 (0·3)	4·7 (0·5)	3·9 (1·1)	<0·001
Attention and working memory	4·5 (1·5)	5·2 (1·0)	4·6 (1·2)	3·1 (1·6)	<0·001	4·5 (1·7)	5·4 (0·9)	4·5 (1·4)	2·8 (1·9)	<0·001
Functional outcome										
mRS	2·0 [1·0-3·0]	2·0 [1·0-3·0]	2·0 [2·0-3·0]	3·0 [2·0-3·0]	<0·001	2·0 [1·0-3·0]	2·0 [1·0-2·0]	2·0 [1·0-3·0]	3·0 [2·0-3·0]	<0·001
Barthel Index	90·0 (17·7)	93·3 (14·6)	89·7 (17·1)	84·7 (21·4)	<0·001	92·0 (15·5)	94·9 (12·0)	92·2 (15·2)	86·6 (19·4)	<0·001
ZDS	45·7 (14·0)	43·3 (12·4)	45·9 (14·6)	49·5 (15·0)	<0·001	46·2 (15·4)	42·9 (14·0)	48·5 (17·0)	49·9 (14·7)	<0·001
EQ5D HUS	0·65 (0·29)	0·71 (0·26)	0·64 (0·29)	0·58 (0·32)	<0·001	0·65 (0·30)	0·72 (0·26)	0·63 (0·30)	0·54 (0·33)	<0·001
EQ-VAS	71·5 (18·9)	74·8 (15·4)	68·6 (20·9)	69·0 (21·1)	<0·001	72·0 (18·9)	75·3 (18·0)	72·0 (17·3)	66·0 (20·7)	<0·001

Data are n (%), mean (SD) or median [IQR]. CP = cognitively preserved. MCI = Mild cognitive impairment. SCI = Severe cognitive impairment. TICS-M = Telephone Interview for Cognitive Status-Modified. mRS = modified Rankin Scale. ZDS = Zung Depression Scale. EQ = EuroQol. HUS = Health Utility Status. VAS = Visual Analogue Scale. Day 90 missing data: ZDS (n=12), EQ-5D HUS (n=1), EQ-VAS (n=13). Day 365 missing data: Barthel index (n=1), ZDS (n=19), EQ-VAS (n=19).

Table 4.4: Unadjusted associations of cognitive impairment on Day 90 and Day 365.

Risk factors	**Day 90**				**Day 365**			
	PSCI, OR (95% CI)	**P**	**SCI, OR (95% CI)**	**P**	**PSCI, OR (95% CI)**	**P**	**SCI, OR (95% CI)**	**P**
Age*	1·04 (1·03-1·06)	<0·001	1·04 (1·02-1·05)	<0·001	1·03 (1·01-1·04)	<0·001	1·04 (1·02-1·05)	<0·001
Treatment	0·84 (0·62-1·13)	0·25	0·77 (0·55-1·08)	0·14	1·06 (0·74-1·51)	0·73	0·87 (0·58-1·30)	0·50
TTN	1·02 (0·93-1·12)	0·56	1·08 (0·98-1·19)	0·12	1·09 (0·96-1·23)	0·15	0·99 (0·87-1·12)	0·88
Female	0·94 (0·69-1·28)	0·71	1·18 (0·83-1·68)	0·33	0·84 (0·58-1·21)	0·36	1·33 (0·88-2·01)	0·16
Recruited in the UK	1·34 (0·96-1·87)	0·08	1·33 (0·90-1·97)	0·14	NA	NA	NA	NA
IMD*	NA	NA	NA	NA	0·93 (0·87-1·00)	0·049	0·92 (0·85-0·99)	0·028
Non-Caucasian*	1·32 (0·80-2·17)	0·27	1·96 (1·18-3·24)	0·008	3·68 (1·79-7·55)	<0·001	5·03 (2·73-9·27)	<0·001
Pre-morbid mRS >0*	1·79 (1·14-2·84)	0·012	2·02 (1·29-3·16)	0·002	1·28 (0·77-2·12)	0·32	1·44 (0·84-2·47)	0·17
Previous stroke or TIA*	1·40 (0·87-2·27)	0·15	1·85 (1·14-3·00)	0·012	1·37 (0·73-2·59)	0·32	1·71 (0·89-3·28)	0·10
Hypertension	1·19 (0·87-1·63)	0·25	0·88 (0·62-1·25)	0·47	1·33 (0·93-1·90)	0·11	1·08 (0·72-1·62)	0·69
Diabetes	1·16 (0·73-1·84)	0·57	1·34 (0·82-2·19)	0·23	1·15 (0·67-1·98)	0·59	1·45 (0·81-2·59)	0·19
Hyperlipidaemia	1·33 (0·92-1·93)	0·12	1·02 (0·67-1·53)	0·91	1·04 (0·68-1·59)	0·84	1·10 (0·68-1·78)	0·68
Atrial fibrillation	1·58 (0·58-4·27)	0·36	1·82 (0·69-4·79)	0·21	1·18 (0·37-3·79)	0·77	2·07 (0·64-6·65)	0·22
Current or previous smoker	1·35 (0·99-1·83)	0·05	1·16 (0·82-1·64)	0·37	1·30 (0·91-1·87)	0·14	1·19 (0·79-1·80)	0·38

Alcohol intake	0·99 (0·99-1·00)	0·60	0·99 (0·98-1·00)	0·06	1·00 (0·99-1·01)	0·31	0·99 (0·98-1·00)	0·18
Systolic blood pressure (mmHg)*	0·99 (0·99-1·00)	0·17	0·99 (0·98-0·99)	0·021	0·99 (0·98-1·00)	0·09	0·99 (0·98-1·00)	0·27
Diastolic blood pressure (mmHg)*	0·98 (0·98-0·99)	0·006	0·98 (0·97-0·99)	0·001	0·98 (0·97-0·99)	0·012	0·98 (0·97-0·99)	0·034
Left hemisphere stroke*	1·81 (1·33-2·47)	<0·001	1·91 (1·35-2·71)	<0·001	1·21 (0·84-1·74)	0·29	1·24 (0·82-1·87)	0·29
Stroke severity (NIHSS)*	1·02 (0·99-1·05)	0·07	1·04 (1·01-1·08)	0·002	1·03 (1·00-1·06)	0·042	1·03 (1·00-1·07)	0·042
Glasgow Coma Scale*	0·84 (0·74-0·96)	0·014	0·82 (0·72-0·93)	0·002	0·78 (0·65-0·92)	0·005	0·78 (0·67-0·91)	0·002
ICH volume*	1·01 (1·00-1·02)	0·05	1·01 (1·00-1·02)	0·020	1·01 (0·99-1·02)	0·12	1·00 (0·99-1·02)	0·23
Presence of IVH*	1·35 (0·79-2·05)	0·15	2·22 (1·46-3·40)	<0·001	1·42 (0·88-2·28)	0·14	1·48 (0·90-2·44)	0·12
Lobar haematoma*	2·02 (1·34-3·05)	0·001	2·10 (1·40-3·14)	<0·001	1·24 (0·79-1·94)	0·33	1·72 (1·07-2·77)	0·023
Cerebral atrophy	1·12 (0·92-1·37)	0·22	1·14 (0·92-1·41)	0·21	1·05 (0·84-1·32)	0·61	1·19 (0·93-1·53)	0·15
Leukoaraiosis*	1·43 (1·21-1·68)	<0·001	1·22 (1·05-1·43)	0·010	1·18 (0·98-1·43)	0·07	1·25 (1·03-1·25)	0·022
Old vascular lesions*	1·47 (1·09-2·00)	0·012	1·07 (0·76-1·51)	0·68	1·43 (1·00-2·05)	0·046	0·87 (0·58-1·31)	0·52

Shown are the odds ratios (OR) and 95% confidence intervals (CI) with p-values. Factors included in the multivariable model are marked with a *. Index of multiple deprivation (IMD) is only available for UK participants and as such is only included in the Day 365 associations. PSCI = Post-stroke cognitive impairment. SCI = Severe cognitive impairment. TTN = Time to neuroimaging. mRS = modified Rankin Scale. TIA = Transient ischaemic attack. NIHSS = National Institute of Health Stroke Scale. ICH = Intracerebral haemorrhage. IVH = Intraventricular haemorrhage. NA = Not available.

Table 4.5: Multivariable associations between cognition status and baseline factors on Day 90 and Day 365.

Risk factors	**Day 90**				**Day 365**			
	PSCI, OR (95% CI)	**P**	**SCI, OR (95% CI)**	**P**	**PSCI, OR (95% CI)**	**P**	**SCI, OR (95% CI)**	**P**
Age	1·05 (1·04-1·07)	<0·001	1·06 (1·04-1·08)	<0·001	1·05 (1·03-1·07)	<0·001	1·09 (1·06-1·12)	<0·001
Non-Caucasian	2·81 (1·58-5·00)	<0·001	4·84 (2·59-9·06)	<0·001	7·01 (3·06-16·03)	<0·001	17·92 (7·78-41·27)	<0·001
Socioeconomic status	NA	NA	NA	NA	0·92 (0·85-0·99)	0·028	0·88 (0·81-0·96)	0·007
NIHSS	NS	NS	1·07 (1·03-1·11)	<0·001	NS	NS	NS	NS
GCS	NS	NS	NS	NS	0·71 (0·58-0·88)	0·002	0·69 (0·56-0·84)	<0·001
Left hemisphere stroke	2·22 (1·58-3·13)	<0·001	2·25 (1·53-3·31)	<0·001	NS	NS	NS	NS
IVH scan	NS	NS	2·05 (1·27-3·31)	0·003	NS	NS	NS	NS
Lobar haematoma	NS	NS	2·18 (1·36-3·50)	0·001	NS	NS	1·91 (1·11-3·29)	0·018
ICH volume	1·03 (1·01-1·04)	<0·001	NS	NS	NS	NS	NS	NS
Leukoaraiosis	1·30 (1·08-1·56)	0·004	NS	NS	NS	NS	NS	NS

Shown are the odds ratios (OR) and 95% confidence intervals (CI) with p-value. NIHSS = National Institute of Health Stroke Scale. GCS = Glasgow Coma Scale. IVH = Intraventricular haemorrhage. ICH = Intracerebral haemorrhage. NA = Not available. NS = Not significant.

4.7 Supplemental Material

Supplementary Table X: Comparison of baseline clinical features in participants with or without cognition data or that died by Day 90 and Day 365.

Baseline Clinical Features	**All**	**Day 90**				**Day 365**			
		With Cognition data	**No Cognition data**	**P**	**Died**	**With cognition data**	**No cognition data**	**P**	**Died**
Participants (%)	2118	693 (32·7)	967 (45·7)		458 (21·6)	496 (23·4)	1066 (50·3)		556 (26·3)
Demographics									
Age (years)	69·2 (13·6)	63·2 (12·4)	69·6 (13·5)	<0·001	77·3 (10·7)	64·5 (12·3)	67·0 (13·7)	<0·001	77·5 (10·5)
Female (%)	916 (43·2)	250 (36·1)	436 (45·1)	<0·001	230 (50·2)	186 (37·5)	451 (42·3)	0·07	279 (50·2)
Treatment (%)	1064 (50·2)	341 (49·2)	492 (50·9)	0·50	231 (50·4)	251 (50·6)	529 (49·6)	0·71	284 (51·1)
Recruited in the UK (%)	1740 (82·3)	499 (72·2)	855 (88·4)	<0·001	386 (84·5)	496 (100·0)	760 (71·4)	<0·001	484 (87·2)
TTN [hours]	1 [1-2]	1 [1-2]	1 [1-2]	0·871	1 [1-2]	1 [1-2]	1 [1-2]	0·88	1 [1-2]
IMD [decile]	6 [3-8]	6 [4-9]	6 [3-8]	0·024	6 [3-8]	6 [4-8]	6 [3-8]	0·004	6 [3-8]
Caucasian (%)	1809 (85·4)	619 (89·3)	766 (79·2)	<0·001	424 (92·6)	447 (90·1)	847 (79·5)	<0·001	515 (92·6)
mRS >0 (%)	592 (28·0)	97 (14·0)	272 (28·1)	<0·001	223 (48·7)	74 (14·9)	244 (22·9)	<0·001	274 (49·3)
Medical history (%)									
Stroke or TIA	378 (17·9)	82 (11·8)	173 (17·9)	0·001	123 (26·9)	44 (8·9)	185 (17·4)	<0·001	149 (26·8)
Hypertension	1313 (62·4)	433 (62·8)	582 (60·4)	0·34	298 (65·9)	269 (54·3)	689 (64·9)	<0·001	355 (64·7)

Hyperlipidaemia	538 (25·6)	151 (21·8)	242 (25·2)	0·11	145 (32·4)	109 (22·0)	241 (22·7)	0·73	188 (34·6)
Diabetes	292 (13·9)	86 (12·4)	145 (15·0)	0·13	62 (13·6)	61 (12·3)	154 (14·5)	0·24	78 (14·1)
Atrial fibrillation	65 (3·1)	18 (2·6)	26 (2·7)	0·89	21 (4·6)	12 (2·4)	25 (2·4)	0·94	28 (5·1)
Smoking- ever	964 (8·0)	354 (52·2)	412 (44·4)	0·002	198 (49·1)	233 (48·2)	481 (46·8)	0·59	250 (50·2)
Alcohol intake [UPW]	1 [0-9]	2 [0-12]	1 [0-7]	<0·001	0 [0-5]	2 [0-13]	1 [0-10]	<0·001	0 [0-4]
Blood pressure (mmHg)									
Systolic	172·7 (27·0)	172·4 (26·3)	173·3 (27·5)	0·48	171·8 (27·2)	172·8 (26·7)	173·8 (27·3)	0·47	170·5 (26·8)
Diastolic	93·3 (18·1)	96·1 (18·0)	93·1 (18·0)	0·001	89·5 (17·7)	94·9 (18·3)	95·0 (17·9)	0·96	88·7 (17·4)
Index event									
Left hemisphere (%)	1020 (49·9)	330 (49·4)	476 (51·1)	0·51	214 (48·1)	227 (47·6)	538 (52·3)	0·08	255 (47·2)
NIHSS (/42)	13·1 (7·4)	9·3 (5·6)	13·2 (7·0)	<0·001	18·7 (6·8)	9·0 (5·9)	12·5 (6·8)	<0·001	17·9 (7·0)
Aphasic (%)	899 (42·4)	170 (24·5)	444 (45·9)	<0·001	285 (62·2)	125 (25·2)	443 (41·6)	<0·001	331 (59·5)
GCS (/15)	13·5 (2·1)	14·4 (1·3)	13·5 (2·0)	<0·001	12·1 (2·5)	14·5 (1·2)	13·6 (1·9)	<0·001	12·4 (2·5)

Data are n (%), mean (SD) or median [IQR]. TTN = Time to neuroimaging. IMD = Indices of multiple deprivation. mRS = modified Rankin Scale. TIA = Transient ischaemic attack. UPW = units per week. NIHSS = National Institute of Health Stroke Scale. GCS = Glasgow coma scale. Day 90 missing data: UK (n=3), IMD (n=416), Stroke or TIA (n=2), Hypertension (n=13), Hyperlipidaemia (n=18), Diabetes (n=4), AF (n=10), Smoking (n=109), Alcohol intake (n=251), Left hemisphere stroke (n=73). Day 365 missing data: UK (n=3), IMD (n=416), stroke or TIA (n=2), Hypertension (n=13), Hyperlipidaemia (n=18), Diabetes (n=4), AF (n=10), Smoking (n=109), Alcohol intake (n=251), Left hemisphere stroke (n=73).

Supplementary Table XI: Comparison of baseline neuroimaging features in participants with or without cognition data or that died by Day 90 and Day 365.

Baseline neuroimaging features	**All**	**Day 90**				**Day 365**			
		With cognition data	**No cognition data**	**P**	**Died**	**With cognition data**	**No cognition data**	**P**	**Died**
Participants (%)	2092	684 (32·7)	955 (45·7)		453 (21·6)	491 (23·5)	1051 (50·2)		550 (26·3)
ICH features									
Volume (mL)	23·4 (27·0)	11·3 (12·4)	20·7 (20·8)	<0·001	47·7 (37·5)	13·0 (14·5)	17·5 (19·1)	<0·001	44·0 (36·2)
Multiple (%)	147 (7·1)	22 (3·2)	54 (5·7)	0·021	71 (15·7)	15 (3·1)	49 (4·7)	0·13	83 (15·1)
Presence of IVH (%)	593 (28·4)	112 (16·4)	279 (29·3)	<0·001	202 (44·6)	88 (18·0)	268 (25·5)	0·001	237 (43·1)
Location (%)									
Lobar	555 (26·6)	129 (18·9)	236 (24·8)	0·005	190 (41·9)	99 (20·2)	227 (21·7)	0·49	229 (41·6)
Deep	1479 (70·9)	535 (78·6)	690 (72·6)	0·006	254 (56·1)	381 (77·8)	789 (75·5)	0·33	309 (56·2)
Infratentorial	51 (2·4)	17 (2·5)	25 (2·6)	0·86	9 (2·0)	10 (2·0)	29 (2·8)	0·39	12 (2·2)
Cerebral amyloid angiopathy (%)	526 (36·2)	109 (24·1)	225 (33·4)	0·001	192 (58·4)	88 (25·8)	207 (29·0)	0·27	231 (57·6)
Pre-existing structural signs									
Cortical atrophy (%)	1916 (91·6)	607 (88·7)	871 (91·2)	0·09	438 (96·7)	432 (88·0)	949 (90·3)	0·16	535 (97·3)
Subcortical atrophy (%)	535 (25·6)	160 (23·4)	251 (26·3)	0·18	124 (27·4)	96 (19·6)	275 (26·2)	0·005	164 (29·8)

Atrophy severity (/4)	1·0 [1·0-2·0]	1·0 [1·0-2·0]	1·0 [1·0-2·0]	0·001	1·0 [1·0-2·0]	1·0 [1·0-1·0]	1·0 [1·0-2·0]	0·001	1·0 [1·0-2·0]
Anterior WMH (%)	808 (38·6)	189 (27·6)	370 (38·7)	<0·001	249 (55·0)	131 (26·7)	370 (35·2)	0·001	307 (55·8)
Posterior WMH (%)	825 (39·4)	195 (28·5)	369 (38·6)	<0·001	261 (57·6)	124 (25·3)	389 (37·0)	<0·001	312 (56·7)
WMH severity (/4)	0·0 [0·0-2·0]	0·0 [0·0-1·0]	0·0 [0·0-2·0]	<0·001	1·0 [0·0-2·0]	0·0 [0·0-1·0]	0·0 [0·0-2·0]	<0·001	1·0 [0·0-2·0]
Old lesions (%)	1296 (62·0)	386 (56·4)	592 (62·0)	0·024	318 (70·2)	263 (53·6)	642 (61·1)	0·005	391 (71·1)
Cortical	1122 (53·6)	323 (47·2)	508 (53·2)	0·017	291 (64·2)	216 (44·0)	549 (52·2)	0·003	357 (64·9)
Lacunar	598 (28·6)	178 (26·0)	277 (29·0)	0·18	143 (31·6)	117 (23·8)	302 (28·7)	0·044	179 (32·5)

Data are n (%), mean (SD) or median [IQR]. ICH = Intracerebral haemorrhage. IVH = Intraventricular haemorrhage. WMH = White matter hyperintensities. Day 90 missing data: ICH volume (n=48), ICH multiple (n=33), Presence of IVH (n=29), ICH location (n=33), Cerebral amyloid angiopathy (663), pre-existing structural signs (n=26). Day 365 missing data: ICH volume (n=48), ICH multiple (n=33), Presence of IVH (n=29), ICH location (n=33), Cerebral amyloid angiopathy (849), pre-existing structural signs (n=26).

Supplementary Table XII: Comparison of baseline clinical features in Caucasian and non-Caucasian participants with cognition data on Day 90 and Day 365.

	With Cognition Data Day 90				With Cognition Data Day 365			
Baseline Clinical Features	**All**	**Non-Caucasian**	**Caucasian**	**P**	**All**	**Non-Caucasian**	**Caucasian**	**P**
Number (%)	693	74 (10·7)	619 (89·3)		496	49 (9·9)	447 (90·1)	
Demographics								
Age (years)	63·2 (12·4)	53·3 (10·8)	64·4 (12·0)	<0·001	64·4 (12·2)	52·9 (10·8)	65·7 (11·7)	<0·001
Female (%)	250 (36·1)	22 (29·7)	228 (36·8)	0·22	186 (37·5)	11 (22·4)	175 (39·1)	0·022
Treatment (%)	341 (49·2)	38 (51·4)	303 (48·9)	0·69	251 (50·6)	23 (46·9)	228 (51·0)	0·58
Recruited in the UK (%)	499 (72·2)	49 (66·2)	450 (72·9)	0·22	496 (100·0)	49 (100·0)	447 (100·0)	-
TTN [hours]	1 [1-2]	1 [1-2]	1 [1-2]	0·55	1 [1-2]	1 [1-2]	1 [1-2]	0·18
IMD [decile]	6 [4-9]	3 [2-7]	7 [4-9]	<0·001	6 [4-8]	4 [2-7]	7 [4-9]	<0·001
mRS >0 (%)	97 (14·0)	9 (12·2)	88 (14·2)		74 (14·9)	6 (12·2)	68 (15·2)	0·58
Medical history (%)								
Stroke or TIA	82 (11·8)	10 (13·5)	72 (11·6)	0·63	44 (8·9)	5 (10·2)	39 (8·7)	0·73
Hypertension	433 (62·8)	45 (60·8)	388 (63·0)	0·71	269 (54·3)	28 (57·1)	241 (54·0)	0·67
Hyperlipidaemia	151 (21·8)	20 (27·0)	131 (21·2)	0·25	109 (22·0)	10 (20·4)	99 (22·1)	0·78
Diabetes	86 (12·4)	19 (25·7)	67 (10·8)	<0·001	61 (12·3)	12 (24·5)	49 (11·0)	0·006
Atrial fibrillation	18 (2·6)	0 (0·0)	18 (2·9)	0·13	12 (2·4)	0 (0·0)	12 (2·7)	0·24
Smoking, ever	354 (52·2)	31 (42·5)	323 (53·4)	0·07	233 (48·2)	20 (40·8)	213 (49·1)	0·27
Alcohol intake [UPW]	2 [0-12]	0 [0-1]	3 [0-14]	<0·001	2 [0-13]	0 [0-3]	3 [0-14]	<0·001
Blood pressure (mmHg)								
Systolic	172·4 (26·2)	184·2 (27·1)	170·9 (25·8)	<0·001	172·7 (26·7)	182·8 (29·2)	171·6 (26·2)	0·005
Diastolic	96·1 (17·9)	103·8 (20·2)	95·1 (17·4)	<0·001	94·9 (18·2)	104·7 (20·8)	93·8 (17·6)	<0·001
Index event								

Left hemisphere (%)	330 (49·4)	30 (42·3)	300 (50·3)	0·20	227 (47·6)	16 (33·3)	211 (49·2)	0·037
NIHSS (/42)	9·2 (5·6)	10·6 (5·4)	9·0 (5·6)	0·024	8·9 (5·8)	11·1 (5·8)	8·7 (5·8)	0·006
Aphasic (%)	170 (24·5)	17 (23·0)	153 (24·7)	0·74	125 (25·2)	11 (22·4)	114 (25·5)	0·64
GCS (/15)	14·3 (1·2)	14·3 (1·3)	14·3 (1·2)	0·95	14·5 (1·2)	14·2 (1·4)	14·5 (1·1)	0·10

Data are n (%), mean (SD) or median [IQR]. Independent-Samples T-Test (continuous variable), Chi Square test for homogeneity (binary variable) and Mann-Whitney U (ordinal variable) were used to determine group differences. TTN = Time to neuroimaging. IMD = Indices of multiple deprivation. mRS = modified Rankin Scale. TIA = Transient ischaemic attack. UPW = units per week. NIHSS = National Institute of Health Stroke Scale. GCS = Glasgow coma scale. Day 90 missing data: UK (n=2), IMD (n=203), Hypertension (n=3), Hyperlipidaemia (n=1), Diabetes (n=1), AF (n=1), Smoking (n=15), Alcohol intake (n=54), Left hemisphere stroke (n=25). Day 365 missing data: IMD (n=9), Hypertension (n=1), Smoking (n=13), Alcohol intake (n=48), Left hemisphere stroke (n=19)

Supplementary Table XIII: Comparison of baseline neuroimaging features in Caucasian and non-Caucasian participants with cognition data on Day 90 and Day 365.

	With Cognition Data Day 90				With Cognition Data Day 365			
Baseline neuroimaging features	**All**	**Non-Caucasian**	**Caucasian**	**P**	**All**	**Non-Caucasian**	**Caucasian**	**P**
Number (%)	684	74 (10·8)	610 (89·2)		491	48 (9·8)	443 (90·2)	
ICH features								
Volume (mL)	11·2 (12·4)	11·5 (11·3)	11·2 (12·5)	0·86	13·0 (14·4)	12·8 (10·9)	13·0 (14·8)	0·92
Multiple (%)	22 (3·2)	4 (5·5)	18 (3·0)	0·25	15 (3·1)	1 (2·1)	14 (3·2)	0·67
Presence of IVH (%)	112 (16·4)	16 (21·6)	96 (15·8)	0·19	88 (18·0)	13 (27·1)	75 (17·0)	0·08
Location (%)								
Lobar	129 (18·9)	3 (4·1)	126 (20·7)	0·001	99 (20·2)	2 (4·2)	97 (21·9)	0·004
Deep	535 (78·6)	70 (95·9)	465 (76·5)	<0·001	381 (77·8)	46 (95·8)	335 (75·8)	0·002
Infratentorial	17 (2·5)	0 (0·0)	17 (2·8)	0·14	10 (2·0)	0 (0·0)	10 (2·3)	0·29
Cerebral amyloid angiopathy (%) (n=452)	109 (24·1)	3 (5·0)	106 (27·0)	<0·001	88 (25·8)	2 (5·3)	86 (28·4)	0·002
Pre-existing structural signs								
Cortical atrophy (%)	607 (88·7)	52 (70·3)	555 (91·0)	<0·001	432 (88·0)	26 (54·2)	406 (91·6)	<0·001
Subcortical atrophy (%)	160 (23·4)	6 (8·1)	154 (25·2)	0·001	96 (19·6)	1 (2·1)	95 (21·4)	0·001
Atrophy severity (/4)	1·0 [1·0-2·0]	1·0 [0·0-1·0]	1·0 [1·0-2·0]	<0·001	1·0 [1·0-1·0]	1·0 [0·0-1·0]	1·0 [1·0-1·0]	<0·001
Anterior WMH (%)	189 (27·6)	9 (12·2)	180 (29·5)	0·002	131 (26·7)	4 (8·3)	127 (28·7)	0·002
Posterior WMH (%)	195 (28·5)	7 (9·5)	188 (30·8)	<0·001	124 (25·3)	3 (6·3)	121 (27·3)	0·001
WMH severity (/4)	0·0 [0·0-1·0]	0·0 [0·0-0·0]	0·0 [0·0-1·0]	<0·001	0·0 [0·0-1·0]	0·0 [0·0-0·0]	1·0 [0·0-1·0]	<0·001
Old lesions (%)	386 (56·4)	28 (37·8)	358 (58·7)	0·001	263 (53·6)	14 (29·2)	249 (56·2)	<0·001
Cortical	323 (47·2)	20 (27·0)	303 (49·7)	<0·001	216 (44·0)	9 (18·8)	207 (46·7)	<0·001
Lacunar	178 (26·0)	13 (17·6)	165 (27·0)	0·07	117 (23·8)	7 (14·6)	110 (24·8)	0·11

Data are n (%), mean (SD) or median [IQR]. Independent-Samples T-Test (continuous variable) and Chi Square test for homogeneity (binary variable) were used to determine group differences. Cerebral amyloid angiopathy (CAA) was adjudicated by neuroradiologists according to the Boston criteria. ICH = Intracerebral haemorrhage. IVH = Intraventricular haemorrhage. WMH = White matter hyperintensities. Day 90 missing data: ICH volume (n=16), ICH multiple (n=12), presence of IVH (n=10), ICH location (n=12), Cerebral amyloid angiopathy (n=241), pre-existing structural signs (n=9). Day 365 missing data: ICH volume (n=10), ICH multiple (n=6), presence of IVH (n=6), ICH location (n=6), CAA (n=155), pre-existing structural signs (n=5).

Supplementary Table XIV: Cognition and functional outcomes of participants by their ethnicity on Day 90 and Day 365.

	With Cognition Data Day 90				With Cognition Data Day 365			
	All	**Non-Caucasian**	**Caucasian**	**P**	**All**	**Non-Caucasian**	**Caucasian**	**P**
Participants	693	74 (10·7)	619 (89·3)		496	49 (9·9)	447 (90·1)	
Cognition outcome								
TICS-M (/39)	23·4 (5·3)	22·2 (7·2)	23·5 (5·0)	0·13	23·4 (5·7)	19·4 (5·3)	23·8 (5·6)	<0·001
<25	207 (29·9)	17 (23·0)	190 (30·7)	0·17	140 (28·2)	10 (20·4)	130 (29·1)	
<21	182 (26·3)	29 (39·2)	153 (24·7)	0·008	129 (26·0)	29 (59·2)	100 (22·4)	
Domains								
Verbal memory	7·2 (3·6)	7·6 (4·7)	7·2 (3·5)	0·49	7·1 (3·7)	5·1 (2·8)	7·4 (3·7)	<0·001
Orientation and mental tracking	7·1 (1·2)	6·9 (1·5)	7·1 (1·1)	0·27	7·1 (1·2)	6·9 (1·2)	7·1 (1·3)	0·29
Language and reasoning	4·4 (0·8)	3·7 (1·1)	4·5 (0·7)	<0·001	4·5 (0·7)	3·7 (1·2)	4·6 (0·6)	<0·001
Attention and working memory	4·5 (1·5)	3·8 (1·8)	4·5 (1·5)	0·001	4·5 (1·7)	3·5 (1·8)	4·6 (1·7)	<0·001
Functional outcome								
mRS	2·0 [1·0-3·0]	2·0 [2·0-3·0]	2·0 [1·0-3·0]	0·16	2·0 [1·0-3·0]	2·0 [1·0-3·0]	2·0 [1·0-3·0]	0·18
Barthel Index	89·9 (17·6)	88·8 (17·6)	90·1 (17·6)	0·55	91·9 (15·5)	89·4 (15·2)	92·2 (15·5)	0·23
ZDS	45·7 (14·0)	45·4 (17·2)	45·7 (13·5)	0·90	46·2 (15·3)	50·8 (17·0)	45·7 (15·1)	0·031

EQ5D HUS	0·6 (0·2)	0·6 (0·2)	0·6 (0·2)	0·15	0·6 (0·3)	0·5 (0·3)	0·6 (0·3)	0·10
EQ-VAS	71·4 (18·9)	63·3 (22·2)	72·3 (18·3)	0·002	72·0 (18·8)	68·6 (21·6)	72·3 (18·5)	0·20

Data are n (%), mean (SD) or median [IQR]. Independent-Samples T-Test (continuous variable), Chi Square test for homogeneity (binary variable) and Mann-Whitney U (ordinal variable) were used to determine group differences. TICS-M = Telephone Interview for Cognitive Status-Modified. mRS = modified Rankin Scale. ZDS = Zung Depression Scale. EQ = EuroQol. HUS = Health Utility Status. VAS = Visual Analogue Scale. Day 90 missing data: ZDS (n=12), EQ-5D HUS (n=1), EQ-VAS (n=13). Day 365 missing data: Barthel index (n=1), ZDS (n=19), EQ-VAS (n=19).

Supplementary Table XV: Functional outcomes of participants with and without cognition data on Day 90 and Day 365.

Functional outcome	**Day 90**			**Day 365**		
	With Cognition Data	**No cognition data**	**P**	**With Cognition Data**	**No cognition data**	**P**
Participants (%)	693	967		496	1066	
mRS, n (%)	693 (100·0)	952 (98·4)		496 (100·0)	654 (61·4)	
mRS, median [IQR]	2·0 [1·0-3·0]	4·0 [3·0-5·0]	<0·001	2·0 [1·0-3·0]	4·0 [2·0-4·0]	<0·001
Barthel Index, n (%)	693 (100·0)	887 (91·7)		495 (99·8)	604 (56·7)	
Barthel Index, mean (SD)	90·0 (17·7)	53·8 (37·0)	<0·001	92·0 (15·5)	61·4 (37·4)	<0·001
EQ-5D-HUS, n (%)	692 (99·9)	901 (93·2)		496 (100·0)	609 (57·1)	
EQ5D HUS, mean (SD)	0·65 (0·29)	0·27 (0·39)	<0·001	0·65 (0·30)	0·33 (0·40)	<0·001
EQ-VAS, n (%)	680 (98·1)	762 (78·8)		477 (96·2)	536 (50·3)	
EQ-VAS, mean (SD)	71·5 (18·9)	57·6 (21·5)	<0·001	72·0 (18·9)	59·4 (22·5)	<0·001
ZDS, n (%)	681 (98·3)	63 (6·5)		477 (96·2)	62 (5·8)	
ZDS, mean (SD)	45·7 (14·0)	52·2 (15·9)	<0·001	46·2 (15·4)	51·0 (16·6)	0·024

Data are n (%), mean (SD) or median [IQR]. mRS = modified Rankin Scale. EQ = EuroQol. HUS = Health Utility Status. VAS = Visual Analogue Scale. ZDS = Zung Depression Scale. Day 90 missing data: mRS (n=15), BI (n=80), EQ-5D HUS (n=67), EQ-VAS (n=218), ZDS (n=916). Day 365 missing data: mRS (n=412), BI (n=463), EQ-5D HUS (n=457), EQ-VAS (n=549), ZDS (n=1023).

Supplementary Table XVI: Unadjusted associations of cognitive impairment on Day 90 and Day 365 including participants that died.

Risk factors	**Day 90**				**Day 365**			
	PSCI, OR (95% CI)	**P**	**SCI, OR (95% CI)**	**P**	**PSCI, OR (95% CI)**	**P**	**SCI, OR (95% CI)**	**P**
Age*	1·07 (1·06-1·09)	<0·001	1·84 (1·07-1·10)	<0·001	1·07 (1·06-1·08)	<0·001	1·09 (1·07-1·10)	<0·001
Treatment	0·89 (0·69-1·16)	0·25	0·91 (0·72-1·15)	0·47	1·05 (0·78-1·41)	0·71	0·96 (0·74-1·23)	0·76
TTN	1·00 (0·92-1·09)	0·93	1·02 (0·94-1·10)	0·60	1·05 (0·94-1·17)	0·31	0·97 (0·89-1·06)	0·57
Female*	1·31 (1·00-1·72)	0·045	1·64 (1·29-2·09)	<0·001	1·26 (0·94-1·71)	0·11	1·71 (1·32-2·22)	<0·001
Recruited in the UK*	1·81 (1·34-2·43)	<0·001	1·90 (1·44-2·51)	<0·001	NA	NA	NA	NA
IMD*	NA	NA	NA	NA	0·93 (0·88-0·98)	0·013	0·94 (0·89-0·98)	0·010
Non-Caucasian*	1·02 (0·65-1·61)	0·90	1·13 (0·75-1·68)	0·54	2·33 (1·18-4·57)	0·014	1·97 (1·18-3·30)	0·009
Pre-morbid mRS >0*	4·56 (3·06-6·78)	<0·001	5·27 (3·85-7·22)	<0·001	4·11 (2·73-6·19)	<0·001	4·88 (3·49-6·82)	<0·001
Previous stroke or TIA*	2/37 (1·57-3·59)	<0·001	2·85 (2·03-4·02)	<0·001	3·35 (1·98-5·64)	<0·001	3·84 (2·51-5·86)	<0·001
Hypertension*	1·23 (0·94-1·61)	0·12	1·03 (0·81-1·32)	0·48	1·62 (1·20-2·18)	0·001	1·45 (1·12-1·88)	0·004
Diabetes	1·18 (0·79-1·77)	0·40	1·24 (0·87-1·76)	0·22	1·22 (0·78-1·93)	0·37	1·33 (0·90-1·96)	0·15
Hyperlipidaemia*	1·68 (1·22-2·33)	0·001	1·50 (1·11-1·97)	0·003	1·59 (1·12-2·26)	0·009	1·74 (1·29-2·35)	<0·001
Atrial fibrillation*	2·02 (0·84-4·88)	0·11	2·09 (1·03-4·25)	0·040	1·97 (0·76-5·10)	0·15	2·61 (1·14-5·98)	0·022

IHD*	2·47 (1·38-4·41)	0·002	1·90 (1·23-2·93)	0·004	2·55 (1·37-4·73)	0·003	2·31 (1·43-3·72)	0·001
Current or previous smoker	1·18 (0·90-1·55)	0·21	0·99 (0·77-1·25)	0·93	1·27 (0·94-1·71)	0·11	1·14 (0·88-1·48)	0·30
Alcohol intake*	0·99 (0·98-1·00)	0·049	0·98 (0·98-0·99)	<0·001	0·99 (0·98-1·00)	0·12	0·98 (0·98-0·99)	<0·001
Systolic blood pressure (mmHg)*	0·99 (0·99-1·00)	0·17	0·99 (0·99-1·00)	0·06	0·99 (0·98-1·00)	0·033	0·99 (0·99-1·00)	0·07
Diastolic blood pressure (mmHg)*	0·98 (0·97-0·98)	<0·001	0·97 (0·97-0·98)	<0·001	0·97 (0·97-0·98)	<0·001	0·98 (0·97-0·98)	<0·001
Left hemisphere stroke*	1·53 (1·17-2·01)	0·002	1·31 (1·03-1·66)	0·025	1·13 (0·83-1·52)	0·42	1·07 (0·83-1·39)	0·57
Stroke severity (NIHSS)*	1·12 (1·10-1·15)	<0·001	1·18 (1·15-1·20)	<0·001	1·14 (1·11-1·17)	<0·001	1·17 (1·15-1·20)	<0·001
Glasgow Coma Scale*	0·59 (0·53-0·67)	<0·001	0·56 (0·51-0·61)	<0·001	0·49 (0·41-0·58)	<0·001	0·49 (0·44-0·56)	<0·001
ICH volume*	1·04 (1·03-1·05)	<0·001	1·05 (1·04-1·06)	<0·001	1·04 (1·03-1·05)	<0·001	1·04 (1·03-1·05)	<0·001
Presence of IVH*	2·92 (2·05-4·18)	<0·001	4·22 (3·11-5·72)	<0·001	3·09 (2·09-4·58)	<0·001	3·29 (2·39-4·53)	<0·001
Lobar haematoma*	3·32 (2·30-4·79)	<0·001	3·30 (2·47-4·41)	<0·001	2·42 (1·67-3·49)	<0·001	2·95 (2·16-4·02)	<0·001
Cerebral atrophy*	1·32 (1·11-1·58)	0·002	1·36 (1·16-1·58)	<0·001	1·44 (1·17-1·77)	<0·001	1·59 (1·33-1·90)	<0·001
Leukoaraiosis*	1·84 (1·58-2·14)	<0·001	1·66 (1·48-1·86)	<0·001	1·76 (1·50-2·08)	<0·001	1·86 (1·62-2·13)	<0·001
Old vascular lesions*	1·84 (1·41-2·41)	<0·001	1·56 (1·23-1·99)	<0·001	2·11 (1·56-2·85)	<0·001	1·72 (1·32-2·24)	<0·001

Shown are the odds ratios (OR) and 95% confidence intervals (CI) with p-values. Factors included in the multivariable model are marked with a *. Recruited in the UK is not included in the Day 365 associations as all participants at Day 365 are from the UK. IMD is only available for UK participants and as such is only included in the Day 365 associations. Shown are odds

ratios (OR) and 95% confidence intervals (CI) with p-values from the unadjusted binary logistic regression. PSCI = Post-stroke cognitive impairment. SCI = Severe cognitive impairment. TTN = Time to neuroimaging. mRS = modified Rankin Scale. TIA = Transient ischaemic attack. IHD = Ischaemic heart disease. NIHSS = National Institute of Health Stroke Scale. ICH = Intracerebral haemorrhage. IVH = Intraventricular haemorrhage. NA = Not available.

Supplementary Table XVII: Multivariable associations between cognition status and baseline factors on Day 90 and Day 365 including participants that died.

Risk factors	**Day 90**				**Day 365**			
	PSCI, OR (95% CI)	**P**	**SCI, OR (95% CI)**	**P**	**PSCI, OR (95% CI)**	**P**	**SCI, OR (95% CI)**	**P**
Age	1·07 (1·05-1·08)	<0·001	1·08 (1·06-1·10)	<0·001	1·07 (1·05-1·09)	<0·001	1·11 (1·08-1·13)	<0·001
IMD	NA	NA	NA	NA	0·90 (0·84-0·97)	0·008	0·89 (0·83-0·96)	0·003
Non-Caucasian	2·72 (1·53-4·83)	0·001	3·97 (2·18-7·22)	<0·001	7·61 (3·23-17·92)	<0·001	11·76 (5·37-25·75)	<0·001
Pre-stroke disability	NS	NS	1·76 (1·13-2·73)	0·012	NS	NS	NS	NS
Stroke severity (NIHSS)	1·04 (1·01-1·08)	0·011	1·08 (1·04-1·12)	<0·001	1·06 (1·02-1·10)	0·003	1·09 (1·05-1·14)	<0·001
GCS	NS	NS	0·80 (0·69-0·92)	0·003	0·71 (0·57-0·87)	0·001	0·75 (0·63-0·89)	0·001
Left hemisphere stroke	1·98 (1·41-2·78)	<0·001	1·67 (1·18-2·36)	0·004	NS	NS	NS	NS
IVH scan	NS	NS	2·06 (1·37-3·09)	<0·001	NS	NS	NS	NS
Lobar haematoma	NS	NS	NS	NS	NS	NS	NS	NS
ICH volume	1·03 (1·02-1·05)	<0·001	1·04 (1·02-1·05)	<0·001	1·03 (1·01-1·04)	<0·001	1·03 (1·02-1·04)	<0·001
Leukoaraiosis	1·34 (1·12-1·60)	0·001	NS	NS	NS	NS	1·32 (1·09-1·60)	0·004
Old vascular lesions	NS	NS	NS	NS	1·51 (1·00-2·27)	0·046	NS	NS

Shown are the odds ratios (OR) and 95% confidence intervals (CI) with p-values. NIHSS = National Institute of Health Stroke Scale. GCS = Glasgow Coma Scale. IVH = Intraventricular haemorrhage. ICH = Intracerebral haemorrhage. NA = Not available. NS = Not significant. All models were statistically significant ($p<0{\cdot}001$) and showed an excellent to outstanding level of discrimination. Model A (PSCI Day 90, n=1099, $R^2 = 0{\cdot}42$, AUC = 0·852, 95% CI, 0·830 to 0·875). Model B (SCI Day 90, n=1099, $R^2 = 0{\cdot}59$, AUC= 0·896, 95% CI, 0·878 to 0·914). Model C (PSCI Day 365, n=915, $R^2 = 0{\cdot}44$, AUC = 0·866, 95% CI, 0·843 to 0·890). Model D (SCI Day 365, n=915, $R^2 = 0{\cdot}60$, AUC = 0·906, 95% CI, 0·888 to 0·924).

5 Intensive versus guideline blood pressure and lipid-lowering in participants with previous stroke: Extended follow-up off treatment from the 'Prevention of Decline in Cognition After Stroke Trial' (PODCAST) randomised control trial

5.1 Abstract

5.1.1 Background

There is limited evidence for specific therapeutic strategies for preventing cognitive decline after stroke; however, hypertension and hyperlipidaemia are potential targets for therapeutic intervention.

5.1.2 Methods

PODCAST investigated the effectiveness of intensive vs guideline blood pressure (BP) and lipid-lowering on cognitive outcomes in participants with a recent stroke. The primary cognition measure was the Telephone Interview for Cognitive Status-modified (TICS-M) with cognitive impairment defined as TICS-M <21. An extended follow-up off-treatment was performed by telephone at a median time of 60 months from randomisation. Treatment effects were assessed using an independent samples t-test of the mean area under the curve and adjusted multiple linear regression. The Wei-Lachin test was used for a global analysis of multiple outcomes.

5.1.3 Results

Follow-up was performed at an average of 33.0 [31.0-37.0] months after randomised treatment had ended. Cognition scores did not differ between the intensive versus guideline BP (n=59) and lipid (n=57) lowering groups across all time points or the extended assessment. Intensive lipid-lowering was associated with a tendency to better global outcomes (Wei-Lachin test, p=0.08) and global cognition (p=0.06).

5.1.4 Conclusion

Intensive BP and lipid-lowering did not alter cognition and did not have any long-lasting effects on cognition in participants approximately 5 years after stroke. However, the use of an analysis of global outcome and global cognition suggested that previous intensive lipid-lowering might still be partially effective at 33 months and further trials are needed to confirm this finding.

5.2 Introduction

Stroke is a major cause of worldwide adult disability and death [258]. Stroke is associated with an increased risk of cognitive impairment and dementia with one in ten patients and over a third of patients developing dementia after first-ever stroke and recurrent stroke, respectively [92]. Post-stroke cognitive impairment (PSCI), which includes post-stroke dementia (PSD) and lesser degrees of cognitive impairment, is common after stroke and persists long term [263, 333, 334]. PSCI can worsen the quality of life and independence whilst also increasing the risk of depression, institutionalisation, and mortality [260-262, 292, 333].

PSCI is a major socioeconomic burden on patients, their families and society and yet there is limited evidence for specific therapeutic strategies for preventing cognitive decline after stroke. However, hypertension and hyperlipidaemia are ideal targets for therapeutic intervention and may potentially reduce PSCI by lessening cerebrovascular burden, recurrent stroke and other vascular diseases [47, 335-338].

Most stroke and other vascular trials did not have cognition or dementia as the primary outcome and further research is required to elucidate the relationship between BP and lipid-lowering and PSCI/PSD.

The phase IIb PODCAST trial investigated the effectiveness of intensive blood pressure (BP) and lipid-lowering on cognitive outcomes in participants with recent stroke. It showed in participants with normal cognition and a recent stroke, intensive lowering of BP and lipids were safe and feasible but did not affect cognition assessed using the Addenbrookes Cognitive Examination-Revised over two years [339]. However, intensive lipid-lowering showed significantly improved scores on other cognition outcomes and global cognition

and functional outcome [339, 340]. Here we report the findings from an extended telephone follow-up performed after randomised treatment had ceased to assess whether treatment effects on cognition and functional status were continued long-term.

5.3 Methods

5.3.1 Study design and participants

PODCAST was a pilot multicentre prospective randomised open-label blinded endpoint (PROBE) trial that investigated the effectiveness of intensive blood pressure and lipid-lowering on cognitive outcomes in participants with a recent stroke. The trial design, statistical analysis plan, baseline data and main paper have been published [339, 341, 342], and the full protocol is at http://www.podcast- trial.org/PodcastProtocolV16.pdf. In summary, participants with a sub-acute stroke were assigned to at least 6 months of intensive or guideline BP lowering (<125 mmHg or <140 mmHg respectively); the subset of participants with ischaemic stroke was also randomised to intensive or guideline lipid lowering in a partial factorial design (target LDL-cholesterol <1.4 mmol/l (or total cholesterol <3.1 mmol/l if LDL-cholesterol cannot be calculated) or <3.0 mmol/l (or total cholesterol <5.0 mmol/l if LDL-cholesterol cannot be calculated) respectively) [341].

The main inclusion criteria comprised sub-acute (3-7 months) ischaemic stroke (IS) or intracerebral haemorrhage (ICH); telephone-mini mental state examination (t-MMSE) score >16 (scale range 0-22 [310]) for participants aged over 70 years or 17-20 if age 60-70; independence (modified Rankin Scale, mRS <3, scale range 0-6 [343]); and systolic BP 125-170 mmHg. Ischaemic stroke participants were included if their total cholesterol was 3-8 mmol/L. Participants had to have the capacity and be willing to give consent, and to have an informant who was willing to give consent and complete the informant questionnaire on cognitive decline in the elderly (IQCODE). Key exclusion criteria are given in the main paper [339]. Brain CT or MRI were used to confirm stroke diagnosis and type, and to differentiate stroke sub-types.

The additional study reported here was a continuation of the PODCAST trial, which was approved by the United Kingdom (UK) National Research Ethics Committee (the UK, approval IRAS 18461, date 21 October 2016). The daily conduct of the trial was run by the Stroke Trials Unit at the University of Nottingham, UK. Written informed consent was obtained from each participant and informant before enrolment into the additional study. Participants had ceased randomised treatment and were on their regular prophylaxis as prescribed by their general practitioner.

5.3.2 Outcomes

Outcomes were assessed by a trained assessor via telephone. The primary cognition measure was the telephone interview for cognitive status-modified (TICS-m), a validated global cognition measure that has been used clinically as a screening test for PSCI and PSD in stroke patients. TICS-m covers orientation in time, attention and calculation, memory, and language assessments. It has a total score of 39; a cutoff score <21 was used to identify PSD, this having sensitivity and specificity of 92% and 80% respectively [116]. Secondary cognitive measures include semantic verbal fluency (animal naming), t-MMSE and IQCODE. Functional outcomes included dependency (mRS), disability (Barthel Index, BI), mood (short Zung Depression scale, ZDS), and quality of life (European quality of life 5-dimensions 3-levels, EQ-5D-3L, and EQ-visual analogue scale, EQ-VAS). Since stroke and dementia can be fatal, a score for death was included for each functional and cognition outcome: mRS 6, BI -5, ZDS 102.5, EQ-5D-3L 0, and -1 for EQ-VAS, TICS-M, animal naming, and t-MMSE [266, 267, 344].

Tablet counts are the total number of tablets the participant was taking, and the dose adjusted tablet count is the sum of the tablet dose / maximum licensed dose.

5.3.3 Statistical analysis

Between-group differences were determined using the Chi-square test (binary variables), Mann-Whitney U test (ordinal variables) and independent sample t-test (continuous variables). Standard deviation (SD) and Mean difference (MD) with 95% confidence intervals (95% CI) were used to report treatment effects. Comparison of treatment group differences across all time points using an independent sample t-test of the mean area-under-the-curve (AUC) of the outcome. Comparison of treatment effect at the extended assessment by multiple regression of mean score was used to determine MD and significance, with adjustment for baseline value, systolic BP, total cholesterol, and treatment assignment. The Wei-Lachin test is a simple 1 degree of freedom test obtained from a simple sum of the component statistics. It is a simultaneous test for multiple differences in means, proportions or life-times, and combinations thereof, all on potentially different scales [345]. It was used for assessing a global analysis of multiple outcomes; analyses were performed using the multivariate directional Wilcoxon test and the effect sizes are the Mann-Whitney difference (and 95% CI) for each of the individual outcomes and for the combined outcome (using the Wei-Lachin procedure). Significance was set at $p<0.05$ and 95% CI. Statistical analysis was performed using Statistical Package for Social Sciences version-24 (SPSS-24, IBM, Armonk, NY), SAS University Edition, R version 3.6 and Microsoft Excel.

5.4 Results

A total of 83 participants from 19 UK sites were enrolled between 7 October 2010 and January 2014. 41 and 42 participants were assigned to intensive and guideline BP lowering groups, respectively. Participants with ischaemic stroke were assigned to either intensive (n=39) or guideline (n=38) lipid-lowering groups. 59 (71%) participants, including 17 participants that died, provided information at follow-up at a median time of 60 months after stroke onset and 33 months from the cessation of randomised treatment. The 59 participants were 74.7 (6.8) years of age, with 46 (78.0%) being male (Table 5.1); when compared to participants who did not have an extended follow-up, those reported here were less likely to have had an intracerebral haemorrhage as their index event, and more likely to report memory problems and have lower blood pressure at baseline.

5.4.1 Drug management

The number of antihypertensive tablets in participants randomised to intensive BP lowering rose significantly from 0.9 at the last on-treatment assessment to 2.1 at the extended assessment. However, the dose-adjusted number of tablets rose non-significantly from 1.0 at the last on-treatment assessment to 1.4 at the extended assessment. The total adjusted dose remained consistently higher in the intensive BP versus guideline BP group, however, this difference was not significant across all time points but was significantly higher at the extended assessment (Table 5.2).

The number of tablets in participants randomised to intensive lipid-lowering rose non-significantly from 0.8 at the last on-treatment assessment to 1.0 at the extended assessment, however, the number of tablets in participants randomised to the guideline lipid-lowering rose significantly from 0.3 to 1.0. The

dose-adjusted number of tablets in the intensive lipid group dropped significantly from 1.5 at the last on-treatment assessment to 0.8 at the extended assessment. The dose-adjusted number of tablets were significantly higher across all time points, including the extended assessment, in the intensive lipid-lowering group in comparison to the guideline lipid group (Table 5.3).

5.4.2 Cognitive and functional outcomes

TICS-m, t-MMSE and animal naming, in the intensive BP lowering group and the guideline group, did not differ significantly across all time points or at the extended assessment which adjusted for randomisation variables (Table 5.2, Figure 5.1). The cognition scores of the intensive lipid group were consistently higher than the guideline group on the TICS-M, T-MMSE and animal naming, however, these differences were non-significant across all time points including the extended assessment (Table 5.3, Figure 5.1). The Wei-Lachin test (Figure 5.2) suggested that the intensive lipid-lowering group had a better global cognition (Figure 5.2) although this did not reach statistical significance (global cognition, p=0.06). Global cognition (p=0.10, Figure 5.2) did not differ between intensive vs guideline BP lowering.

Functional outcomes (mRS, BI, EQ-HUS, EQ-VAS, ZDS) showed no consistent significant differences between the intensive BP lowering group and the guideline group (Supplementary Table XVIII). The intensive lipid-lowering group also showed no consistent significant differences in functional outcomes in comparison to the guideline group (Supplementary Table XIX). The Wei-Lachin test (Figure 5.2) suggested that the intensive lipid-lowering group had a better global outcome (Figure 5.2) although this did not reach statistical significance

(global outcome, p=0.08). Global outcome (p=0.52, Figure 5.2) did not differ between intensive vs guideline BP lowering.

5.5 Discussion

This additional follow up of participants from the PODCAST trial showed that there were no residual effects of randomised antihypertensive treatment on long-term cognitive or functional outcomes when assessed individually. The cognition and functional outcomes of participants from the intensive lipid-lowering was consistently better in comparison to the guideline albeit non-significantly. This was supported by the global outcome and global cognition outcomes displayed by the Wei-Lachin analysis that favoured intensive lipid-lowering.

It has been suggested that blood pressure lowering may benefit cognitive function [346]. Hypertension treatment after stroke preserves cognition through the prevention of recurrent stroke and probably other so far undefined mechanisms. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that long-term blood pressure lowering after stroke with perindopril was associated with reduced cognitive decline [347]. This effect was more pronounced in patients with recurrent stroke, suggesting a beneficial effect due to secondary stroke prevention. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study showed cognition was not affected using telmisartan [348]. Also, antiplatelet, or antihypertensive treatment did not affect cognition in The Secondary Prevention of Small Subcortical Strokes (SPS3) trial [349]. Furthermore, a study by Ihle-Hansen et al showed no association between participant scores on cognition measures and different blood pressure goals [350]. Lastly, the Scandinavian Candesartan Acute Stroke Trial (SCAST) showed candesartan did not affect cognitive function at 6 months [351]. Cognition was often a secondary outcome in these studies and overall, no

consistent benefit was seen on cognitive function from antihypertensive intervention, which is consistent with our results.

Secondary stroke prevention with statin therapy slightly reduced the risk of recurrent stroke [47]. Statins lower Low-density lipoprotein (LDL) cholesterol and may lower the risk of ischaemic stroke and have a beneficial effect on endothelial activity, platelet function, and inflammation [336]. A Cochrane systematic review found statins to have no benefit on cognition [352]. The Japan Statin Treatment Against Recurrent Stroke (J-STARS) study showed no clear benefit on cognition after intervention with pravastatin [353]. Our results also showed intensive lipid-lowering did not significantly benefit cognition. On the other hand, our study showed global outcome and global cognitive outcome favoured intensive lipid-lowering albeit non-significantly. Our results support the suggestion that if cognition were to benefit from lipid-lowering then statin intensity (type and dose), which were the main differences between the treatment groups, facilitates this effect [339]. Statins have several beneficial effects which include reduced inflammation, impeded platelet activation, enhanced endothelial function and decreased coagulability, in addition to lowering total, LDL and non-high-density lipoprotein cholesterol [354, 355]. A systematic review showed that statins lower the risk of dementia and cognitive impairment, but these findings were diminished in higher-quality studies [356].

PODCAST was a high-fidelity trial and measured multiple aspects of cognition and function. However, it has several important limitations. Firstly, the original sample size was small (83) reflecting the limited interest in participating hospital sites, in part related to the cost of atorvastatin (which at the time was not generic) [342]. Compounding this, data were only available for 59 of the 83 enrolled participants (including those who had died throughout the trial) at the

extended follow-up time point. The small sample size means the study was underpowered and so may display both type I (false positive) and type II (false neutral) errors. The availability of only a subset of participants from the original trial may also have led to selection bias, manifest as the presence of fewer participants with an intracerebral haemorrhage. Analyses were adjusted statistically for baseline randomisation factors, so baseline cognition differences are unlikely to explain the observed favouring of intensive lipid-lowering.

Second, the difference in systolic blood pressure (SBP) between the intensive and guideline groups were not maintained long-term and the intensive group did not reach its SBP target (<125 mmHg), in part because there was a reluctance by hospital investigators to escalate doses because of the perceived risk of causing adverse events. Similarly, the two target lipid levels were not reached and were 50-60% of the original LDL-cholesterol target. Third, executive function and visuospatial function were not assessed as the cognition measures were not an extensive neuropsychological examination. And last, the treatment may not have been given for a long enough period as some participants were followed up for less than two years.

In conclusion, intensive BP and lipid-lowering did not alter cognition and did not have any long-lasting effects on cognition in participants approximately 5 years after stroke. An improved global outcome and global cognition outcome were observed in the intensive lipid-lowering group and further studies are needed to confirm this finding.

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Table 5.1: Clinical characteristics at randomisation, by intensive vs guideline BP lowering and by intensive vs guideline lipid-lowering

	All	**With additional follow up**	**Without additional follow up**	**P**	**Intensive BP**	**Guideline BP**	**Intensive lipids**	**Guideline lipids**
Number	83	59	24		27	32	28	29
Demographics								
Age (years)	74.0 (6.8)	74.7 (6.8)	72.5 (6.4)	0.17	73.4 (6.6)	75.8 (6.9)	75.3 (6.7)	74.9 (6.5)
Sex, male (%)	64 (77.1)	46 (78.0)	18 (75.0)	0.77	21 (77.8)	25 (78.1)	21 (75.0)	24 (82.8)
Time to randomisation [months]	4.0 [3.0-5.0]	4.0 [4.0-5.0]	4.0 [3.0-5.0)	0.64	4.0 [4.0-5.0]	4.0 [3.3-4.0]	4.0 [3.3-4.8]	4.0 [4.0-5.0]
Time from randomisation to extended assessment [months]	57.0 [34.0-69.0]	60.0 [56.0-71.0]	27.5 [20.3-36.3]	<0.001	63.0 [54.0-72.0]	59.5 [56.3-71.0]	59.0 [53.5-70.5]	63.0 [57.5-71.5]
Time from last assessment on treatment to extended assessment	-	33.0 [31.0-37.0]	-	-	33.0 [31.0-37.0]	33.0 [31.25-37.0]	33.0 [32.0-37.0]	33.0 [31.0-37.0]
Pre-morbid mRS <2 (%)	60 (72.3)	42 (71.2)	18 (75.0)	0.72	17 (63.0)	25 (78.1)	20 (71.4)	21 (72.4)
Medical history (%)								
Memory problems	34 (44.2)	28 (50.9)	6 (27.3)	0.06	14 (56.0)	14 (46.7)	10 (37.0)	17 (65.4)
Hypertension	69 (83.1)	48 (81.4)	21 (87.5)	0.49	22 (81.5)	26 (81.3)	23 (82.1)	23 (79.3)
Hyperlipidaemia	73 (88.0)	50 (84.7)	23 (95.8)	0.15	21 (77.8)	29 (90.6)	25 (89.3)	23 (79.3)

Diabetes mellitus	17 (20.5)	12 (20.3)	5 (20.8)	0.96	8 (29.6)	4 (12.5)	6 (21.4)	5 (17.2)
Atrial fibrillation	15 (18.1)	12 (20.3)	3 (12.5)	0.40	6 (22.2)	6 (18.8)	9 (32.1)	3 (10.3)
Stroke	8 (9.6)	5 (8.5)	3 (12.5)	0.57	1 (3.7)	4 (12.5)	2 (7.1)	3 (10.3)
Smoking, ever (%)	56 (67.5)	37 (62.7)	19 (79.2)	0.14	20 (74.1)	17 (53.1)	14 (50.0)	22 (75.9)
Alcohol [upw]	3.0 [0.0-10.0]	3.0 [0.0-10.0]	1.5 [0.0-7.5]	0.40	3.0 [0.0-10.0]	4.0 [1.0-9.5]	3.0 [0.3-10.0]	4.0 [0.0-11.0]
Index stroke ‡								
Ischaemic (%)	77 (92.8)	57 (96.6)	20 (83.3)	0.034	26 (96.3)	31 (96.9)	28 (100.0)	29 (100.0)
Haemorrhagic (%)	6 (7.2)	2 (3.4)	4 (16.7)		1 (3.7)	1 (3.1)	0 (0.0)	0 (0.0)
Side, right weakness (%)	30 (47.6)	21 (47.7)	9 (47.4)	0.97	10 (43.5)	11 (52.4)	12 (54.5)	8 (40.0)
Dysphasia (%)	23 (27.7)	19 (32.2)	4 (16.7)	0.15	10 (37.0)	9 (28.1)	9 (32.1)	9 (31.0)
NIHSS (/42)	0.8 (1.1)	0.8 (1.1)	0.8 (1.2)	0.91	0.7 (1.1)	0.8 (1.1)	0.6 (0.9)	0.9 (1.3)
Haemodynamics and lipids								
Systolic BP (mmHg)	147.1 (18.6)	144.9 (17.8)	152.6 (19.9)	0.08	142.7 (18.2)	146.8 (17.4)	142.0 (19.1)	147.3 (16.6)
Diastolic BP (mmHg)	82.1 (11.1)	80.8 (10.7)	85.2 (11.9)	0.12	80.7 (10.2)	81.0 (11.2)	80.4 (11.2)	81.0 (10.5)
Heart rate (bpm)	71.5 (14.2)	71.0 (13.8)	72.6 (15.5)	0.64	70.5 (12.6)	71.5 (14.9)	71.8 (16.3)	70.1 (11.6)

Total cholesterol	4.0 (0.8)	3.9 (0.8)	4.2 (1.0)	0.19	3.8 (0.6)	4.0 (0.9)	4.0 (0.7)	3.8 (0.8)
Neuroimaging features								
Cerebral atrophy	8 (9.6)	7 (11.9)	1 (4.2)	0.28	3 (11.1)	4 (12.5)	4 (14.3)	3 (10.3)
Leukoaraiosis	21 (25.3)	13 (22.0)	8 (33.3)	0.28	5 (18.5)	8 (25.0)	6 (21.4)	7 (24.1)
Old vascular lesions	19 (22.9)	12 (20.3)	7 (29.2)	0.38	4 (14.8)	8 (25.0)	5 (17.9)	7 (24.1)
Brain frailty	0.6 (0.7)	0.5 (0.7)	0.7 (0.8)	0.46	0.4 (0.6)	0.6 (0.7)	0.5 (0.6)	0.6 (0.7)

Data are mean (SD) or n (%). UPW = Units per week. mRS = modified Rankin scale. TICS-M = Telephone Interview for Cognitive Status-Modified. NIHSS = National Institute of Health Stroke Scale. BP = Blood pressure. BPM = beats per minute. The lipid treatment group were not matched for a history of memory problems, atrial fibrillation, and smoking at baseline (p=0.039, p=0.044, p=0.043).

Table 5.2: Primary and secondary cognition by treatment group: intensive (I) vs guideline (G) blood pressure lowering. Comparison of the mean area-under-the-curve (AUC) of the outcome across all time points using an independent sample t-test. Comparison of the extended assessment by multiple linear regression of mean score with adjustment for baseline value, systolic blood pressure, total cholesterol, and treatment assignment.

	0m	**6m**	**12m**	**18m**	**24m**	**36m**	**All Timepoints**	**Last assessment on-treatment**	**Extended Assessment**	**Last vs extended assessment P**
Tablets										
No. participants	59	58	55	49	52	37	59	59	42	
Group I	1.8 (1.0)	1.9 (1.1)	1.9 (1.3)	1.7 (1.4)	1.4 (1.5)	1.5 (1.5)	1.7 (0.9)	0.9 (1.4)	2.1 (1.2)	0.006
G	1.6 (1.0)	1.6 (1.1)	1.5 (1.1)	1.6 (1.0)	1.3 (1.3)	1.4 (1.1)	1.5 (0.9)	0.9 (1.2)	1.8 (1.3)	0.004
MD (95% CI)	0.2 (-0.3, 0.7)	0.3 (-0.2, 0.8)	0.4 (-0.2, 1.1)	0.1 (-0.6, 0.8)	0.1 (-0.6, 0.9)	0.1 (-0.8, 0.9)	0.2 (-0.3, 0.6)	0.0 (-0.7, 0.6)	0.3 (-0.5, 2.2)	
P							0.97		0.76	
Dose-adjusted										
No. participants	59	58	55	49	52	37	59	59	42	
Group I	1.8 (1.3)	2.3 (1.8)	2.3 (2.1)	2.2 (2.2)	1.7 (2.1)	1.2 (1.4)	1.8 (1.5)	1.0 (1.9)	1.4 (1.0)	0.89
G	1.8 (1.3)	1.8 (1.3)	1.6 (1.3)	1.8 (1.4)	1.3 (1.7)	0.8 (0.8)	1.6 (1.1)	0.9 (1.1)	0.8 (0.5)	0.87
MD (95% CI)	0.0 (-0.7, 0.6)	0.5 (-0.3, 1.3)	0.7 (-0.3, 1.6)	0.4 (-0.7, 1.4)	0.4 (-0.6, 1.5)	0.4 (-0.4, 1.2)	0.2 (-0.4, 0.9)	0.1 (-0.6. 0.9)	0.6 (0.0, 1.0)	
P							0.90		0.014	
TICS-M										
No. participants	59	55	57	44	53	46	59	59	59	
Group I	23.5 (3.9)	22.2 (4.9)	22.0 (8.6)	24.2 (6.4)	23.0 (8.6)	18.0 (13.2)	21.0 (6.4)	24.0 (6.8)	14.3 (12.8)	<0.001
G	23.9 (4.1)	24.3 (3.9)	23.5 (7.6)	23.6 (4.6)	23.9 (7.1)	21.1 (9.8)	23.0 (4.9)	25.2 (5.3)	17.9 (11.6)	<0.001
MD (95% CI)	-0.4	-2.1	-1.5	0.6	-0.9	-3.1	-2.0 (-5.0, 0.9)	-1.2 (-4.4, 1.9)	-3.6 (-10.0, 2.7)	

		(-2.4, 1.7)	(-4.5, 0.3)	(-5.9, 2.7)	(-2.8, 3.9)	(-5.3, 3.3)	(-9.9, 3.7)			
P								0.60		0.33
T-MMSE										
No. participants		59	55	57	44	54	46	59	59	59	
Group	I	20.2 (2.1)	19.4 (3.1)	18.5 (6.3)	20.6 (3.3)	17.4 (7.3)	14.2 (10.0)	17.7 (4.1)	18.8 (5.0)	11.8 (10.1)	<0.001
	G	20.6 (1.4)	20.6 (1.7)	19.3 (5.5)	20.3 (2.3)	19.8 (4.2)	17.4 (7.2)	19.3 (2.5)	20.6 (1.4)	15.1 (9.1)	0.001
MD (95% CI)		-0.4 (-1.3, 0.5)	-1.1 (-2.6, 0.2)	-0.7 (-3.9, 2.3)	0.3 (-1.4, 2.0)	-2.4 (-5.8, 1.0)	-3.2 (-8.5, 2.1)	-1.7 (-3.5, 0.1)	-1.8 (-3.6, 0.0)	-3.3 (-8.3, 1.6)	
P								0.40		0.18
Animal naming										
No. participants		59	55	57	44	54	46	59	59	59	
Group	I	14.3 (5.7)	15.4 (5.6)	13.2 (7.0)	17.4 (7.1)	15.7 (8.9)	12.2 (10.0)	13.6 (6.3)	15.7 (7.6)	9.2 (9.4)	<0.001
	G	17.7 (5.1)	17.0 (5.6)	16.9 (6.4)	17.0 (5.9)	16.2 (7.3)	15.2 (8.3)	16.5 (4.9)	17.2 (6.1)	12.9 (9.5)	0.011
MD (95% CI)		-3.4 (-6.2, 0.5)	-1.6 (-4.6, 1.4)	-3.6 (-7.2, 0.0)	0.4 (-3.6, 4.3)	-0.5 (-4.9, 3.9)	-3.0 (-8.4, 2.5)	-2.9 (-5.7, 0.0)	-1.5 (-5.0, 2.1)	-3.7 (-8.6, 1.2)	
P								0.09		0.61

Data are mean, standard deviation (SD) and mean difference (MD) with 95% confidence intervals (CI). TICS-M = Telephone Interview for Cognitive Status-Modified. T-MMSE = Telephone-Mini Mental State Examination.

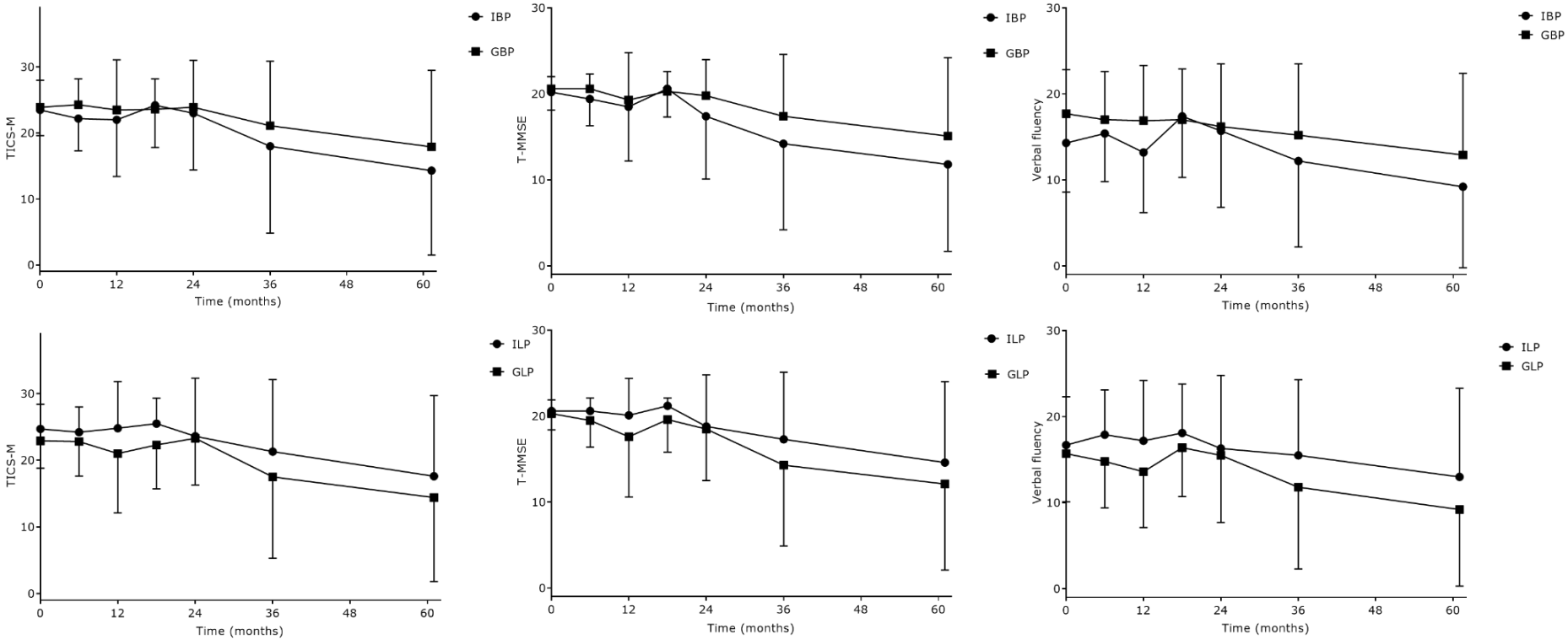
Table 5.3: Primary and secondary cognition by treatment group: intensive vs guideline lipid-lowering. Comparison of the mean area-under-the-curve (AUC) of the outcome across all time points using an independent sample t-test. Comparison by multiple linear regression of mean score with adjustment for baseline value, systolic blood pressure, total cholesterol, and treatment assignment.

	0m	6m	12m	18m	24m	36m	All Timepoints	Last assessment on-treatment	Extended Assessment	Last vs extended assessment P
Tablets										
No. participants	57	56	53	47	50	35	57	57	40	
Group I	1.5 (0.5)	1.4 (0.6)	1.4 (0.8)	1.3 (0.6)	0.9 (0.7)	1.0 (0.5)	1.3 (0.4)	0.8 (0.9)	1.0 (0.5)	0.62
G	0.9 (0.1)	0.9 (0.2)	0.9 (0.4)	0.9 (0.3)	0.6 (0.5)	0.7 (0.4)	0.8 (0.1)	0.3 (0.4)	1.0 (0.0)	<0.001
MD (95% CI)	0.6 (0.3, 0.7)	0.5 (0.1, 0.9)	0.5 (0.2, 0.9)	0.4 (0.1, 0.7)	0.3 (0.0, 0.6)	0.3 (0.0, 0.6)	0.5 (0.2, 0.6)	0.5 (0.1, 0.9)	0.0 (-0.1, 0.2)	
P							<0.001		0.39	
Dose-adjusted										
No. participants	57	56	53	47	50	35	57	57	40	
Group I	1.2 (0.5)	2.1 (1.3)	2.3 (1.6)	1.8 (1.4)	1.3 (1.3)	1.0 (0.7)	1.6 (0.8)	1.5 (1.6)	0.8 (0.5)	0.011
G	0.9 (0.3)	0.9 (0.4)	0.8 (0.6)	0.7 (0.4)	0.4 (0.5)	0.4 (0.3)	0.7 (0.2)	0.2 (0.3)	0.4 (0.2)	0.05
MD (95% CI)	0.3 (0.0, 0.5)	1.2 (0.7, 1.7)	1.5 (0.8, 2.2)	1.1 (0.4, 1.7)	0.9 (0.2, 1.4)	0.6 (0.2, 1.0)	0.9 (0.6, 1.3)	1.3 (0.6, 1.9)	0.4 (0.1, 0.7)	
P							<0.001		0.016	
TICS-M										
No. participants	57	53	55	42	51	44	57	57	57	
Group I	24.7 (3.7)	24.2 (3.8)	24.8 (7.0)	25.5 (3.8)	23.6 (8.7)	21.3 (10.8)	23.6 (4.8)	26.8 (4.5)	17.6 (12.1)	<0.001
G	22.9 (4.1)	22.8 (5.2)	21.0 (8.9)	22.3 (6.6)	23.3 (7.0)	17.5 (12.2)	20.6 (6.3)	22.6 (6.8)	14.4 (12.6)	<0.001
MD (95% CI)	1.8 (-0.2, 4.0)	1.4 (-1.0, 3.9)	3.8 (-0.5, 8.1)	3.2 (-0.1, 6.6)	0.3 (-4.1, 4.8)	3.8 (-3.2, 10.9)	3.0 (0.0, 6.0)	4.2 (1.0, 7.2)	3.2 (-3.4, 9.7)	
P							0.39		0.72	

T-MMSE										
No. participants		57	53	55	42	52	44	57	57	57	
Group	I	20.6 (1.3)	20.6 (1.5)	20.1 (4.3)	21.2 (0.9)	18.8 (6.0)	17.3 (7.8)	19.5 (2.4)	20.8 (1.2)	14.6 (9.4)	0.001
	G	20.3 (1.9)	19.5 (3.1)	17.6 (7.0)	19.6 (3.8)	18.5 (6.0)	14.3 (9.4)	17.6 (4.1)	18.6 (4.8)	12.1 (10.0)	<0.001
MD (95% CI)		0.3 (-0.6, 1.1)	1.1 (-0.2, 2.4)	2.5 (-0.6, 5.7)	1.6 (-0.1, 3.3)	0.3 (-3.0, 3.7)	3.0 (-2.3, 8.3)	1.9 (0.0, 3.6)	2.2 (0.3, 4.0)	2.5 (-2.6, 7.7)	
P								0.58		0.40	
Animal naming											
No. participants		57	53	55	42	52	44	57	57	57	
Group	I	16.7 (5.6)	17.9 (5.2)	17.2 (7.0)	18.1 (5.7)	16.3 (8.5)	15.5 (8.8)	16.4 (5.5)	17.7 (6.2)	13.0 (10.3)	0.019
	G	15.7 (5.6)	14.8 (5.4)	13.6 (6.5)	16.4 (5.7)	15.5 (7.8)	11.8 (9.5)	14.0 (5.8)	15.1 (7.4)	9.2 (8.9)	<0.001
MD (95% CI)		1.0 (-1.9, 4.0)	3.1 (0.1, 6.1)	3.6 (0.0, 7.2)	1.7 (-2.4, 5.8)	0.8 (-3.7, 5.4)	3.7 (-1.9, 9.3)	2.4 (-0.5, 5.4)	2.6 (-1.0, 6.2)	3.8 (-1.3, 8.9)	
P								0.33		0.25	

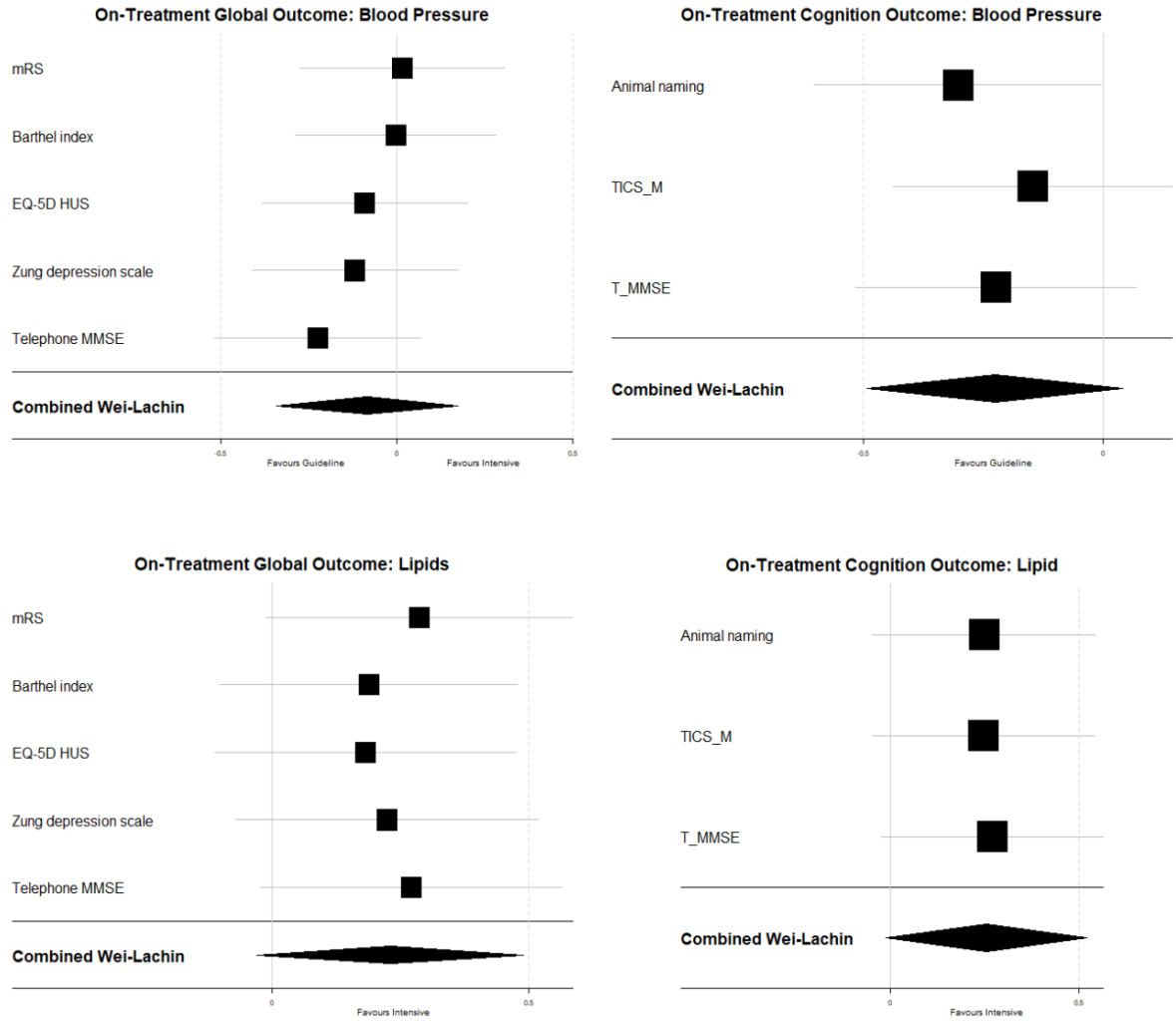
Data are mean, standard deviation (SD) and mean difference (MD) with 95% confidence intervals (CI). TICS-M = Telephone Interview for Cognitive Status-Modified. T-MMSE = Telephone-Mini Mental State Examination.

Figure 5.1: Cognition outcomes over time by treatment assignment



Data are mean and standard deviation. Left to right; changes in the Telephone Interview for Cognitive Status-Modified, Telephone-Mini Mental State Examination and verbal fluency assessments overtime for the intensive vs guideline blood pressure-lowering groups and the intensive vs guideline lipid-lowering groups, respectively.

Figure 5.2: Wei-Lachin for global and cognition outcome by treatment assignment



Analyses were performed using the multivariate directional Wilcoxon test. The effect sizes are the Mann-Whitney difference (and 95% CI) for each of the individual outcomes and for the combined outcome (using the Wei-Lachin procedure). mRS = modified Rankin Scale. EQ-5D = EuroQol Health Utility State. TICS-M = Telephone Interview for Cognitive Status-Modified. T-MMSE = Telephone-Mini Mental State Examination.

5.6 Supplemental Material

Supplementary Table XVIII: Functional outcomes by treatment group: intensive vs guideline blood pressure lowering. Comparison of the mean area-under-the-curve (AUC) of the outcome across all time points using an independent sample t-test. Comparison by multiple linear regression of mean score with adjustment for baseline value, systolic blood pressure, total cholesterol, and treatment assignment.

	0m	6m	12m	18m	24m	36m	All Timepoints	Last assessment on-treatment	Extended Assessment	Last vs extended assessment P
mRS										
No. Participants	59	55	59	44	54	46	59	59	59	
Group I	1.2 (0.8)	1.0 (0.8)	1.5 (1.6)	0.9 (0.6)	1.4 (1.5)	2.4 (2.4)	1.6 (1.1)	1.1 (1.1)	3.0 (2.4)	<0.001
G	1.0 (0.8)	1.2 (0.8)	1.5 (1.5)	1.1 (1.1)	1.5 (1.2)	2.0 (1.8)	1.5 (0.8)	1.1 (0.9)	2.7 (2.1)	<0.001
MD (95% CI)	0.2 (-0.1, 0.6)	-0.2 (-0.7, 0.1)	0.0 (-0.7, 0.8)	-0.2 (-0.8, 0.3)	-0.1 (-0.8, 0.6)	0.4 (-0.8, 1.6)	0.1 (-0.4, 0.6)	0.0 (-0.5, 0.5)	0.3 (-0.9, 1.4)	
P							0.32		0.90	
BI										
No. Participants	59	55	59	44	54	46	59	59	59	
Group I	98.7 (2.9)	96.6 (10.5)	87.2 (32.3)	99.5 (1.5)	85.8 (34.6)	70.0 (48.6)	86.9 (19.4)	92.4 (25.9)	60.5 (51.2)	0.001
G	97.7 (4.5)	95.3 (8.3)	91.0 (25.8)	95.8 (8.2)	92.0 (21.6)	84.8 (34.1)	91.3 (11.6)	98.5 (4.7)	71.0 (42.3)	0.002
MD (95% CI)	1.0 (-1.0, 3.1)	1.3 (-3.7, 6.4)	-3.8 (-19.0, 11.2)	3.7 (-0.1, 7.4)	-6.2 (-21.6, 9.3)	-14.8 (-39.4, 9.8)	-4.4 (-12.6, 3.7)	-6.1 (-15.5, 3.1)	-10.5 (-34.9, 13.8)	
P							0.73		0.34	
EQ-HUS										
No. Participants	59	54	59	43	53	46	59	59	59	
Group I	0.8 (0.1)	0.8 (0.1)	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)	0.6 (0.4)	0.7 (0.1)	0.8 (0.2)	0.5 (0.4)	0.001

G	0.8 (0.1)	0.8 (0.1)	0.8 (0.2)	0.8 (0.1)	0.8 (0.1)	0.7 (0.2)	0.7 (0.1)	0.8 (0.1)	0.6 (0.3)	0.001
MD (95% CI)	0.0 (-0.0, 0.0)	0.0 (-0.0, 0.0)	0.0 (-0.1, 0.1)	0.0 (-0.0, 1.0)	0.0 (-0.1, 0.1)	-0.1 (-0.3, 0.0)	0.0 (-0.1, 0.0)	0.0 (-0.1, 0.0)	-0.1 (-0.3, 0.1)	
P							0.50		0.40	
EQ-VAS										
No. Participants	59	54	59	43	54	46	59	59	59	
Group I	74.2 (15.4)	75.5 (18.6)	67.3 (29.4)	74.7 (23.1)	67.8 (30.1)	49.0 (36.0)	65.1 (20.3)	69.3 (25.3)	42.2 (36.1)	0.006
G	74.5 (16.7)	79.1 (14.2)	71.4 (24.8)	75.0 (14.0)	73.0 (18.6)	60.8 (28.7)	70.9 (14.5)	71.9 (17.1)	55.0 (33.4)	<0.001
MD (95% CI)	-0.3 (-8.7, 8.1)	-3.6 (-12.6, 5.3)	-4.1 (-18.2, 10.0)	-0.3 (-11.8, 11.1)	-5.2 (-18.6, 8.2)	-11.8 (-31.0, 7.4)	-5.8 (-14.8, 3.3)	-2.6 (-13.7, 8.4)	-12.8 (-31.0, 5.3)	
P							0.40		0.19	
ZDS										
No. Participants	59	54	57	44	54	46	59	59	59	
Group I	44.6 (12.1)	42.0 (11.7)	50.6 (19.5)	43.3 (9.7)	43.9 (23.3)	59.4 (30.3)	49.3 (13.7)	40.6 (14.5)	66.1 (29.9)	<0.001
G	45.1 (12.6)	45.3 (11.8)	46.7 (19.0)	40.8 (8.8)	43.3 (15.8)	49.6 (21.7)	47.0 (12.2)	41.8 (14.4)	58.8 (26.1)	0.001
MD (95% CI)	-0.5 (-7.0, 5.9)	-3.3 (-9.7, 3.2)	3.9 (-6.4, 14.1)	2.5 (-3.1, 8.2)	0.6 (-10.1, 11.3)	9.8 (-5.7, 25.3)	2.3 (-4.5, 9.1)	-1.2 (-8.8, 6.3)	7.3 (-7.3, 21.9)	
P							0.18		0.36	

Data are mean, standard deviation (SD) and mean difference (MD) with 95% confidence intervals (CI). mRS = modified Rankin Scale. BI = Barthel Index. EQ-5D = EuroQol Health Utility State. EQ-VAS = EuroQol Visual Analogue Scale. ZDS = Zung Depression Scale.

Supplementary Table XIX: Primary and secondary cognition by treatment group: intensive vs guideline lipid-lowering. Comparison of the mean area-under-the-curve (AUC) of the outcome across all time points using an independent sample t-test. Comparison by multiple linear regression of mean score with adjustment for baseline value, systolic blood pressure, total cholesterol, and treatment assignment

	0m	**6m**	**12m**	**18m**	**24m**	**36m**	**All Timepoints**	**Last assessment on-treatment**	**Extended Assessment**	**Last vs extended assessment P**
mRS										
No. Participants	57	53	57	42	52	44	57	57	57	
Group I	1.0 (0.7)	0.9 (0.7)	1.1 (1.1)	0.9 (0.7)	1.4 (1.5)	2.0 (1.9)	1.3 (0.7)	0.9 (0.7)	2.5 (2.2)	0.001
G	1.2 (0.9)	1.4 (0.9)	2.1 (1.7)	1.1 (1.1)	1.5 (1.2)	2.6 (2.2)	1.8 (1.1)	1.4 (1.2)	3.2 (2.2)	<0.001
MD (95% CI)	-0.2 (-0.6, 0.2)	-0.5 (-0.9, -0.0)	-1.0 (-1,7, -0.1)	-0.2 (-0.8, 0.3)	-0.1 (-0.8, 0.7)	-0.6 (-1.9, 0.6)	-0.6 (-1.0, 0.0)	-0.5 (-1.0, 0.0)	-0.7 (-1.9, 0.4)	
P							0.07		0.37	
BI										
No. Participants	57	53	57	42	52	44	57	57	57	
Group I	98.3 (2.7)	98.8 (4.8)	95.0 (19.9)	99.2 (2.3)	88.0 (29.2)	83.5 (37.2)	92.6 (10.5)	99.8 (0.9)	70.3 (44.9)	0.002
G	97.7 (4.9)	93.2 (11.6)	83.1 (35.4)	95.4 (8.6)	89.8 (28.3)	71.0 (46.3)	85.4 (19.2)	91.5 (25.1)	60.0 (48.9)	0.001
MD (95% CI)	0.6 (-1.4, 2.7)	5.6 (0.7, 10.5)	11.9 (-3.4, 27.2)	3.8 (-0.1, 7.7)	-1.8 (-17.8, 14.2)	12.5 (-13.2, 38.2)	7.2 (-1.1, 15.4)	8.3 (-1.2, 17.8)	10.3 (-14.6, 35.3)	
P							0.67		0.51	
EQ-HUS										
No. Participants	57	52	57	41	51	44	57	57	57	
Group I	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.2)	0.7 (0.3)	0.8 (0.1)	0.8 (0.1)	0.6 (0.3)	0.002
G	0.8 (0.1)	0.8 (0.1)	0.7 (0.2)	0.8 (0.1)	0.8 (0.2)	0.6 (0.3)	0.7 (0.1)	0.8 (0.1)	0.5 (0.4)	<0.001

MD (95% CI)	0.0 (-0.0, 0.0)	0.0 (-0.0, 0.1)	0.1 (-0.0, 0.2)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.1 (-0.1, 0.2)	0.1 (-0.0,0.1)	0.0 (0.0, 0.1)	0.1 (-0.1, 0.2)	
P							0.82		0.58	
EQ-VAS										
No. Participants	57	52	57	41	52	44	57	57	57	
Group I	75.1 (14.2)	80.1 (15.4)	75.3 (20.7)	77.7 (10.9)	72.4 (23.7)	59.6 (28.9)	72.4 (13.5)	76.3 (13.3)	53.8 (34.8)	0.003
G	73.0 (18.1)	74.3 (17.2)	62.4 (30.9)	70.5 (23.7)	67.7 (25.8)	48.8 (35.2)	63.1 (19.7)	64.2 (25.5)	42.5 (35.0)	0.001
MD (95% CI)	2.1 (-6.5, 10.8)	5.8 (-3.3, 14.8)	12.9 (-1.1, 26.9)	7.2 (-4.3, 18.8)	4.7 (-9.0, 18.5)	10.8 (-8.9, 30.5)	9.3 (0.2, 18.3)	12.1 (1.2, 23.0)	11.3 (-7.2, 29.8)	
P							0.46		0.31	
ZDS										
No. Participants	57	52	55	42	52	44	57	57	57	
Group I	45.7 (12.1)	43.3 (12.5)	42.3 (14.7)	41.9 (8.2)	44.6 (19.4)	49.1 (23.6)	45.9 (11.8)	39.1 (12.2)	57.8 (27.6)	<0.001
G	44.2 (12.8)	44.4 (11.2)	54.4 (21.7)	41.9 (10.7)	42.9 (20.5)	60.0 (28.2)	50.6 (13.9)	43.7 (16.1)	67.4 (28.4)	<0.001
MD (95% CI)	1.5 (-5.1, 8.1)	-1.1 (-7.7, 5.6)	-12.1 (-22.2, -2.0)	0.0 (-5.9, 5.9)	1.7 (-9.3, 12.8)	-10.8 (-26.7, 5.0)	-4.7 (-11.6, 2.1)	-4.5 (-12.2, 3.0)	-9.6 (-24.4, 5.3)	
P							0.12		0.23	

Data are mean, standard deviation (SD) and mean difference (MD) with 95% confidence intervals (CI). mRS = modified Rankin Scale. BI = Barthel Index. EQ-5D = EuroQol Health Utility State. EQ-VAS = EuroQol Visual Analogue Scale. ZDS = Zung Depression Scale.

6 Cognition, Quality of Life, Fatigue and MRI Correlation During a Therapeutic Controlled Hookworm Infection for the Treatment of Relapsing MS

6.1 Abstract

6.1.1 Background

Cognitive impairment in multiple sclerosis (MS) is common, however, there are no therapeutic interventions for the prevention of cognitive decline in MS. It has been suggested a parasitic infection may protect against multiple sclerosis (MS), prevent relapses, and reduce inflammatory activity.

6.1.2 Objective

In this substudy of the MS WIRMS study, we investigated whether hookworm (HW) treatment influences cognition, quality of life (QOL) and fatigue in MS. The secondary outcome was to determine factors associated with cognitive function.

6.1.3 Methods

The WIRMS trial investigated the safety and efficacy of live hookworm infection in patients with MS for 9 months. Cognition was measured using the Paced Auditory Serial Addition Test (PASAT) performed at baseline, 9 and 12 months. Treatment effects were assessed using an independent-samples t-test and an adjusted multiple linear regression.

6.1.4 Results

Cognition, quality of life and fatigue scores did not differ between HW vs placebo groups. A poorer physical and mental QOL at 9 months and a greater number of T2 lesions at 3 and 9 months were associated with worse cognitive function at 9 months. Worse cognitive function at 12 months was associated with a poorer

physical QOL at 9 months and a greater number of T2 lesions at 3, 9 and 12 months.

6.1.5 Discussion

Live hookworm infection showed no effects on cognitive function, QOL or fatigue. A greater lesion burden and a worse physical and mental quality of life were associated with poorer cognition independent of the participant's baseline cognition.

6.2 Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) and is the most common cause of acquired, non-traumatic disability in young adults [357]. It is clinically characterised by neurological deficits with relapsing-remitting and progressive patterns, whereas pathologically it is characterised by inflammation, demyelination, and neuronal damage and loss. This inflammatory response is associated with an imbalance between proinflammatory cytokines and anti-inflammatory cytokines/regulatory T cells (Tregs) [358].

MS has a broad range of symptoms, due to the widespread nature of the lesions, which include, motor, cognitive and neuropsychiatric symptoms. Also, cognitive deficits can appear independent of motor deficits. This results in symptom profiles and disease progression varies from patient to patient [51].

Cognitive impairment can occur early on in MS, however, it is more frequent and severe in progressive MS [359]. Cognitive impairment affects 40-65% of MS patients and characteristically includes deficits of long-term memory, attention and concentration, executive functioning, the efficiency of information processing, and processing speed [51, 359]. Cognitive impairment can exacerbate a patient's disability level and impacts their quality of life (QoL); therefore, it is important to consider the effect of cognitive impairment on the patient QoL [51, 359].

The demographic, clinical and radiological factors related to cognitive impairment in MS patients have not been fully elucidated yet. The relationship between cognitive impairment and clinical factors such as physical disability, sex, and disease duration are not well established and are inconsistent in the literature

[360-362]. Fatigue is a common symptom in MS; however, subjective reports of cognitive fatigue have shown no association with cognitive impairment [363-365]. On the other hand, fatigability [366] measured objectively, for example, worse performance over time in tasks of sustained mental effect, working memory and visual vigilance suggest fatigue may impact cognitive function [364, 365]. Depression is common in MS, however, the relationship between depression and cognitive function is unclear [367, 368]. Early studies showed no association [367], however, other studies have shown an association between neuropsychological function and depression in MS patients [369, 370]. Furthermore, a literature review [368] found depression was related to cognitive function as long as the studies were adequately powered and used a representative sample of MS patients. Neuroimaging features such as a greater lesion burden and cerebral atrophy have been associated with cognitive impairment in MS [51].

Currently, the efficacy of cognitive rehabilitation as an intervention in MS is low, inconclusive, or preliminary. Pharmacological intervention with either disease-modifying therapies (DMT) or an intervention specifically for improving cognition has shown no clear benefits so far [371, 372]. Therefore, further investigation into cognitive impairment in MS is required to develop prevention, management, and treatment strategies.

To this end, the hygiene hypothesis [373], suggests an infectious agent may protect against autoimmune or inflammatory disease, therefore, a parasitic infection, in theory, may protect against MS via the development and activity of regulatory T cells (Treg). Necator americanus, which is a hookworm parasite, currently had no published trials in MS until recently, when the core Worms for Immune Regulation of Multiple Sclerosis (WIRMS) study was published [374].

The University of Nottingham pioneered a dose-ranging programme in healthy volunteers, which indicated N. americanus is safe and stimulates biological effects [375, 376]. Before the WIRMS study publication, there were no available placebo-controlled published trials of helminth therapy in MS. The WIRMS trial [377] was a phase II, randomised, double-blind, placebo-controlled trial of N. americanus infection (hookworm, HW) in MS. We performed a substudy aimed to determine whether hookworm treatment benefits cognitive function and to determine any factors associated with cognitive function in this cohort.

6.3 Methods

6.3.1 Study design and participants

The WIRMS trial (NCT01470521) was a phase II, single centre, randomised, blinded, placebo-controlled trial. It investigated the safety and efficacy of live hookworm infection (L3 larvae of N. americanus) in patients with MS. HK were manufactured at Queen's Medical Centre, University of Nottingham, UK, per Current Good Manufacturing Practice. The National Research Ethics Service Committee East Midlands gave ethical approval (reference 11/EM/0140). The trial procedures have been published in the main paper [377]. In summary, participants were randomised to either HW infection or placebo (PBO) for a 36-week treatment period followed by a 12-week safety period. Participants were recruited from the MS clinic at the Queen's Medical Centre or by referral. Participants provided written informed consent. Eligible participants had to be aged 18-64, clinically stable, without immunomodulatory treatment, had relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) with superimposed relapses (per the McDonald criteria) [84]. In the last 12 months and 24 months at least 1 or 2 relapses must have been recorded, respectively. At screening and randomisation patients must have a score ranging from 0 to 5.5 on the expanded disability status scale (EDSS) [257]. Patients must have an MRI consistent with MS [378]. Participants were excluded if they had been treated with corticosteroids (within 4 weeks), beta-interferon/glatiramer acetate/immunosuppressive drugs or any investigational agents (within 8 or 12 weeks) before baseline or had bone marrow transplantation or monoclonal antibodies at any time.

6.3.2 Outcomes

The primary objective of this substudy was to determine whether hookworm (HW) treatment influences cognition, quality of life and fatigue in MS. The secondary objective was to determine the factors associated with cognitive function.

6.3.3 Clinical assessment and neuroimaging

At the screening, we collected the participant's demographics, medical and MS history. The participants level of disability (EDSS) [257], quality of life (Multiple Sclerosis Quality of Life-54 (MSQOL-54))[254] and fatigue (Fatigue Severity Scale (FSS))[379] were assessed at screening and month 9. Cognitive function, specifically auditory information processing speed, flexibility and calculation ability were assessed at screening and month 9 using the Paced Auditory Serial Addition Test (PASAT) [380, 381], a component of the Multiple Sclerosis Functional Composite (MSFC) [246, 382, 383]. The PASAT is scored as the number of correct answers given out of 60, which was then converted to a Z-score. Participants underwent an MRI scan at baseline, month 9 and month 12. T2 and gadolinium (Gd) lesion numbers were acquired using T2 and T1-weighted (including Gd) sequences for the whole cohort. Total lesion volume was calculated using the in house developed software [NeuROI] (https://www.nottingham.ac.uk/research/groups/clinicalneurology/neuroi.aspx).

6.3.4 Statistical analysis

Standard deviation (SD) and interquartile range [IQR] were used to report between and within-group comparisons. Between-group comparisons were determined using the Chi-square test, Mann-Whitney U test, and independent-samples t-test. Within-group differences were determined using a Paired-samples t-test. Treatment effects were assessed using an independent-samples

t-test and significant between-group differences underwent post-hoc analysis by multiple linear regression with adjustment for baseline cognition. Unadjusted and adjusted associations using Kendall's Tau-B or multiple linear regression with adjustment for baseline cognition were done to determine factors associated with cognition. All statistical analysis was performed using the Statistical Package for Social Sciences version-24 (SPSS-24, IBM, Armonk, NY) and significance was set at $p<0.05$.

6.4 Results

A total of 71 participants were enrolled between September 17, 2012, and March 26, 2015. 35 and 36 participants were randomly assigned to HW and PBO groups, respectively. Of these, 66 participants completed the 9-month treatment period, and 61 participants completed the 3-month safety follow-up. The 71 participants were 43.0 (9.7) years of age, with 51 (71.8%) being female and 58 (81.7%) had relapsing-remitting MS, and there was no baseline demographic, clinical or radiological differences between HW and placebo groups (Table 6.1).

A comparison of between-group differences (Table 6.2) showed the PASAT-3, in the HW group and the PBO group, differed significantly at 9 months, however, this was non-significant after adjusting for baseline PASAT-3 score. The MSQOL-physical and mental and the FSS, in the HW group and the PBO group, did not differ significantly at baseline or 9 months. A comparison of within-group differences (Table 6.2) showed the PASAT-3, MSQOL-54-physical and mental, and the FSS did not differ between baseline and 9 months in either the HW or PBO groups.

Table 6.3 shows the unadjusted associations of worse performance on the PASAT-3 at 9-months were female sex, HW treatment group, secondary progressive MS, a greater time since first MS symptoms, greater disability (EDSS at baseline, 3m and 9m), worse physical QOL (MSQOL-54-Physical at baseline and 9m), and worse mental QOL (MSQOL-54-Mental at 9m). The unadjusted associations of worse performance on the PASAT-3 at 12-months were female sex, greater disability (EDSS at baseline and 9m), poorer physical QOL (MSQOL-54-Physical at baseline and 9m), worse mental QOL (MSQOL-54-Mental at baseline and 9m) and a greater number of T2 lesions at 9m and 12m. After adjustment for baseline PASAT-3 score (Table 6.4), a worse physical and mental

QOL at 9m and a greater number of T2 lesions at 3m and 9m were associated with worse PASAT-3 performance at 9m. Worse performance on the PASAT-3 at 12m was associated with a worse physical QOL at 9m and a greater number of T2 lesions at 3m, 9m and 12m (Table 6.4).

6.5 Discussion

In this cohort, we showed that there were no effects of randomised live hookworm infection on cognitive function, quality of life, or fatigue. We also showed that the cognition and functional outcomes did not change significantly over the 9-month treatment period in all participants and either group. The PASAT-3 score at 9 months, once adjusted for baseline PASAT-3 score, showed a negative association with the number of T2 lesions at 3 months and 9 months, whereas it showed a positive association with the physical and mental components of the MSQOL-54 at 9 months. The number of T2 lesions at 3, 9 and 12 months and physical QOL at 9 months was also associated with the PASAT-3 score at 12 months. These associations were weak; however, previous studies have also shown that a greater lesion burden and worse QOL were associated with cognitive dysfunction. [51, 384].

It has been suggested that an infectious agent, such as a parasite, may protect against autoimmune effects of MS via the upregulation of T-reg cells [385]. The Treg cells in MS are often deficient in either number or function and an elevated inflammatory response may reflect a dysfunction in immunoregulation [386, 387]. Therefore, the upregulation of Treg cells via a parasitic infection to enhance immunoregulation may benefit MS patients. Natural parasitic infections for example, with the nematode Trichuris, has shown an inverse relationship with MS in epidemiological data, however, it often coexists with other parasitic infections [388, 389]. Furthermore, MS patients that were naturally infected with gastrointestinal parasites showed a milder disease course in comparison with matched uninfected MS controls in an observational study over 5 years [390]. Moreover, a therapeutic parasitic infection in a study investigating the safety and

efficacy of Trichuris suis ova in MS patients found potentially favourable MRI outcomes and immunoregulatory changes [391].

This was the largest MS study of therapeutic hookworm infection to date and the main trial demonstrated that therapeutic HW infection in MS patients was feasible and safe [377], however, there was no difference between the cumulative number of active MRI lesions in the treatment groups (primary outcome). Furthermore, it was suggested that the low level of disease activity in this cohort was responsible for the lack of noticeable differences between treatment groups, however, MRI inactivity was significantly higher in the HW group [377]. Cognitive decline in MS is often associated with new lesions [392], therefore, the low level of disease activity may also in part by preventing us from seeing any cognitive differences between the treatment groups and within the groups over time.

This study has some limitations. The sample size was small due to the logistical limitations of the intervention, which meant that the WIRMS trial was a single-centre study. Therefore, identifying significant clinical effects was difficult due to the small sample size. Further to this point, the results of this study may display both types I and type II errors, consequently. Cognition was not the primary outcome of the WIRMS trial and the cognition assessments that were used were not an extensive neuropsychological examination which would have been beyond the scope of the WIRMS trial. The PASAT-3 test is part of a composite score used in MS assessment and clinical trials, the MSFC, and as such is a good screening tool but an incomplete one for cognitive assessment. The PASAT assesses attention, information processing speed and calculation, therefore several domains of cognition were not assessed in this trial. The PASAT has been criticised as a screening tool as it is unpopular with patients as it depends on a

certain level of mathematical ability and often leads to stress and agitation, therefore the PASAT is vulnerable to the practice effect and patient drop out, respectively [393-395]. The Symbol Digit Modalities Test (SDMT) [396], which in comparison to the PASAT is more valid and reliable [397], has recently been recommended as an early cognition screen in MS [190]. As the participants experienced little disease progression over the intervention period, the WIRMS trial required a longer intervention period to allow for enough time to pass to show potential clinical benefits, especially regarding cognition, which often deteriorates slowly in MS cohorts [359].

In conclusion, live hookworm infection showed no effects on cognitive function, quality of life or fatigue over 6 months. A greater lesion burden and a worse physical and mental quality of life were associated with poorer cognition independent of the participant's baseline cognition. In the future, this type of intervention trial is feasible, given an appropriate design, infrastructure, more funding and or a cost-effective version of the intervention.

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Table 6.1: Baseline demographic, clinical and radiological characteristics of all randomised patients.

Patient characteristics	All	Hookworm	Placebo	P
Number of patients	71	35	36	
Demographic characteristics				
Age (years, SD)	43.5 (9.7)	43.7 (8.7)	43.3 (10.7)	0.88
Sex (no. of subjects, %)				0.94
Female	51 (71.8)	25 (71.4) 10	26 (72.2) 10	
Male	20 (28.2)	(28.6)	(27.8)	
Clinical characteristics				
Type of relapsing MS (no. of subjects, %)				
RRMS	58 (81.7)	31 (88.6)	27 (75.0)	0.13
SPMS with superimposed relapses	13 (18.3)	4 (11.4)	9 (25.0)	
Time from first symptoms of MS (years, SD)	11.4 (8.7)	11.7 (8.3)	11.1 (9.2)	0.79
Time from MS diagnosis (years, SD)	6.2 (5.7)	6 (5.9)	6.5 (5.7)	0.70
Time from last relapse (days)	160.5 (99.3)	149.9 (78.1)	169.6 (115.6)	0.54
Number of relapses				
Previous year	1.4 (1.0)	1.6 (0.8)	1.3 (0.5)	0.25
Previous 2 years	2.2 (0.9)	2.3 (1.0)	2.1 (0.8)	0.79
Previous 3 years	2.7 (1.4)	2.8 (1.5)	2.5 (1.3)	0.96
EDSS score	3.1 (1.3)	3.1 (1.3)	3.3 (1.4)	0.56
PASAT-3	44.3 (11.4)	43.0 (10.6)	45.7 (12.1)	0.33
PASAT-3 Z score	0.00	-0.11	0.11	
MSQOL-54 Physical	60.3 (20.5)	60.6 (20.5)	60.0 (20.8)	0.90
MSQOL-54 Mental	65.5 (22.8)	66.2 (20.5)	64.8 (25.0)	0.79
FSS	36.1 (18.2)	34.0 (19.3)	38.2 (17.1)	0.36
Previous DMT				
Glatiramer	4	2	2	0.96
IFN-b	15	7	8	0.38
Other	2	1	1	0.97
MRI characteristics				
Gd lesions	1.0 (2.0)	1.1 (2.5)	0.8 (1.5)	0.52
T2 lesions	16.6 (8.3)	16.3 (8.7)	17.0 (8.0)	0.74
Lesion volume (ml)	13.8 (15.6)	12.9 (14.3)	14.8 (16.9)	0.63

Data are either n (%), mean (SD) or median [IQR]. MS = multiple sclerosis. RRMS= relapsing-remitting multiple sclerosis; SPMS= secondary-progressive multiple sclerosis; EDSS=expanded disability status scale; PASAT = Paced Auditory Serial Addition Test; MSQOL= multiple sclerosis quality of life-54; FSS= fatigue severity scale. IFN = interferon; MRI = magnetic resonance imaging; Gd= gadolinium.

Table 6.2: Cognition and functional outcomes by treatment group: hookworm (HW) vs placebo (PBO).

	Group	Baseline	9 months	P
N		70	66	
PASAT-3 Z score	HW	-0.03 [-0.47,0.40]	0.05 [-1.08,0.57]	0.98
	PBO	0.40 [-0.20,0.75]	0.57 [-0.29,1.10]	0.14
	P	0.12	0.034*	
N		70	63	
MSQOL-54 Physical	All	60.00 [43.00,77.50]	64.00 [42.00,83.00]	0.96
	HW	55.50 [43.00,83.25]	69.00 [40.25,83.75]	0.75
	PBO	63.50 [43.50,75.75]	63.00 [43.00,82.50]	0.70
	P	0.98	0.87	
N		70	63	
MSQOL-54 Mental	All	71.00 [47.50,86.00]	76.00 [49.00,88.00]	0.58
	HW	70.50 [47.50,84.50]	74.50 [52.25,85.00]	0.75
	PBO	73.00 [46.75,86.75]	77.00 [45.50,88.00]	0.65
	P	0.93	0.98	
N		61	59	
FSS	All	41.00 [23.00,52.00]	39.00 [20.00,47.00]	0.39
	HW	36.00 [19.00,53.00]	37.00 [15.00,42.75]	0.57
	PBO	44.00 [25.75,52.00]	40.00 [20.00,49.00]	0.58
	P	0.38	0.45	

Data are either n or median [IQR]. Comparison of between and within-group differences by Independent-samples t-test and Paired-samples t-test, respectively. *Non-significant (p=0.13) on post-hoc analysis by multiple linear regression with adjustment for baseline PASAT-3 Z score. PASAT = Paced Auditory Serial Addition Test; MSQOL= multiple sclerosis quality of life-54; FSS= fatigue severity scale.

Table 6.3: Univariate associations of PASAT-3 performance at 9 and 12 months.

	PASAT-3 at 9 months		**PASAT-3 at 12 months**	
	r_s	**P**	**r_s**	**P**
Visit 1 (Baseline)				
Age, years	-0.038	0.65	0.023	0.79
Sex, female	-0.205	0.048	-0.275	0.011
Treatment group, hookworm	-0.219	0.034	-0.114	0.29
Type of MS, SP	-0.209	0.044	-0.061	0.57
Time since first symptoms, years	-0.182	0.037	-0.090	0.32
Time since diagnosis, years	0.017	0.84	0.005	0.95
Time since last relapse, days	-0.096	0.42	-0.130	0.29
EDSS	-0.241	0.008	-0.215	0.023
FSS	-0.155	0.09	-0.098	0.31
MSQOL-54 Physical	0.210	0.015	0.229	0.012
MSQOL-54 Mental	0.150	0.08	0.256	0.005
Visit 7 (3 months)				
EDSS	-0.185	0.040	-0.153	0.10
Total T2 lesion, number	-0.149	0.08	-0.177	0.05
Total Gd lesion, number	-0.140	0.15	-0.174	0.09
Lesion volume (ml)	-0.057	0.52	-0.148	0.11
Visit 13 (9 months)				
EDSS	-0.232	0.009	-0.194	0.039
FSS	-0.112	0.22	-0.174	0.06
MSQOL-54 Physical	0.292	0.001	0.207	0.025
MSQOL-54 Mental	0.272	0.002	0.196	0.034
Total T2 lesion, number	-0.164	0.05	-0.190	0.037
Total Gd lesion, number	0.025	0.79	-0.008	0.93
Lesion volume (ml)	-0.055	0.53	-0.148	0.11
Visit 15 (12 months)				
Total T2 lesion, number	-	-	-0.199	0.039
Total Gd lesion, number	-	-	-0.057	0.60

Kendall's TAU-B (Binary and continuous variables).MS = multiple sclerosis. SP = Secondary progressive. EDSS=expanded disability status scale; PASAT = Paced Auditory Serial Addition Test; MSQOL= multiple sclerosis quality of life-54; FSS= fatigue severity scale. Gd= gadolinium.

Table 6.4: Associations with PASAT-3 Z score at 9 or 12 months with adjustment for baseline PASAT-3 Z score.

	PASAT-3 at 9 months		**PASAT-3 at 12 months**	
	Beta	**P**	**r_s**	**P**
Visit 1 (Baseline)				
Age, years	-0.028	0.71	-0.003	0.97
Sex, female	-0.083	0.28	-0.101	0.23
Treatment group, hookworm	-0.116	0.13	-0.028	0.73
Type of MS, SP	-0.101	0.19	-0.047	0.57
Time since first symptoms, years	-0.091	0.24	0.031	0.71
Time since diagnosis, years	-0.020	0.79	-0.016	0.85
Time since last relapse, days	-0.028	0.67	-0.089	0.26
EDSS score	-0.126	0.11	-0.066	0.43
FSS	-0.123	0.12	-0.087	0.32
MSQOL-54 Physical	0.129	0.10	0.151	0.07
MSQOL-54 Mental	0.028	0.72	0.146	0.09
Visit 7 (3 months)				
EDSS	-0.058	0.47	-0.022	0.80
Total T2 lesion, number	-0.204	0.007	-0.242	0.003
Total Gd lesion, number	-0.144	0.06	-0.101	0.23
Lesion volume (ml)	-0.049	0.55	-0.122	0.16
Visit 13 (9 months)				
EDSS	-0.124	0.11	-0.061	0.47
FSS	0.059	0.46	-0.056	0.51
MSQOL-54 Physical	0.250	0.001	0.202	0.016
MSQOL-54 Mental	0.221	0.006	0.149	0.08
Total T2 lesion, number	-0.210	0.005	-0.258	0.001
Total Gd lesion, number	-0.050	0.52	-0.059	0.47
Lesion volume (ml)	-0.043	0.59	-0.117	0.18
Visit 15 (12 months)				
Total T2 lesion, number	-	-	-0.278	0.001
Total Gd lesion, number	-	-	-0.095	0.27

Multiple regression with adjustment for baseline PASAT-3 Z score as a covariate. MS = multiple sclerosis. SP = Secondary progressive. EDSS=expanded disability status scale; PASAT = Paced Auditory Serial Addition Test; MSQOL= multiple sclerosis quality of life-54; FSS= fatigue severity scale. Gd= gadolinium.

7 General Discussion

7.1 General rational and background

Dementia and cognitive impairments are major global health and socioeconomic burdens. They impact not just those living with the disease but also their families and society. Due to the world's ever-growing and ageing population, the global prevalence of dementia and cognitive impairment will inevitably rise. Therefore, we must determine which risk factors or interventions can help to delay the onset or even reduce the number of people who suffer from the disease.

Stroke is a leading cause of acquired cognitive impairment and dementia, second only to Alzheimer's disease (AD) [398]. Meanwhile, multiple sclerosis (MS) although less common than stroke, also causes cognitive impairment and in rare cases overt dementia. Despite the differences in the pathophysiology of these two diseases, cognitive deficits are common in both, however, the cognitive domains that are affected can differ. The pattern of cognitive domains affected varies depending on factors such as disease severity, type, and lesion volume/number and location. Specific domains are also more likely to be affected depending on the disease group. For example, executive function is commonly affected after stroke, whereas, slowed information processing speed is a hallmark cognitive deficit in MS. On the other hand, the risk factors for cognitive impairment in these two disease groups share some similarities regarding neuroimaging factors but can differ in terms of clinical and demographic features. The risk factors for cognitive impairment in both diseases are still not fully understood and require further research to better understand the specific and non-specific factors. Furthermore, there is currently no

recommended intervention for preventing cognitive decline and there is limited evidence for any specific therapeutic intervention.

There are demographic, clinical, and radiological differences between ischaemic stroke (IS) and intracerebral haemorrhage (ICH) survivors. Therefore, the prevalence of cognition after stroke as well as which factors are associated with cognitive decline must be determined specifically for IS and ICH. To this end, the prevalence, and the clinical and radiological predictors of post-stroke cognitive impairment (PSCI), following an ischaemic stroke (IS) or transient ischaemic attack (TIA) were investigated using data from the ENOS and TARDIS trials (Chapter 3). This is one of the largest international hospital-based studies of PSCI to date, which involved 4798 participants from the ENOS or TARDIS trials. Cognition assessment at 3 months after stroke found the prevalence of PSCI was 34.2%. Furthermore, the independent predictors of PSCI at 3 months were older age, greater stroke severity (National Institute of Health Stroke Scale (NIHSS)), pre-stroke disability (modified Rankin Scale (mRS)), non-UK participants, history of atrial fibrillation, lower systolic blood pressure, higher heart rate and after excluding participants that died before 3 months, a higher small vessel disease score (severe leukoaraiosis, severe atrophy, old lacunar infarct).

Age and stroke severity are both well-known predictors of cognitive impairment after stroke [92, 263]. Despite the exclusion of patients with pre-stroke dependence, pre-stroke disability recorded on the mRS was associated with cognitive impairment after stroke. This suggests there may have been underlying neurodegenerative pathology before their stroke. Further to this small vessel disease features such as severe leukoaraiosis, severe atrophy and old lacunar infarcts were also associated with a cognitive impairment which supports the theory that a combination of neurodegenerative and vascular

pathologies exacerbate the cognitive decline. Although non-UK participants appeared to have a higher risk of PSCI this is most likely due to technical or cultural differences with the cognitive assessments. The association between AF and PSCI was related to stroke severity and patient mortality.

Blood pressure is often considered to be an ideal target for stroke interventions but has a complex relationship with cognition, with previous studies suggesting a U or J-shaped relationship [302-304]. Here, blood pressure associations were also complex. A higher baseline SBP was associated with cognitive impairment however, once adjusted for stroke severity, SBP was also associated with cognitive impairment. Therefore, while SBP may influence stroke severity and brain frailty, a lower baseline SBP may be related to a reduction in cerebral perfusion and brain tissue metabolism. The mechanism by which, a higher heart rate, is associated with cognitive decline is unclear especially in this study, however, previous studies have suggested it may be related to vagal dysfunction [309].

Moving on from IS, we investigated cognition in a large cohort of ICH survivors using data from the Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2) trial (Chapter 4). We investigated the clinical and radiological predictors of PSCI as well as the prevalence of cognitive deficits using telephone-based cognitive assessments. This is one of the largest cohorts of ICH survivors that focused on mild and severe cognitive impairment and involved 693 participants from the TICH-2 trial. At 3 months post-ICH, mild and severe cognitive impairment were prevalent in 29.9% and 26.3% of participants, respectively. At 1-year post-ICH, mild and severe cognitive impairment was prevalent in 28.2% and 26.0% of participants, respectively. The independent associations of early severe cognitive impairment (SCI) were older age, non-

Caucasian ethnicity, left hemisphere stroke, greater stroke severity (NIHSS), lobar ICH, and intraventricular haemorrhage (IVH). In addition to the above factors, early PSCI (any cognitive impairment, which includes both mild and severe cognitive impairment) was also associated with a greater baseline ICH volume and a greater degree of leukoaraiosis but was not associated with lobar ICH, IVH and baseline stroke severity. The independent associations of long-term SCI were older age, non-Caucasian ethnicity, a greater level of deprivation (Index of Multiple Deprivations (IMD)), reduced level of consciousness (Glasgow coma scale (GCS)) and lobar ICH.

Long-term PSCI was associated with all the above factors apart from lobar ICH. As with the IS participants in Chapter 3, older age, and hematoma size (stroke severity) are well-defined predictors of cognitive decline [320-324]. We also showed a participant's baseline level of consciousness (GCS) after an ICH, which often reflects stroke severity, was associated with long-term SCI. Our results suggested that ICH survivors that suffered from a lobar ICH, independent of stroke severity, are more likely to have greater severity of early and long-term cognitive impairment. This is most likely because cortical functions are often affected in lobar ICH [323]. The long-term severe cognitive decline of lobar ICH participants may be related to underlying cerebral amyloid angiopathy (CAA) and its associations with global cognitive decline and Alzheimer's disease (AD) [330]. This supports the hypothesis that an ongoing process of cognitive decline due to vascular and/or neurodegenerative pathologies is then exacerbated by a stroke and in this case an ICH. Unfortunately, AD biomarkers such as Apolipoprotein E were not captured in any of the studies (ENOS, TARDIS or TICH-2, Chapter 3 or 4). As discussed in Chapter 4, the association between cognition and ethnicity is unclear in the literature [92]. However, studies in mixed stroke cohorts as well

as IS and ICH specific cohorts have shown black, Hispanic and Southeast Asian ethnic groups to have worse cognition in comparison to white people [92, 324, 399]. The specific ethnicity of the IS participants in ENOS or TARDIS (Chapter 3) was not captured. However, it was shown that non-UK participants were more likely to suffer from PSCI compared to UK participants. In TICH-2 (Chapter 4), non-Caucasian ethnicity was also strongly associated with both early and long term PSCI and its severity. Potential race-related factors that could affect cognition, include genetic, cultural, language and socioeconomic. Both studies had a small number of non-UK or non-Caucasian participants and it is difficult to determine which of these factors, if not a combination of them, may be influencing cognition in these cohorts. However, the level of deprivation of the area the participant lived in was used as a surrogate marker of socioeconomic status in UK participants for this population (Chapter 4). It was shown that a greater level of deprivation was associated with long-term cognitive impairment. Furthermore, non-Caucasian patients were more likely to be from an area of greater deprivation and as such may reflect the participants access to healthcare and educational level.

As stated earlier, there is limited evidence for specific therapeutic strategies for preventing cognitive decline, however, hypertension and hyperlipidaemia are potential therapeutic targets in stroke survivors. The Prevention of Decline in Cognition after Stroke Trial (PODCAST, Chapter 5) was a pilot multicentre prospective randomised open-label endpoint (PROBE) trial that investigated the effectiveness of intensive vs guideline blood pressure and lipid-lowering on cognitive outcomes in patients with a recent stroke. The cognition scores did not differ for either treatment group across all time points including the additional follow-up when adjusting for randomisation variables (baseline cognition score,

total cholesterol, blood pressure). However, the intensive lipid group in comparison to the guideline group had consistently higher cognition scores despite non-significance. The Wei-Lachin test also suggested that the intensive lipid-lowering group had a better global outcome and a better numerical global cognition outcome, however, this did not reach statistical significance. There was no difference in the global outcome and global cognition outcome of the BP treatment groups. The functional outcomes did not differ for either treatment group at any time point. There were no residual effects of the randomised antihypertensive treatment on long-term cognitive or functional outcomes as assessed individually during the additional follow up of participants from the PODCAST trial. The cognition outcomes of the participants that underwent intensive lipid-lowering were consistently numerically better in comparison to the guideline group albeit non-significantly. However, the Wei-Lachin analysis supported this and showed that the global outcome and global cognition outcomes also favoured the intensive lipid-lowering group despite non-significance. Statins have several potential pathophysiological modes of action, for example, reduced inflammation, impeded platelet activation, enhanced endothelial function, and decreased coagulability, in addition to lowering total, LDL and non-high-density lipoprotein cholesterol. Our results suggest that if cognition were to benefit from lipid-lowering then statin intensity, through type and dose, which were the main differences between the treatment groups, facilitates this effect [354, 355].

Lastly, the Worms for Immune Regulation of Multiple Sclerosis (WIRMS) trial (Chapter 6) investigated the effectiveness of live hookworm infection on cognition in multiple sclerosis (MS) patients, as well as the clinical and radiological associations of cognitive function in MS patients. Cognitive

impairment in MS patients, in comparison to stroke patients, is also common, however, the pattern of cognitive deficits differs with memory, attentional and information processing speed deficits being a staple of MS cognitive dysfunction, whereas executive function deficits are often associated with post-stroke cognitive impairment [359]. As with stroke patients, cognitive impairment in MS patients worsens their functional disability as well as their quality of life [51, 359] and there is currently no effective cognitive rehabilitation or pharmacological intervention [371, 372, 400]. MS is an immune-mediated inflammatory disease of the central nervous system. The hygiene hypothesis [373] suggests an infectious agent, such as a parasitic infection, may protect against an autoimmune inflammatory disease like MS. The WIRMS trial was a phase II, randomised, double-blind, placebo-controlled trial of N. americanus infection (hookworm, HW). Participants were infected with 25 N. americanus larvae or placebo during a 9-month treatment period followed by a 3-month safety period. The Paced Auditory Serial Addition Test (PASAT), a component of the Multiple Sclerosis Functional Composite (MSFC), was performed at baseline, 9 months and 1 year to assess the participants' cognition via their auditory information processing speed and flexibility, and calculation ability. We showed that there were no effects of hookworm infection on cognitive function, quality of life or fatigue over the 6 months of active treatment. We also showed there was no significant change in the cognition and functional outcomes over time in all participants and either treatment group. The PASAT-3 score at 9 months, once adjusted for baseline PASAT-3 score, showed a negative association with the number of T2 lesions at 3 months and 9 months, whereas it showed a positive association with both the physical and mental components of the MSQOL-54 at 9 months. The number of T2 lesions at 3, 9 and 12 months and physical QOL at 9

months were also associated with the PASAT-3 score at 12 months. Despite these weak associations, in part reflecting the short duration of the trial and the relatively small sample size, poorer QoL [384] and greater lesion burden [51] have been associated with cognitive dysfunction in previous studies. The main study showed that treatment with the HW was safe and well-tolerated, however, there was no difference between the cumulative number of active MRI lesions in the treatment groups (primary outcome). This was most likely due to a low level of disease activity in the treatment arm, which had a substantially greater proportion of participants with no disease activity in comparison to the placebo group [377]. As an increase in total lesion volume and cortical lesions are often tied with cognitive decline in MS, this is likely why no cognitive differences were observed between the two treatment groups and within the groups over time.

7.2 Limitations with recommendations for the future

There are limitations to the current work. Firstly, a person's level of education is believed to contribute to a person's cognitive reserve, which refers to the individual differences in neural pathways and cognitive processes that may affect a person's ability to compensate for brain pathology. Studies in stroke, MS and dementia have shown that a greater level of education, as an indicator of cognitive reserve, is protective and vice versa [91, 92, 361, 401]. Unfortunately, none of the clinical studies (ENOS, TARDIS, TICH-2, WIRMS) accounted for a participant's level of education. Cognition was not the primary outcome in these intervention trials and as such, it is not surprising that education level was not collected from participants. The PODCAST trial did collect the age of the participant when they left full-time education via Addenbrooke's Cognitive Examination-Revised (ACE-R), however, as the additional follow up was done over the telephone the ACE-R was not used as it does not have a validated

telephone version. Future work should therefore collect a person's level of education as well as other markers of cognitive reserve such as intelligence quotient, employment and leisure activities.

As stated previously a person's ethnicity has been associated with cognitive function in previous stroke studies and whether cognitive impairment varies by race in MS is unknown [92, 324, 399, 402]. However, the ENOS, TARDIS, PODCAST and WIRMS trials only collected either the region the participants were from or collected very specific ethnicities. This made collating them into larger groups for meaningful analysis difficult or did not account for ethnicity. On the other hand, in the future, collecting a participant's ethnicity alone is unlikely to be sufficient as there is a myriad of race-related factors that could be associated with cognitive function. Therefore, future work should try to account for race-related factors that are not often considered such as education, region (rural, suburban, urban), socioeconomic status, healthcare access, and genetic (AD biomarkers).

Thirdly, it is important to assess either pre-morbid or baseline cognition as many stroke and MS patients have pre-existing cognitive deficits. However, due to the nature of acute stroke trials, we did not collect data on pre-existing cognitive function and therefore we did not exclude pre-existing cognitive impairment in Chapters 3 and 4. Fortunately, we were able to minimise the overestimation of the prevalence of PSCI by excluding participants with pre-stroke dependency, as these participants are more likely to have pre-existing significant cognitive deficits. Furthermore, a major challenge for stroke cognition studies is the exclusion of participants that had a severe stroke as they were less likely to complete the follow-ups and therefore participants with severe strokes may not be fully represented in these analyses (Chapter 3, 4, 5). As such this may lead

to an underestimation of factors associated with stroke severity. This was mitigated by including participants that died, as this was usually following very severe strokes. Future research should endeavour to assess pre-morbid cognitive function and or include baseline cognition to combat the overestimation of the prevalence of cognitive deficits. Furthermore, to prevent missing cognitive data due to either the severity of the stroke or MS or the myriad of other reasons that could prevent a participant from completing an assessment, future research should include an informant-based cognition questionnaire, which will be explored in more detail later in the discussion.

Cognitive deficits are a long-term consequence of stroke and MS, however, only the PODCAST trial (Chapter 5) assessed cognition beyond 1-year and therefore most of our results reflect the relatively early stages of cognitive decline and may not reflect the long-term risk of cognitive impairment. Previous research has already investigated the long-term prevalence of cognitive impairment in both stroke and MS and to some extent even the long-term risk factors. However, future work should consider these recommendations. Recently, the protocol of a major observational study of post-stroke cognition has shown that they will be collecting many of the factors that were discussed here [403].

The ENOS, TARDIS and TICH-2 trials were all international trials, that used the English validation version of the cognition and functional assessments, translated by the assessor in the country of recruitments national language. In the future, it is therefore imperative that for any cognition or functional assessment that the participant is assessed in their native language using a validated version where possible. If there is no validated version for a country of recruitments native language, then the study team should create a translated version of the assessment to ensure consistency.

Stroke and MS are always a huge shock to the patient which leads to an emotional impact. Both stroke and MS are major causes of morbidity and long-term disability and are also a socioeconomic burden to the patient, their family and society. Chapter 3 and 4 both showed that stroke participants that suffered from cognitive impairment were more likely to be dependent on a family member/carer, suffer from depression and have a worse quality of life. Whereas a worse cognitive performance from MS participants in Chapter 6 was associated with a worse physical and mental quality of life. The relationship between cognition, depression and cognitive fatigue is still unclear and require further exploration. Future clinical trials should always aim to include functional assessments alongside cognitive assessments. Both subjective and objective assessments should be used for depression, fatigue, and quality of life. Furthermore, unemployment is often a consequence of these functional and cognitive deficits and as such employment status should also be accounted for. Overall, future research should aim to determine whether depression and fatigue correlate to specific cognitive domains and whether it is determined by a certain degree of cognitive impairment. This should also be used in conjunction with neuroimaging which can be used to determine whether lesions in specific locations or disconnection due to demyelination or neuronal damage are related to depression and fatigue alongside cognitive deficits.

Magnetic resonance imaging (MRI) was either not done or only performed in a small number of participants in the stroke trials (ENOS, TARDIS, TICH-2, PODCAST). This is mainly due to the accessibility of an MRI scan in acute stroke settings where a computed tomography (CT) scan is more widely available. This meant that neuroimaging features such as cerebral microbleeds, disseminated superficial siderosis and the enlargement of perivascular spaces were not

captured in these trials. Neuroimaging is critically important in the diagnosis and management of both stroke and MS; however, it can also be used to improve our understanding of how cognitive dysfunction occurs. Large structural changes that occur in both stroke and MS patients such as large lesions/infarcts, advanced atrophy or advanced leukoaraiosis can be identified on computed tomography (CT), however, MRI, especially at higher magnetic field strength, can be used to identify subtle brain alterations. For example, in stroke specifically, the Standards for Reporting Vascular changes on Neuroimaging initiative provided a detailed overview of neuroimaging changes associated with small vessel disease [404]. On the other hand, it has been suggested that cognitive impairment in both stroke and MS is related to a disconnection of the brain network, therefore functional MRI or diffusion-weighted MRI with brain tractography and network construction should be used in smaller cognition studies to determine the structural networks and which alterations are associated with specific cognitive deficits. Future trials should therefore endeavour to perform MRI scans; however, this may remain difficult for large acute stroke trials as patients with severe stroke struggle to tolerate them. Unfortunately, there are no specific imaging markers that can differentiate between vascular injury and neurodegenerative pathology.

It has been suggested that neuroinflammation in both stroke and MS patients via several inflammatory mechanisms exacerbate the natural central nervous system ageing which consequently leads to cognitive impairment. The stroke clinical trials (ENOS, TARDIS, TICH-2, PODCAST) did not collect any inflammatory markers and the WIRMS trial investigated T cell and T regulation markers as well as MRI with gadolinium to identify enhanced lesions, which is a marker of inflammation. Future cognition studies should aim to include MRI with

gadolinium as a marker of inflammation as it is more practical but studies could include cerebrospinal fluid markers of inflammation such as matrix metalloproteinases, albumin ratio, myelin basic protein and neurofilament light, however, it is difficult to do this serially [405-410]. This will allow us to better understand the association between inflammation and cognitive impairment, whilst also helping to identify potential targets for interventions aimed at preventing or delaying cognitive impairment.

The cognition assessments that were used were not extensive neuropsychological examinations. In the stroke trials, these were telephone-based cognition assessments and as such did not assess executive and visuospatial function. As the WIRMS trial was not a primary cognition study, there was no extensive neuropsychological assessment nor a global cognition screen. The PASAT, a test of attention, information processing speed and calculation was used. Therefore, any future cognition research should ideally use a face-to-face extensive neuropsychological assessment in conjunction with an informant-based cognition questionnaire. This will not always be possible to do due to a participant's health or even due to trial costs. Telephone-based cognitive assessments should therefore be used in support of extensive neuropsychological assessments, as they are cost-effective and allows for the inclusion of participants that may otherwise have been lost to follow up. Furthermore, informant-based questionnaires, such as the IQCODE for stroke patients and the MS Neuropsychological Screening Questionnaire Informant, are complementary to brief telephone and brief cognitive assessments, as they can often be done over the phone and cover several weaknesses of a telephone-based and brief cognitive assessment. For example, the IQCODE has relevance to daily function, is not affected by education level, is not directly threatening to

the self-esteem of the participant, and should experience fewer communication difficulties due to the patient's cognitive abilities [411-416]. Other informant assessments include the Ascertain Dementia 8 questionnaire [417] and the General Practitioner's Assessment of Cognition informant component [418], however, they were not specifically designed for use in either Stroke or MS [419].

Recently the European Stroke Organisation [420] recommended that the IQCODE (or an equivalent) followed by a short cognition test battery and then an extended cognition test battery should be included in acute stroke trials to detect pre and post-stroke cognitive impairment. Also, it is recommended that depression, which is known to impact cognition, is assessed as well using a short depression scale such as the Beck Depression Inventory [420, 421]. Furthermore, this can replicate in MS trials using the MS Neuropsychological Screening Questionnaire Informant, the Brief International Cognitive Assessment for Multiple Sclerosis and then either the Brief Repeatable Battery of Neuropsychological tests or the Minimal Assessment of Cognitive Function in MS. The Beck Depression Inventory is also validated for both stroke and MS [422, 423].

Future research must identify the degree of cognitive impairment that the participants are suffering from as potentially disease-modifying treatments may be more effective at different stages of cognitive decline. It also allows researchers to determine which clinical and radiological factors influence the degree of cognitive impairment patients suffer from.

Towards this, the terms used to describe cognitive deficits due to stroke have varied over time and lead to the development of several different diagnostic

criteria designed to define vascular dementia (VaD). The National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria [424], the State of California Alzheimer's Disease Diagnostic and Treatment Centers criteria [425], the Diagnostic Statistical Manual-IV criteria [426, 427], and the International Classification of Diseases-10 criteria [428] are the four commonly used sets of criteria for VaD. However, the National Institute of Neurological Disorders and the Canadian Stroke Network [429] highlighted several limitations of the current criteria and suggested some recommendations. This lead to the development of a criteria for vascular cognitive disorders (VCD) by the International Society for Vascular Behavioural and Cognitive Disorders, which took into account the limitations of and recommendations to the aforementioned criteria's and also harmonizes with the 5th iteration of the Diagnostic Statistical Manual [427, 430]. Future stroke research should endeavour to use a diagnostic criterion for vascular dementia, ideally, the criteria developed by International Society for Vascular Behavioural and Cognitive Disorders should be used as it improves on the limitations of previous criteria's and will help to remove the ambiguity surrounding the definition and diagnosis of VaD.

Whereas, in MS, cognition is often defined as either intact or impaired according to certain thresholds for performance. These definitions of impaired cognition often varied across studies and can therefore affect prevalence estimates. Furthermore, studies often classify a patient as cognitively impaired based on their overall performance across several tests that measure different cognitive functions, however, this threshold can be met by failing a single memory or speed test or a combination of tasks. Patients classified as cognitively impaired are often heterogeneous as they can suffer from different single-domain or

multi-domain cognitive deficits, therefore, future work should aim to classify cognitively impaired patients based on which and to what degree the domains are affected. This will allow for a better comparison of patients within and across studies and improve the ability to interpret results such as determining which clinical and neuroimaging factors are associated with cognitive impairments [431].

The PODCAST trial (Chapter 5) and the WIRMS trial (Chapter 6), one of which was the only longitudinal study of cognition, were hampered by small sample size. In the case of PODCAST, the recruitment target was not met due to feasibility issues and intervention costs, in participating by primary care and hospital sites. WIRMS meanwhile, was a single-centre study due to logistical limitations of the immunoparasitology component of the study. Recruitment was full but in hindsight calculating sample size based on the proportion of participants with no disease activity may have been more appropriate than the primary outcome of the WIRMS trial. These small sample sizes also meant that the studies may have been underpowered, and it is, therefore, difficult to determine any meaningful clinical benefits. Consequently, our results may display both types I (false positive) and type II errors (false neutral). The recruitment targets were not met in the PODCAST trial, whereas the people recruited to the WIRMS trial did not experience a disease progression over the intervention period. Both studies required longer intervention periods to allow for the intervention targets to be met whilst also giving them enough time to show potential clinical benefits in terms of cognition. However, in the future, this type of intervention trial is feasible, given an appropriate design, infrastructure, more funding and or a cost-effective version of the intervention.

7.3 Conclusion

Overall, this thesis has further highlighted just how prevalent cognitive impairment is in both ischaemic stroke and intracerebral haemorrhage patients as well as elucidating the risk factors of cognitive decline after stroke. Furthermore, we demonstrated that cognitive impairment after IS and ICH were both associated with older age, a greater stroke severity, and non-UK/non-Caucasian ethnicity. Blood pressure and heart rate were both associated with cognitive impairment after IS and may be potential therapeutic (pharmacological or lifestyle) targets. Importantly, a greater level of social deprivation, a surrogate marker of socioeconomic status, was associated with cognitive impairment after ICH.

It has also investigated potential therapeutic interventions for the prevention of cognitive decline in stroke and MS patients. Despite the lack of meaningful clinical benefits in these small studies, blood pressure and lipid interventions in stroke patients, and parasitic infection in MS patients, are still feasible and require further study.

This thesis emphasised that future clinical trials in people with cognitive impairment should be longitudinal studies that are designed to account for a participant's; level of education, intelligence quotient, employment, leisure activities, ethnicity, and other race-related factors (region (rural, suburban, urban), socioeconomic status, healthcare access, and should perform MRI scans and genetic analysis (AD biomarkers)) where possible. Future trials should assess cognition using a short cognition test battery in conjunction with an informant-based cognition questionnaire and then an extended cognition test battery. Telephone-based cognitive assessments should be used in conjunction with face-to-face assessments. Any intervention-based trial in cognition should

also allow for long intervention and assessment periods due to the long-term nature of cognitive decline. Large studies of both stroke and MS should collect markers of cognition even if cognition is not the primary outcome as more data in a variety of patients is needed.

Lastly, there is a need to balance the 'perfect methodology' of the information (demographic, clinical, genetic and neuroimaging) collected from the participant and the extent and type of cognition and functional assessments that are performed. Of course, a direct assessment will always be preferable especially in clinical practice, however, in the future remote centralised assessment could be used to address logistical and economic issues in large multicentre clinical trials. In conclusion, cognitive impairment due to stroke or multiple sclerosis is a socioeconomic burden that will continue to grow without further research into its risk factors and in turn potential interventions.

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