The Psychological and Cognitive Impact of Cerebrovascular Disease

Thesis submitted for the degree of D. Phil

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“We are here to help each other get through this thing, whatever it is.”

Kurt Vonnegut

ABSTRACT

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Patients who experience a Transient Ischaemic Attack (TIA) or a stroke are at risk of subsequent psychological and cognitive disorders but there is limited research into the impact of transient or minor events. Psychological disorders include depression, anxiety disorders and post-traumatic stress disorder with their risk factors and prevalence rates after a TIA poorly described. Furthermore, whilst depression and anxiety after a major stroke is associated with increased risk of recurrent stroke and all-cause mortality it is not clear if the same can be said after a minor stroke or a TIA. Cognitive disorders after a stroke are a heterogenous condition including fixed or progressive cognitive impairment due to a stroke lesion, cognitive impairment accelerated by a stroke and cognitive impairment secondary to the coexistent pathology that also led to the stroke. However, the prevalence rates and associated factors for pre-stroke and post-stroke dementia have not been updated to reflect the impact of methodological factors on studies or the more recent improvements in stroke care. Recently, there has been a move to telephone cognitive assessments, particularly in research studies, and as such there is a need for accurate description of their potential limitations.

Overall, the aims of my thesis are to describe the prevalence and risk-factors for anxiety and depression disorders after a TIA or minor stroke and the prevalence and associated factors for pre-stroke and post-stroke dementia. Additionally, I aim to describe the potential limitations of telephone cognitive assessments.

I have collected and analysed data from the Oxford Vascular Study (OxVasc) which is an ongoing prospective, population-based incidence study of acute vascular disease in Oxfordshire, UK. The study population comprises approximately 92,729 individuals registered with eight general practices and uses multiple overlapping “hot” and “cold” methods to identify all relevant patients. Additionally, I collated and analysed data from the Treatment in Morning versus Evening (TIME) study which is a prospective, randomised open-label study comparing morning dosing of usual antihypertensive medication with evening dosing with a cognitive function sub-study (TIME-COG) of simple tests of cognition, administered via telephone, in participants aged 70 years or older.

There are several clinically relevant findings in this thesis which improve understanding of the psychological and cognitive consequences of a TIA or stroke. First, I have described the prevalence rate and associated factors for post-TIA anxiety and depression disorders. Second, I have described the prognosis of post-TIA anxiety and depression disorders. Third, I have described the prevalence and associated factors for pre-stroke dementia with particular attention to the impact of methodological factors. Forth, I have described the prevalence and associated factors for post-stroke dementia with particular attention to the impact of patient selection. Finally, I have described the potential impediments to telephone cognitive assessments with particular attention to the impact of time-of-day and change in season.

DECLARATION

I certify that this thesis entitled, “The Psychological and Cognitive Impact of Cerebrovascular Disease” was performed whilst I was a full-time postgraduate student at the University of Oxford.

I declare that this thesis is of my own composition, and the research contained herein is my own original work under the supervision of Professor Peter Rothwell and Professor Sarah Pendlebury. No portion of this work has been submitted in support of an application for any other degree.

CANDIDATE CONTRIBUTION

The data for this thesis are from two sources: The Oxford Vascular Study and The Treatment in Morning versus Evening – Cognitive Function Sub-Study.

The Oxford Vascular Study (OxVasc) is supervised by Professor Peter Rothwell with the day-to-day ascertainment, assessment and follow-up performed by clinical fellows and research nurses.

I participated as one of four full-time clinical fellows from 2016 – 2020 during which time I was responsible for patient ascertainment and assessment. This would involve running the daily acute Transient Ischaemic Attack (TIA) clinic ascertaining and assessing the patients referred with a suspected TIA or minor stroke. Additionally, I supervised the research nurses who ran the TIA follow-up clinics and ascertained patients who had been admitted to the John Radcliffe Hospital.

Over my research time-period I recruited a significant proportion of patients whose data are used in this thesis, though I would also like to acknowledge the help of other clinical fellows and research nurses in this process. I have also reviewed and cleaned all depression and anxiety related data collected on all patient episodes in this thesis. This has required a review of the OxVasc study records, hospital records and the primary care records.

The Treatment in Morning versus Evening – Cognitive Function Sub-Study (TIME-COG) is supervised by Professor Peter Rothwell with the telephone cognitive assessments completed by four research nurses. Over my research time-period I reviewed and cleaned all the TIME-COG data.

All systematic reviews and meta-analyses were undertaken by myself with guidance from my supervisors (Professor Rothwell, Professor Pendlebury).

ACKNOWLEDGEMENTS

The work presented in this thesis would not have been possible without a lot of strong coffee, a musical theatre playlist but most importantly the help and support of a whole team of people. I would like to thank both Professor Peter Rothwell and Professor Sarah Pendlebury for their support, guidance and encouragement over the years. Without their valuable input and attention to detail this thesis would be but a shell of itself. I am also grateful to the Oxford Biomedical Research Council for generously funding my studies.

Additionally, I would like to thank all my colleagues at the Centre for Prevention of Stroke and Dementia, University of Oxford including the clinical fellows, research nurses and therapists, administrators and database managers. Not only for their commitment to patient care and data collection but for their excellent supply of home-made cakes and for their unshakable sympathetic ear on the more difficult days. A special mention goes to Emily-Rose Vaughan-Fowler for her assistance clearing a way through the mountains of yellow folders that had become my irksome companions over the long months. I particularly wish to thank Dr. Linxin Li for her quiet but steady support in all matters and particularly for her endless patience in guiding me through the hitherto unfamiliar world of statistics.

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CHAPTER 1

INTRODUCTION

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Over 13 million people worldwide have a stroke each year.[1] Historically, research has focused on the causes and the physical consequences of major strokes. Yet, life after stroke is more than a collection of changing motor scores and secondary prevention medications. Stroke survivors often grieve the loss of the person they were before, feel frustration at their new inabilities, are anxious about a recurrence, worry about the financial implication and experience a multitude of other emotional and cognitive sequelae.[2] Furthermore, psychological and cognitive disorders after a stroke hinder recovery and are associated with increased mortality.[3,4] Thus far though research into these psychological consequences and specifically the impact of minor strokes and transient ischaemic attacks (TIAs) has been overlooked.

1.1 The psychological impact of stroke and transient ischaemic attack

Psychological disorders after a stroke are common and include depression, anxiety disorders, post-traumatic stress, apathy, psychosis, pathological affect and catastrophic reactions. The aetiology of psychological consequences of a stroke are poorly understood. Is it a psychological reaction to a traumatic event or a direct manifestation of the stroke lesion itself and its disruption to relevant neuronal circuits? An individual's premorbid state is important with maladaptive and negative thought processes increasing the risk of post-event psychological disorders.[5] Their social support also impacts with isolation and socio-economic deprivation increasing the risk of post-stroke depression and anxiety disorders.[6-8] Yet, the location of the stroke lesion itself can convey a specific risk suggesting it is an interplay of the stroke, a person's premorbid personality and their social environment that conveys the overarching risk.[9,10]

1.1.1 Depression

Approximately 1 in 3 patients experience post-stroke depression in the first year after a major stroke.[11] Its consequences are myriad: poorer functional recovery, increased mortality, increased risk of recurrent stroke and an overall lower self-reported quality of

life.[11-13] Depression itself is a heterogeneous disorder ranging from dysthymia to disruptive mood dysregulation disorder.[14] However, outside of psychiatric literature the term 'depression' is often used interchangeably to mean major depressive disorder. The diagnostic criteria for a major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) are described in table 1.1.[14]

Similar to depression in general, biological, social and psychological factors all collectively impact upon an individual's risk of post-stroke depression.[15] The foremost predictors of depression after a stroke are the severity of the stroke, the resultant disability and a history of pre-stroke depression.[11,13] Yet, by definition a TIA is not associated with any persistent neurological impairment so it is unclear if the predictors of depression after a TIA will be the same as after a stroke. Additionally for stroke patients the location of the lesion and the presence of moderate-to-severe small vessel disease also convey specific risks for depression. A TIA with an acute infarct on imaging has a different risk of stroke recurrence to an imaging negative TIA and a TIA with underlying small vessel disease has a different risk of recurrence to a TIA without underlying small vessel disease.[16,17] Therefore, will the presence or absence of an acute infarct or small vessel disease affect the risk of depression after a TIA? A single study on the impact of an acute infarct upon the subsequent risk of depression after a TIA found no association but was limited to only 103 patients and included atypical TIAs also.[18]

Few studies have attempted to identify the prevalence and associated risk factors for depression after a TIA.[19] Where studies have been completed they have been limited by factors such as a small sample size, the use of postal questionnaires rather than face-to-face assessments and assessment at only a single time point.[20-22] Understanding the risk factors for depression after a TIA and how they may differ from those for depression after stroke will also convey a greater understanding of the differing influences of the biopsychosocial model of post-stroke depression. Furthermore, understanding who is at

greater risk of depression after a TIA may permit heightened clinician awareness and, as such, earlier intervention to mediate the negative resultant impact.

1.1.2 Anxiety disorders

Approximately 1 in 3 patients experience anxiety disorders in the first year after a stroke.[6] Although the prevalence of anxiety disorders is similar to that of depression after a stroke it has garnered significantly less attention in research.[6] Yet in its own right it is associated with lower quality of life after stroke and additionally has been demonstrated to be a predictor for subsequent post-stroke depression.[11] Anxiety disorders encompass a range of conditions which share the underlying theme of excessive fear of an imminent threat and anticipation of a future threat.[14] They include separation anxiety disorder, selective mutism, social anxiety disorder, panic disorder, phobic disorders and generalised anxiety disorder.[14] Few studies have attempted to sub-type the anxiety disorder after a stroke but where attempted have found that phobic disorders and generalised anxiety disorders predominate.[23] Phobic disorders are characterised by disproportionate fear of a situation which when encountered leads to significant anxiety and as such the individual attempts to avoid the situation. Whereas a generalised anxiety disorder is characterised by persisting, pervasive and excessive anxiety that is irrespective of the situation. The DSM-5 diagnostic criteria for phobic disorders and generalised anxiety disorder are described in table 1.1. Predictors of anxiety disorders after a stroke include younger age, female gender, co-morbid depression and stroke severity.[24-26]

Whilst little is known about anxiety disorders after a stroke, even less is known about them after a TIA. A previous systematic review on psychological disorders after a TIA identified only one study on anxiety and this was limited to assessment only 14 days after the event.[27,28] Since then further studies on anxiety after a TIA have been published but again are limited by small sample sizes, postal assessments or assessment at only a single time point.[20,23,29] A longitudinal study of anxiety disorders after a TIA, their predictors and their outcomes is required.

1.1.3 Other psychological disorders

Other psychological disorders reported after a stroke include post-traumatic stress disorder, apathy, psychosis, catastrophic reactions and pathologic affect.[5,30] In general, there is limited literature on their prevalence, associated factors or outcomes in either stroke or TIA patients.

Post-traumatic stress disorder (PTSD) affects approximately 23% of patients in the first year after a stroke.[31] PTSD is characterised by the development of characteristic symptoms (such as fear-based re-experiencing) after exposure to one or more traumatic events.[14] Whilst the outcomes of post-stroke PTSD are unknown, PTSD due to acute coronary syndrome is associated with increased risk of recurrent cardiac events and increased mortality.[32,33] Two studies on PTSD after a TIA reported rates of between 25% to 30% in the first 3 months after the event.[22,34]

Apathy affects approximately 35% of patients of patients after a stroke and whilst often occurs in the context of depressive or cognitive disorders can additionally occur independently.[35] Apathy is characterised by a lack of emotion or interest and is associated with a poorer functional outcome and lower quality of life.[35,36] A single study on apathy after a TIA reported a rate of 35% immediately after the event.[21]

Psychotic disorders affect up to 5% of patients after a stroke and include delusional disorders, schizophrenia-like psychosis, and mood disorders with psychotic features.[37] Only one study on symptoms of psychosis after a TIA has been published but it similarly found a prevalence of 5% three-to-six months after the event.[38]

Catastrophic reactions are a rare consequence of stroke, described as disruptive emotional outbursts of anxiety, agitation or anger. They are most often seen in patients with expressive aphasia though their actual prevalence rate is unknown.[39,40] There are no studies reporting on catastrophic reactions after a TIA.

Pathological affect, or emotional incontinence, is inappropriate emotional expression which is not connected to the patient's underlying feelings (e.g. the patient may have uncontrollable laughing but does not feel happy).[5,41] It occurs in around 20% of stroke patients and particularly in the acute phase. There are no studies reporting on pathological affect after a TIA.

1.2 The cognitive impact of stroke and transient ischaemic attack

Cognition is defined as the mental processes by which one acquires knowledge, retains it and applies it.[42] Broadly speaking cognition includes six sub-domains: attention, memory, executive function, language, visuospatial function and social cognition.[14] Cognition, and its subdomains, can be assessed through means of a screening test (such as the Mini-Mental State Examination or the Montreal Cognitive Assessment) or a more detailed neuropsychological battery (such as the neuropsychological battery recommended by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) Vascular Cognitive Impairment (VCI) Harmonization Standards working group).

With increasing age comes a natural decline in some cognitive subdomains with memory and executive function more vulnerable but language often being preserved.[43] However, in some individuals a neurodegenerative disease process occurs resulting in significant impairment in one or more of the subdomains which may be diagnosed as mild cognitive impairment (MCI) or cognitive impairment no dementia (CIND). Ultimately this process may continue to progress resulting in an impairment in functioning and as such be described as a dementia. At any point an individual may have the additional cognitive insult of a stroke with the relationship complicated further by the increased risk of stroke in patients with dementia or cognitive impairment.[44-46]

Yet cognitive impairment after a stroke is not a homogenous condition. It ranges from a fixed or progressive cognitive impairment due to a stroke lesion, cognitive impairment accelerated by a stroke and cognitive impairment secondary to the coexistent pathology

that also led to the stroke. The stroke itself, whether that be a single strategic infarct, multiple cortical or subcortical infarcts, intracerebral haemorrhage, or hypoperfusion may then transform a patient with either known or unknown cognitive impairment or even a normal cognitive state to a patient with post-stroke cognitive impairment or post-stroke dementia.[47] Further to this, additional insults at the time of stroke, such as infection, delirium and post-stroke seizures may all accelerate the process.[48]

The prevalence of post-stroke cognitive impairment ranges from 20% to 80% due to heterogeneity in studies and a lack of clarify regarding its definition.[49] Even for the diagnosis of dementia after a stroke, where the definition is somewhat clearer, prevalence rates remain heterogeneous particularly with regards to the population they study.[48] A meta-analysis in 2009 reported a pooled prevalence rate of new onset dementia in the first year after a stroke of 20%.[48] Yet, this review was limited by being skewed towards hospital-based studies which tend to overlook more minor strokes that did not require hospital admission. Subsequently a population-based study, with complete ascertainment of all stroke events and all dementia diagnoses, has provided a more accurate representation of the impact of stroke on cognition and as such an update to the previous systematic review is required.[50]

Furthermore, through the years there has been an improvement in secondary prevention, a roll out of stroke units and hyperacute stroke units, the introduction of thrombolysis and more recently of thrombectomy. Collectively all these interventions have either reduced the severity of the stroke or reduced the rate of recurrence of stroke.[51-54] As both severity and stroke recurrence strongly increase the risk of post-stroke dementia, if these decrease it could be postulated that the rate of post-stroke dementia should also decrease.[48] No study has currently assessed the time-trends in post-stroke dementia.

Post-stroke dementia is but one facet of the relationship between stroke and cognition. To understand the impact of stroke on cognition also requires an understanding of the pre-morbid cognitive state of the population who have a stroke. Being able to describe the

prevalence, subtypes and independent associations of pre-stroke dementia informs the understanding of the subsequent impact of a stroke on cognition. Patients with pre-stroke dementia do worse: they have poorer functional outcomes, are more likely to be discharged to a care home and have an increased mortality rate.[55-57]So even in its own right, an understanding of the burden of pre-stroke dementia is required for planning of clinical and social services. However, the reported prevalence rates of pre-stroke dementia range from 1% to 25% depending on population studied and method of assessment.[58,59] As such a meta-analysis is required in order to describe the prevalence and independent associations of pre-stroke dementia and to address the methodological issues in studies.

Finally, there is the question regarding the impact of a TIA on cognition. By definition, a TIA should not leave any residual neurology but that does not mean there is no cognitive impact. After a TIA up to one third of patients have a persistent impairment in one or more cognitive subdomains.[60] Studies on the prevalence of dementia before and after a TIA are now required.

1.3 . Cerebrovascular dysfunction associated with hypertension

Over time elevated blood pressures overwhelm the cerebrovascular's intrinsic autoregulatory ability leading to numerous vascular changes: atherosclerosis, lipohyalinosis, hypertrophy and vessel stiffening.[61,62] One of the outcomes of these changes is to increase the susceptibility of the brain to vascular insufficiency and as such it is no surprise that hypertension is a powerful risk factor for ischaemic strokes, intracranial haemorrhages and TIAs.[63] The cerebrovascular changes secondary to hypertension often predate the cerebrovascular event by many years.[63-65] Similarly, hypertension, particularly midlife hypertension, has been demonstrated to be associated with subsequent cognitive impairment and the development of both Alzheimer's and vascular dementias.[66,67] The relationship between hypertension and dementia is complex with longitudinal studies demonstrating that both hypotension and hypertension are associated with the risk of cognitive decline.[68] Further adding to the confusion are the conflicting observational studies

and randomised controlled trials of anti-hypertensives to prevent dementia with a meta-analysis reporting no net benefit.[69-75] However, many of the studies have been limited by too short a follow-up, early cessation, unequal drop-outs and limited blood pressure difference between groups.[69,71,73,76] Given that it is mid-life rather than latter-life blood pressure that demonstrates the strongest association with dementia, longitudinal studies of extended duration are required to resolve this matter. Telephone cognitive assessments potentially provide a unique method for longitudinal cognitive studies to achieve this by both reducing attrition and being cost-effective.

1.4 Telephone cognitive assessments

Telephone forms of cognitive assessment are increasingly being recognised as a convenient method for reaching and retaining a larger subject population. They facilitate screening for dementia in rural areas where otherwise geography may negatively impact upon clinic attendance. They are often at increased convenience to both examiner and examinee and can be performed at a reduced cost compared to face-to-face assessments. It is therefore no surprise that telephone cognitive assessments have been incorporated in numerous longitudinal studies of ageing.[77-80] The first telephone cognitive assessment tool that was developed was the Telephone Interview for Cognitive Status (TICS).[81] First developed in 1988 it has since been adapted into numerous languages and validated in a range of clinical conditions from post-stroke subjects to Alzheimer's disease.[81-91] Yet, the telephone brings different difficulties to a cognitive assessment compared to face-to-face testing. Hearing impairments may be amplified and the assessor can exert less control over the assessment environment. Despite this there is currently a lack of reporting of their potential limitations of telephone assessments. An understanding of their feasibility, any impediments to their administration and the impact of those impediments is required.

1.5 The Oxford Vascular Study

1.5.1 Study population

The Oxford Vascular Study (OxVasc) is a longitudinal, prospective, population-based cohort study of all incident and recurrent acute vascular events (transient ischaemic attack, stroke, acute coronary and peripheral vascular events) in Oxfordshire, UK.[92-94] The study population is defined by registration with eight general practices (figure 1.1) and comprises approximately 92,728 individuals. Recruitment began 1st April 2002 and is ongoing. In Oxfordshire, an estimated 97% of the population is registered with a general practice, with most non-registered individuals being young adults.[93]

1.5.2 Case ascertainment

Ascertainment combines prospective daily searches for acute events ("hot pursuit") and retrospective searches of hospital-care and primary-care administrative and diagnostic coding data ("cold pursuit").[92,93] The multiple overlapping "hot" and "cold" pursuit methods have been demonstrated to achieve near complete case ascertainment.[94]

Hot pursuit includes:

i) Weekday "TIA clinic" to which participating general practitioners and the local accident and emergency (A&E) department referred all individuals with suspected TIA or stroke.
ii) Daily searches of admissions to the John Radcliffe Hospital
iii) Daily searches of A&E and Eye Hospital attendances
iv) Identification of patients who died on arrival to the hospital via the Bereavement Office
v) Daily searches of patients from the study population in whom a troponin-I has been requested
vi) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory.

Cold pursuit includes:

i) Monthly searches of all practice diagnostic codes.

ii) Monthly practice-specific list of all patients admitted to all acute and community NHS hospitals.
iii) Monthly listings of all referrals for brain or carotid imaging studies
iv) Monthly reviews of all death certificates and coroners reports
v) Practice-specific listings of all ICD-10 death codes from the local Department of Public Health.

As soon as possible after the event a study clinician reviews the patient with a structured interview and examination with data collected using event-specific forms (Appendix I for TIA and stroke). Information includes details of the clinical event, medication, past medical history (including past history of anxiety, depression and dementia) and investigations relevant to their event.

1.5.3 Definition of Transient Ischaemic Attack and stroke

In this thesis a stroke is defined, according to the World Health Organisation (WHO) criteria, as acute focal neurological symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.[95] A Transient Ischaemic Attack (TIA) is defined as an acute focal neurological symptoms lasting less than 24 hours which is thought to be caused by inadequate cerebral or ocular blood supply.[95]

1.5.4 Diagnostic work-up

At ascertainment TIA and ischaemic stroke patients routinely had brain imaging (CT or MRI), vascular imaging (carotid Doppler, CT-angiography or MR-angiography), 12-lead electrocardiography (ECG) and routine bloods (including (including full blood count, clotting, glucose, C-reactive protein, Erythrocyte Sedimentation Rate, liver function, renal function, thyroid function, electrolytes and lipid profile. Further investigations (such as R-test ECG monitoring) were done where clinically indicated at the 1-month follow-up review.

The imaging protocol of OxVasc has been published previously.[17,96] From the commencement of the study until March 31, 2010 MRI and MR angiography were

performed in only select cases, but from April 1, 2010 onwards these became the first-line imaging methods for all cases where feasible. Patients were scanned predominantly with 2 scanners – Achieva, Philips Healthcare (1.5T MRI) and Magnetom Verio, Siemens Healthcare (3T MRI). Details of scan parameters are provided in table 1.2.

After completion of all investigations the cases were reviewed by a senior neurologist (PMR) and the aetiology classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria: cardioembolic, large artery disease, small vessel disease, undetermined, unknown, multiple and other.[97]

1.5.5 Follow-up of cases

All surviving patients are followed-up face-to-face at 1,6, 12, 60 and 120 months after their event by a research nurse or physician. The follow-up assessment includes cognitive assessments (Montreal Cognitive Assessment: MoCA and Mini-Mental State Examination: MMSE), mood assessment (EuroQol-5D, and Geriatric Depression Scale) and assessment for recurrent events. If face-to-face is not possible then telephone follow-up is performed and Telephone-Montreal Cognitive Assessment (T-MoCA) and the modified-Telephone Interview for Cognitive Status (TICS-m) used for cognitive assessment instead. Recurrent events are ascertained at the time of the follow-up or through the 'hot' and 'cold' pursuit methods described earlier. These included recurrent strokes, acute myocardial infarction (ST elevation myocardial infarction, non-ST elevated myocardial infarction) and acute peripheral vascular disease events (including aortic aneurysm dissections / rupture and acute limb / bowel ischaemia). Deaths occurring during follow-up similarly were identified through the 'hot' and 'cold' pursuit methods. Cause of death was determined through coroner's reports, death certificates and coding from the Office for National Statistics National Health Service Central Registrar. Where there was a lack of clarify regarding the cause the hospital notes pertaining to the final admission were also reviewed where available. The data used in this thesis is confined to the assessments performed at the 1, 6, 12 and 60 month follow-up assessments (Appendix II-IV).

1.5.6 Definition and ascertainment of dementia cases

Multiple methods were used to identify all cases of dementia and reduce attritional biases.[98] Dementia was defined as pre- or post-event according to whether the diagnosis was made before or after the ascertainment event.[99] The diagnosis made by a senior study physician with expertise in dementia (STP) according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition. Pre-event dementia diagnosis was made using information obtained from the baseline clinical assessment (with the patient and an informant) and any prior dementia diagnosis (hand-searching of the entire primary care record including consultations, clinic letters and hospital documentation). Post-event dementia was diagnosed using baseline and follow-up clinical and cognitive assessment data and hand-searching of primary care records (up to 5 years' follow-up or death).[98-100] Where testing could be completed, without impediment, then a MMSE of <24 that persisted upon follow-up was used to diagnose dementia. Where testing could not be completed due to problems such as visual impairment or aphasia then hand-searching of study, primary care, hospital and death records were used to diagnose dementia.[50]

1.5.7 Definition and ascertainment of symptoms of depression and anxiety

Multiple methods were used to identify premorbid cases of anxiety and depression. Either a self-reported history at the baseline interview, a primary care coding for depression and / or anxiety disorders or the prescription of a therapeutic dose of an anti-anxiety or antidepressant in the patient's pre-event medication history were used to define cases of depression and anxiety.[101] At baseline patients were asked to report if they "often felt sad or depressed." A single question for screening of depressive disorders has been shown to have a sensitivity of 71%-86% and specificity of 78%-83% for post-stroke depression.[102,103] At the 1-month and 12-month follow-up assessments patients were asked to self-rate whether they had any, moderate or extreme symptoms of anxiety and / or depression as part of the EuroQol-5D assessment (Appendix II, IV). From July 2014 onwards patients were also asked at these time points to complete the Geriatric Depression Scale (GDS).

The GDS has been validated in both a stroke and TIA population with depression defined as a score greater than 5.[104]

1.5.8 Patient consent and ethical approval

All eligible patients are provided with an information sheet (Appendix V) and if in agreement and have capacity then written consent is obtained (Appendix VI). If a patient lacks the ability to consent the assent is obtained from the patient's next of kin (Appendix VII). OxVasc is approved by Oxfordshire Clinical Research Ethics committee (OREC A 05/Q1604/70)

1.6 The Treatment In Morning versus Evening – Cognitive Function Sub-Study

1.6.1 Treatment in Morning versus Evening (TIME) study

The Treatment in Morning versus Evening (TIME) study is a prospective, randomised open-label study comparing morning dosing of usual antihypertensive medication with evening dosing to determine the impact upon rate of cardiovascular events. TIME recruited participants through adverts on the radio, primary care practices, newspapers, hospital clinics, pharmacies and research study databases.[105] Participants self-enrol through the study website (www.timestudy.co.uk) where the process confirms their eligibility. Participants are eligible if they are aged 18 years or older, diagnosed and on treatment for hypertension with at least one antihypertensive medication and have a valid email address. Participants who take twice daily antihypertensive therapy, work shift patterns including a night shift, unwilling to consent to follow up, unwilling to permit access to their medical records, or have participated in another clinical trial of an investigational medicinal product within the last 3 months were all excluded. Participants consent, enter baseline demographic data and subsequently can enter patient-reported outcomes all through the study website. Once entered into the trial they are then randomly allocated to either morning dosing (06:00 to 10:00) or evening dosing (20:00 to 00:00) of their usual antihypertensive medication. Endpoints are detected by record linkage to hospital records and death certification, by regular email contact with participants or their nominated surrogate and

review of their primary and secondary care records.[106] TIME enrolment has ceased with randomisation of 21,116 participants over a 2-year period and now is continuing follow-up.[105]

1.6.2 TIME-Cognitive Function (TIME-COG) sub-study

The TIME-Cognitive Function sub-study aims to determine whether there is any difference between morning and evening dosing of antihypertensive medication on simple tests of cognition in participants aged 70 years or older.

1.6.3 TIME-COG study population

Participants enrolled in TIME who are aged 70 years or older at enrolment were additionally offered the opportunity to volunteer for TIME-COG. Apart from sufficient hearing and sufficient English language comprehension to complete testing by telephone no further exclusion criteria were applied. Participants who volunteered were then contacted by a research nurse to confirm eligibility and arrange an appointment for telephone testing. The research nurses were blinded to the participants' randomised treatment allocation in the main trial.

1.6.4 TIME-COG cognitive assessment

At baseline TIME-COG participants completed the T-MoCA and the TICS-m (Appendix VIII & IX). Both are screening cognitive assessment tools that are sensitive for the detection of mild cognitive impairment.[81-83,107] The MoCA has been demonstrated to be sensitive for vascular-pattern cognitive impairment.[108,109] The TICS-m is more weighted towards memory and language than the T-MoCA so is considered more useful for the detection of Alzheimer's-type cognitive decline as well as vascular cognitive impairment.[107] The administration of the two tests by telephone takes between 15 and 30 minutes and is well tolerated by participants.[82] Prior to completion of the tests participants were asked not to write questions down on paper during testing and to avoid 'revising' answers prior to subsequent test appointments. During the test the assessor would document any potential impediments that occurred such as hearing difficulties or interruptions. The baseline

assessment was done within one week of randomisation into the main trial and then repeated after 6 months, one year and annually for the duration of the TIME trial follow-up.

1.6.5 TIME-COG sample size

In the Syst-EUR study the annual risk of significant sustained cognitive decline in patients aged 70 to 79 years with hypertension was 4.0%.[72] However, this was based on the mini-mental state examination (MMSE) with the TICS-m and T-MoCA assessments used in TIME-COG being more sensitive than the MMSE.[110] As such TIME-COG is powered on the basis of a 5% expected annual rate of cognitive decline in those on the usual (morning) timing of antihypertensive medication. Therefore, a sample size of 600 (300 per group) provides 80% power to detect a 50% increase in the rate of cognitive decline in the evening dosing group (adverse safety signal) or a 45% decrease in the rate of cognitive decline (efficacy signal) after four year follow-up assuming a drop-out rate of 10% per year.

1.6.6 Patient consent and ethical approval

The patient information sheets for TIME (Appendix X) and TIME-COG (Appendix XI) are located on the study website where having read them the participants can then enter a valid email address to start the process of enrolment. After validating their email address and entering their baseline details participants are asked to complete an electronic consent form (Appendix XII). TIME is approved by the Tayside Committee on Medical Research Ethics (MREC reference 11/AL/0309; UKCRN identifier 17071).

1.7 Aims of thesis

The aims of my thesis are to determine the following:

1. The prevalence rates, and temporal trends, of depression and anxiety disorders after a TIA and a minor stroke.
2. The risk factors for depression and anxiety disorders after a TIA and a minor stroke.
3. The risk of recurrent vascular event and death associated with depression and anxiety disorders after a TIA and a minor stroke.
4. The prevalence of pre- and post-stroke dementia.
5. The methodological factors impacting upon the reported rates of pre- and post-stroke dementia.
6. The independent associations of pre- and post-stroke dementia.
7. The prevalence and the impact of impediments to completion of telephone cognitive assessments.
8. The impact of time-of-day and season the outcome of telephone cognitive assessments.

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Major depressive disorder

A. Five (or more) of the following, present most days, nearly every day, for at least 2-weeks. At least one must be either depressed mood or loss of interest or pleasure.
    a. Depressed mood
    b. Diminished interest or pleasure in all, or nearly all activities
    c. Significant change in weight or in appetite
    d. Insomnia or hypersomnia
    e. Psychomotor agitation or retardation
    f. Fatigue or loss of energy
    g. Worthlessness or excessive or inappropriate guilt
    h. Diminished ability to think or concentrate
    i. Suicidal ideation, thoughts of death or suicide attempt
B. Symptoms causing significant distress or functional impairment.
C. Not due to the effects of a substance or another medical condition.
D. Symptoms not better explained by another psychotic disorder.
E. No manic or hypomanic episodes.

Generalised anxiety disorder

A. Excessive anxiety and worry, most days, at least 6 months, about a number of events or activities
B. Difficult to control the worry
C. Associated with at least three of the following
    a. Restlessness
    b. Easily fatigued
    c. Difficulty concentrating
    d. Irritability
    e. Muscle tension
    f. Sleep disturbance
D. Symptoms cause significant distress or functional impairment
E. Not attributable to another medical condition or substance
F. Not better explained by another mental disorder

Specific phobia

A. Marked fear or anxiety about a specific object or situation
B. The object or situation almost always provokes immediate fear or anxiety
C. The object or situation is actively avoided or endured with intense fear or anxiety
D. The fear or anxiety is disporoportionate to the real risk posed
E. Symptoms last for 6 months or more
F. Symptoms or avoidance cause significant distress or functional impairment
G. Not better explained by another mental disorder

Table 1.1 Diagnostic criteria for major depressive disorder, generalised anxiety disorder and specific phobia. Adapted from DSM 5th Edition.[14]



Figure 1.1: The eight OxVasc primary care practices. 19 Beaumont Street OX1 2NA, Berinsfield Health Centre OX10 7NE, Bartlemas Surgery OX4 1XD, The Key Medical Practice OX5 1AP, Malthouse Surgery OX14 3JY, Marcham Road Health Centre OX14 1BT, The Abingdon Surgery OX14 3LB, Church Street Practice OX12 9BN. (At the initiation of OxVasc The Key Medical Practice consisted of two separate practices both of which were enrolled in the study: Exeter and Kidlington. The practices were merged into The Key Medical Practice on the 1st October 2015).

MR parameters	OxVasc scanner 1 Magnetom Verio, Siemens Healthcare	OxVasc scanner 2 Discovery MR750, GE Healthcare	OxVasc scanner 3 Achieva, Philips Healthcare	OxVasc scanner 4 Signa HDxt, GE Healthcare
Field strength (T)	3	3	1.5	1.5
T1W TR/TE/TI (ms)	2000/1.94/880	-	701/16	-
T2W TR/TE (ms)	6000/96	5800/94	5061/100	3760/100
FLAIR TR/TE/TI (ms) (3D)	9000/88/2500	9600/130/2350	11000/140/2800	8080/112/2200
Diffusion TR/TE (ms)	5300/91	6000/84	2891/73	6100/71
GRE / SWI TR/TE (ms) (3D)	GRE 504/15	GRE 500/20	GRE 694/23	GRE 560/25
Pixel bandwidth (Hz)	240 (T1W) 220 (T2W) 202 (FLAIR) 1374 (Diffusion) 200 (GRE)	- 50 (T2W) 41.7 (FLAIR) 250 (Diffusion) 31.3 (GRE)	87.4 (T1W) 88.5 (T2W) 375 (FLAIR) 25.3 (Diffusion) 109.3 (GRE)	- 47.6 (T2W) 31.3 (FLAIR) - 75 (GRE)
Matrix	256x256 (T1W) 320x320 (T2W) 192x192 (FLAIR) 130x130 (Diffusion) 320x256 (GRE)	- 512 (T2W) 384x224 (FLAIR) 128x128 (Diffusion) 288x224 (GRE)	118x214 (T1W) 356x193 (T2W) 236x159 (FLAIR) 97x84 (Diffusion) 256x163 (GRE)	416x256 (T2W) 256x224 (FLAIR) 128x128 (Diffusion) 288x192 (GRE)
No. of slices	208 (T1W) 25 (T2W) 50 (FLAIR) 25 (Diffusion) 25 (GRE)	25	25 (T1W) 25 (T2W) 28 (FLAIR) 25 (Diffusion) 22 (GRE)	25
Slice thickness (mm)	1 (T1W) 5 (T2W) 3 (FLAIR) 5 (Diffusion) 5 (GRE)	5	5	5
Inter-slice gap (mm)	0 (T1W) 1 (T2W) 0 (FLAIR coronal) 1 (Diffusion) 1 (GRE)	1	1	1
Voxel size (mm^3)	1.0x1.0x1.0 (T1W) 0.8x0.8x5.0 (T2W) 1.0x1.0x3.0 (FLAIR) 1.8x1.8x5.0 (Diffusion) 0.9x0.8x5.0 (GRE)	-	0.53x0.53x5.0 (T1W) 0.65x0.65x5.0 (T2W) 0.82x0.81x5.0 (FLAIR) 1.74x1.73x5.0 (Diffusion) 0.90x0.90x5.0 (GRE)	-

Table 1.2 Image sequence parameters of the study population

CHAPTER 2

PREVALENCE, TEMPORAL TREND AND SUSCEPTIBILITY FACTORS ASSOCIATED WITH DEPRESSION AFTER A TRANSIENT ISCHAEMIC ATTACK VERSUS A MINOR STROKE: A POPULATION-BASED STUDY AND SYSTEMATIC REVIEW

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2.1 Abstract

Objectives: Whilst depression is accepted to be common in patients after a major stroke relatively little is known about its' prevalence or predictors in patients in the first year after a Transient Ischaemic Attack (TIA) or minor stroke.

Methods: I assessed the prevalence of depression 1 month and 12 months after a TIA and minor stroke in a longitudinal population-based study (OxVasc) along with associated factors. A systematic review was then undertaken of the prevalence rates of depression in TIA patients with the results collated into a meta-analysis at pre-specified follow-up points.

Results: Among 558 patients with a TIA/minor stroke the prevalence of depression was 21.0% (n=117/558) at one-month and 15.7% (n=72/459) at twelve-months. Depression at one-month was associated with pre-morbid depression (adjusted OR 2.29, 95% CI 1.42-3.69, p=0.001). Depression at twelve-months was associated with depression at one-month (aOR 13.07, 7.01-24.34, p>0.001). In the systematic review (including OxVasc) the pooled prevalence rate of depression after a TIA in longitudinal studies was 19.4% (95% CI 16.1% – 22.9%) acutely (0 – 1 months) and 12.8% (9.9%-16.1%) sub-acutely (3 – 12 months) with consistency across studies (p heterogeneity: acutely=0.270, sub-acutely=0.782). However, postal studies found reported lower rates compared with face-to-face studies (within initial 6 months: 6.0% vs 16.6%) The pooled prevalence of depression after a TIA compared with after a minor stroke differed significantly by 12-months (11.4% vs 21.4%, OR 0.46, 95%CI 0.31-0.38, p<0.001) though was similar at one-month (14.5% vs 19.9%, OR 0.74, 95%CI 0.52-1.03, p=0.078).

Conclusion: One-month after a TIA or minor stroke 1-in-5 patients and at 12-months nearly 1-in-6 had depression. The 1-month prevalence of depression was similar for both the TIA and minor stroke population suggesting that acutely equal attention should be given to both populations, particularly in those with a premorbid history of depression.

2.2 Introduction

It is accepted that a major stroke can lead to a depressive disorder with a pooled prevalence rate in the first year after a stroke estimated at 29%.[1] However, the psychological impact of a transient ischaemic attack (TIA) and minor stroke is less well understood. A TIA is commonly defined as associated with no residual neurological impairment but given the lifestyle and medication changes that are subsequently required, patients may subsequently describe changes in mood. Furthermore, the relationship is complicated by the fact that the underlying risk factors for a stroke or TIA (e.g. hypertension) may in themselves be associated with psychological changes irrespective of the cerebrovascular event.[2] The extent to which pre-morbid risk factors compared with the stroke-specific insult differentially influence the risk of developing depression after a cerebrovascular event is not fully known. A previous study found that even patients with no residual neurological impairment after a minor stroke had higher rates of post-event fatigue than patients after a TIA suggesting a central, or lesion-related, contribution to the psychological symptoms.[3] Comparing and contrasting the prevalence rates of, and risk factors for, depression in patients after a TIA to those after a minor stroke may illuminate answers to these questions.

Currently there is a paucity of data on the prevalence and factors associated with depressive disorders after a TIA. A single systematic review on psychological symptoms after a TIA, published in 2014, found that there were only five, relatively small, studies reporting specific post-TIA prevalence rates for depression.[4] Therefore, in a large longitudinal population-based study I analysed the prevalence of depression in the first year after a TIA versus minor stroke and the associated risk factors. I then undertook a systematic review of studies on the prevalence of psychological distress after a TIA to include studies published since 2014.

I aim to answer the following questions. Firstly, what is the temporal trend within the first year in prevalence rates of depression after a TIA? Secondly, are the rates of depression after a TIA similar to after a minor stroke? Thirdly, what are the factors that suggest a person is more susceptible to developing depression after a TIA or a minor stroke?

2.3 Methods

2.3.1 Population-Based Study

The Oxford Vascular Study (OxVasc) is a longitudinal, prospective population-based study of the incidence and outcomes of all acute vascular events in Oxfordshire, UK. The study population comprises 92,728 individuals registered with nine General Practices in Oxfordshire. As described in Chapter One, ascertainment of patients is through both 'hot' and 'cold' methods which have been demonstrated to achieve near complete ascertainment of all acute vascular events. Recruitment began 1st April 2002 and is ongoing.

All patients with TIA, ischaemic or haemorrhagic stroke were reviewed by a study physician (such as myself) as soon as possible after their initial presentation either on a hospital ward or in an outpatient neurovascular clinic. A structured interview and examination (including the National Institutes of Health Stroke Scale (NIHSS)) were completed and the primary care record reviewed. Patients are additionally asked at baseline if they "often feel sad or depressed." If capacitous, patients gave informed consent to participate, otherwise assent was gained from a relative.

A TIA was defined, according to the World Health Organisation (WHO) criteria, as focal neurological symptoms lasting less than 24 hours with a stroke defined as symptoms lasting more than 24 hours and the probability of the event being defined according to National Institute of Neurological and Communicative Disorders and Stroke (NINDS) criteria.[5] The senior study neurologist (PMR) subsequently reviewed all cases to confirm diagnosis and management. For the purposes of this study I included consecutive patients with first (in study) probable or definite TIA or minor ischaemic stroke (defined as NIHSS < 5) who were recruited into OxVasc from 16 July 2014 until 15 July 2018. Patients who died prior to the one month assessment (n=17), who didn't consent to join the study (n=40) or were ascertained more than one month after their event (n=12) were excluded.

Patients were subsequently further reviewed face-to-face at 1-month and 12-months by a study nurse or physician with a structured interview which included the Geriatric Depression Scale (GDS). The GDS has been validated in both a stroke and TIA population with depression defined as a score greater than 5.[6] To minimise attrition, if a participant was unable to attend hospital for their follow-up then a home visit was completed instead. I defined pre-morbid depression as a composite of self-reported history from the structured interview, GP coding in their primary care record or pre-event use of antidepressant medication. At baseline, 1-month and 12-month antidepressant medication was defined as that prescribed at a therapeutic dose according to Maudsley Prescribing Guidelines.[7] Socio-economic deprivation was defined by the indices of multiple deprivation (IMD) for the subject's baseline post-code and treated as binary (greater deprivation equating to an IMD score >17.398). Low education was defined as leaving school aged 16 or less without any further subsequent formal education. Vascular risk factors were defined as either self-reporting at baseline, from primary care records, or for hyperlipidaemia the prescription of a lipid-lowering agent in the baseline medication history. A recurrent cerebrovascular event was defined as a TIA, ischaemic stroke, subarachnoid haemorrhage or intracerebral haemorrhage.

2.3.2 Systematic Review and Meta-Analysis

To identify studies on post-TIA depression I searched Ovid Medline (1946 onwards), EMBASE (1974 onwards) and PsychInfo (1806 onwards) using a comprehensive search strategy up until 30 June 2020 for any form of psychological distress after a TIA (Appendix XIII). Relevant review articles were hand-searched for further studies. The review was completed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Studies were included if they reported on the prevalence of depression at any time point after a probable or definite TIA in a series of consecutively recruited eligible patients. Both tissue-based and time-based definitions of TIA were eligible for inclusion. Studies were required to use a validated measure in order to quantify frequencies, though to maximise yield, the measure did not have to have been validated specifically in a stroke or TIA population.

Studies on only sub-sets of a TIA population (e.g. post carotid endarterectomy) were included in the review but the prevalence data were not included in the meta-analysis. Studies were excluded if the data relevant to the TIA population could not be isolated from the data of a mixed population of stroke and TIA, if the full text of the paper was unavailable or if a translation of a non-English study was unavailable. Where multiple studies used a subset or the whole of the same data set, the duplicate studies were only included if frequencies at different time points were reported, otherwise the study of the largest patient series was included. Risk of bias was assessed for each study using principles from Cochrane and a systematic review of tools for assessing quality and susceptibility to bias in observational studies in epidemiology.[8,9] From the included studies information was extracted on the study characteristics (type, follow-up duration, recruitment method, proportion of eligible assessed, assessment method, tools used and their cut-off values) and participant characteristics (mean age, gender, proportion with psychological symptoms and associated factors). Where provided, data on control (non-TIA/stroke) and minor stroke (defined according to the individual paper) patients were also extracted.

2.3.3 Statistical Analysis

For the OxVasc data, I calculated the prevalence rate of depression after a TIA and after a minor stroke at baseline, 1-month and 12-months. I compared continuous variables by Students T-test and categorical variables by X^2 test. Statistical significance was defined as $p < 0.05$. Patients who completed 1-month and then also 12-months of follow-up were compared with those with incomplete follow-up. Univariate associations between baseline characteristics and subsequent post-event depression were determined by binary logistic regression and subsequently with age / sex adjustments. The results of the latter analysis were used to inform the variables to include in the multivariate regression analysis ($p<0.05$ in age/sex adjusted analysis). Age and sex were forced into the multivariate regression analysis as they have been found to be associated with depression in prior studies. A sensitivity analysis was performed

excluding patients who had either a pre-morbid history of depression or had reported often feeling sad at baseline.

In the meta-analysis I calculated pooled prevalence rates for depression (including the OxVasc data) according to pre-specified time frames after a TIA. Firstly, in only longitudinal studies that reported prevalence rates at different time points in the same cohort (acutely: 0 – 1 months, sub-acutely: 6 – 12 months) and secondly in both longitudinal and point prevalence studies (baseline, 1-6 months, 12-months). The 95% confidence intervals of the pooled prevalences were calculated to allow for extra-binomial variation because standard methods of calculating confidence intervals produce artificially narrow intervals if there is heterogeneity of risk between different studies.[10] Analyses of heterogeneity of prevalence across studies were done with X^2 tests. I also calculated the pooled odds ratios for depression after a TIA, versus a minor stroke acutely (0 – 1 months) and at a 12-months in those studies that reported these data. Finally, I calculated the pooled prevalence rates of depression stratified by study method or exclusion criteria. Statistical analyses were performed using SPSS Statistics 26.

2.4 Results

2.4.1 Population-Based Study

There were 661 (254 minor stroke, 407 TIA) patients with their first in study event recruited between July 2014 and July 2018. Of these, 84.4% completed at least 1-month of follow up and 69.4% completed both the 1-month and 12-month assessments. Reasons for not completing follow-up are given in table 2.1.

Patients who did not complete any follow up compared to those who completed at least one month were more likely to be older (mean age (s.d) = 73.0 (14.5) vs 69.5 (14.1), p=0.021), female (65.0% vs 49.8%, p=0.005) and have a history of ischaemic heart disease (21.4% vs 12.0%, p=0.011). However, there were no significant differences in socio-economic deprivation, education history and pre-morbid depression. There was a greater proportion of patients with atrial fibrillation (19.2% vs 9.8%, p=0.008) and diabetes (22.2% vs 13.3%,

p=0.029) in those who completed only the 1-month assessments compared with those who completed both the 1-month and 12-month follow up assessments. Additionally the patients who failed to complete the 12-month assessments had higher GDS scores at 1-month (mean (s.d) = 3.5 (3.1) vs 2.8 (2.8), p=0.007) and were more likely to have had depression at 1-month (33.3% vs 18.3%, p=0.001) (table 2.2).

Overall, 21.0% (n=117/558) of patients had depression at 1-month and 15.7% (n=72/459) at 12 months (p=0.031). Analysing only those patients who completed both the 1- and 12-month assessments the rates were 18.3% (84/459) and 15.7% (n=72/459) at 1 and 12-months respectively (p=0.295). Between 1-month and 12-months there was a greater decrease in prevalence of depression in TIA patients (18.3% to 13.9%) compared with minor stroke patients (18.3% to 18.9%), though the differences were not significant (TIA: p=0.146, minor stroke: p=0.889). When stratified by age cohorts the highest prevalence after a TIA at 1-month was in patients aged under 75 years (18.9%) but at 12-months in patients aged 75 years and older (15.7%) (figure 2.1).

Having depression at 1-month after a TIA / minor stroke was associated with a pre-morbid history of depression, (adjusted OR 2.29, 95% CI 1.42-3.69, p=0.001), reporting often feeling sad at baseline (3.24, 1.96-5.36, p<0.001) and a past history of peripheral vascular disease (2.56, 1.03-6.36, p=0.044) in a multivariate analysis (table 2.3). For the TIA patients alone depression at 1-month was additionally associated with socio-economic deprivation (2.49, 1.20-5.17, p=0.015) but not with duration or character of TIA symptoms or the ABCD2 score (table 2.4, table 2.9). Similarly depression at 1-month in the minor stroke patients was associated with reporting often feeling sad at baseline and premorbid depression but not with the mean baseline NIHSS (table 2.5, table 2.9).

Having depression at 12-months after a TIA / minor stroke in an unadjusted analysis remained associated with feeling sad at baseline, premorbid depression and socio-economic deprivation but additionally with a prior history of TIA / stroke and with depression at 1-month. However, after adjustment only depression at 1-month remained associated (aOR 13.07, 7.01-24.34,

p<0.001) (table 2.3), a relationship that was preserved for both TIA patients (14.33, 6.23-32.96, p<0.001) and minor stroke patients (12.21, 4.57-32.58, p<0.001) alone (table 2.7-2.9). Recurrent events between the 1-month and 12-month assessments were not associated with depression at 12-months (age/sex aOR 2.22, 0.89-5.54, p=0.088), though analysis was limited by low numbers (n=25/459).

Excluding patients with pre-morbid depression and those that reported feeling sad at baseline showed that 13.4% (n=47/352) at 1-month and 10.9% (n=32/294) at 12-months had depression (p=0.335). There were no baseline factors associated with depression at 1-month but the presence of depression at 1-month predicted depression at 12-months (aOR 12.32, 5.26-28.83. p<0.001) (table 2.9, Appendix XIV).

For the 459 TIA / minor stroke patients who completed up to 12-months, of those who were depressed at 1-month 54.7% were still depressed at 12-months, with similar persistence rates in TIA (51.9%) and minor stroke patients (60.0%) separately. Of those who were depressed at 12-months, 36.1% had not been depressed at 1-month (figure 2.2). Given the small number of such cases (n=26) further analysis for underlying factors associated with delayed onset depression was not attempted.

In terms of treatment, 5.4% of TIA / minor stroke patients were prescribed antidepressants at baseline, 7.9% at 1-month and 7.9% at 12-months. Of the 84 patients with depression at 1-month, only 13.1% were on an antidepressant at 1-month and only 15.5% were on an antidepressant at 12-months. Prescription of psychological therapies was not recorded.

2.4.2 Systematic Review and Meta-Analysis

The search of electronic databases identified 511 articles (including 114 duplicates) of which 15 were eligible for inclusion, with an additional 4 studies identified through hand-searching references of relevant review articles (figure 2.3, table 2.10).[11-29]

The most frequent reason for exclusion after the full text review was the inability to isolate the TIA data from a TIA / stroke population accounting for 38% (21 of 54) of exclusions (Appendix

XV). Of the 19 studies included 16 were cohort studies and 3 were cross-sectional studies. Where stated the majority of studies used the time based World Health Organisation definition of TIA (n=10/19) with 4 of the 19 studies using a tissue-based (negative brain imaging) definition. However, pooled prevalence rates of post TIA depression were similar irrespective of method of case definition (figure 2.5). The presence or absence of a pre-morbid psychological disorder was described in only 5 of 19 studies. Where stated, studies that excluded pre-morbid depression had overall a lower pooled prevalence rate of post TIA depression (12.5%, 95% CI=9.2%-16.1%) compared with studies that included pre-morbid depression (15.2%, 10.1%-21.1%) though the difference was not significant (p=0.190) (figure 2.5).

The majority of studies (n=10/19) were single centre (neurovascular clinic referrals or stroke ward admissions) with patient numbers ranging from 25 to 186.[18,16] Three studies were multi-centre based,[13,19,21] two studies were specifically focused on a sub-population (younger adults, carotid artery stenosis),[18,21] two were longitudinal studies of aging,[14-15] one a nationwide random sampling[25] and one relied on primary care coding[11]. Data on participation rates for TIA patients alone were often lacking but where provided participation ranged from 35% to 84%.[11,14] Low participation rates or lack of reporting of participation rate was identified as a major source of potential bias (figure 2.4). The majority of studies completed face-to-face assessments to assess depression but three studies relied on postal questionnaires[17,19,22] and two on telephone assessments[13,27]. The pooled prevalence of post-TIA depression using a postal questionnaire (6.0%, 2.1%-11.7%) was significantly lower (p<0.001) than that of face-to-face studies (16.6%, 12.3-21.4%) (figure 2.5). Further details of the susceptibility to bias for the included studies are presented in figure 2.4 and appendix XVI.

The most commonly utilised assessment tool was the Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), which has been validated in a stroke population,[7,29-32] and was used in 7 of the 19 studies[11,16,17,19,20,22,23] with most using the cut-off of ≥ 8 to define possible depression. One study used the higher cut-off of ≥ 11 for definite depression

explaining perhaps why that study found one of the lowest rates of depression after a TIA (5.0%).[17] Other tools used included Center for Epidemiologic Studies Depression Scale (CES-D),[14,15,26] Hamilton Rating Scale for Depression (HSRD),[18] Geriatric Depression Scale (15 GDS),[18] a version of the Beck Depression Inventory (BDI-II),[12,21] Montgomery Asberg Depression Rating Scale (MADRS),[12] a version of the Patient Health Questionnaire (PHQ-8, PHQ-9),[13,27] Major Depression Inventory (MDI),[28] Taiwanese Depression Questionnaire (TDQ)[25] and the Neuropsychiatric Inventory (NPI)[24]. Of these the MDI, TDQ and NPI have not been validated in a stroke population (table 2.11). In addition to using a standardised tool two studies also included the prescription of antidepressants as a means of capturing prevalence rates.[13,28]

In terms of generalisability of the participant population, eight studies excluded patients with prior stroke/TIA,[14-16,18,19,26,28] four studies excluded patients with pre-morbid dementia,[12,15,20,24] and two excluded patients with current or recent depression prior to the event.[15,20] Three studies excluded those with high modified Rankin scores (>2) or if they were care home residents.[11,12,22,28]

In studies that assessed TIA patients at the time of the event the pooled prevalence rate of depression was significantly heterogeneous (p het<0.001) with rates ranging from 4% to 38%.[12,19,23,26,27] In longitudinal cohort studies that reported at more than one time-point, the pooled prevalence of depression after a TIA was 19.4% acutely (0 – 1 month) decreasing to 12.8% sub-acutely (3-12 months) (p=0.006) with general agreement in the rates between studies (acutely: p het=0.270, sub-acutely: 0.782) (figure 2.6).[12,28,29] By including studies that reported at only a single time-point the pooled prevalence rates were 13.3% at 1 – 6 months[14,20,22,24,27,29] and 12.2% at 12-months[12,13,28] (p=0.450) but this increased the heterogeneity between the studies (1 – 6 months: p het=0.029, 1 year: 0.301) (figure 2.7)

There is general agreement amongst the studies that the risk of depression after a TIA is associated with a younger age, female gender, lower MMSE and socio-economic deprivation.[11-13,15,19-21] Two studies found that a recurrent (or prior) stroke / TIA was associated

with an increased risk of depression but one found it was not.[13,15,20] One study found that TOAST category did not affect rates of depression whereas another found an increased risk for large artery atherosclerosis and reduced risk for cardioembolic.[16,21] There was only one study that looked at Diffusion Weighted Imaging (DWI) status in a TIA population and found that it was not associated with risk of depression but it was limited by small numbers (only 28 DWI positive patients) (table 2.10).[23]

Three studies reported on the prevalence of depression in a minor stroke population as well as a TIA population[12,19,28]. The pooled prevalence rates of depression were similar in the first month after an event (TIA: 14.5% (2.5%-32.5%), minor stroke: 19.9% (5.0%-40.4%)). However, the prevalence differed by 12-months (TIA: 11.4% (8.8%-14.4%), minor stroke: 21.4% (17.0-26.1%)). To account for differences in study design pooled odds ratios were calculated instead which found similar results. Acutely (0-1 months) there was no significant difference between the risk of depression after a TIA compared with a minor stroke (OR=0.74, 95% CI=0.52-1.03, p=0.078) though there was by 12-months (OR=0.46, 0.31-0.68, p<0.001) (figure 2.8).

Seven studies reported on the prevalence of depression in a matched control population finding rates ranging from 0%-15% in controls.[14-16,18,19,25,26] One study, which found a prevalence rate of 1.3% in the control population (versus 4% in TIA patients), also reported that TIA patients scored a mean 0.51 points higher on the HADS-D scale at baseline and 0.96 points higher at 12 months.[19] Two studies, reporting cross-sectionally, found that TIA patients had a more than doubled risk of a depression disorder compared to matched controls.[14,25]

2.5 Discussion

The systematic review and population-based study evaluated the results from 19 studies and the Oxford Vascular Study to describe and update what is currently known about the prevalence of depression in the first year after a TIA compared with a minor stroke.

In the acute time period after a TIA the pooled prevalence of depression after a TIA was 19.4% which is lower than the reported pooled prevalence rate after (any) stroke of 29%.[1] However, in my meta-analysis the rate of depression after a TIA was similar to that after a minor stroke. By 3 – 12 months though the prevalence of depression after a TIA had decreased to 12.8% and was less than that of the minor stroke population.

The prevalence rates in the meta-analysis were generally lower than those found in the Oxford Vascular Study population which is likely due to multiple reasons. Studies in the meta-analysis, were in general, limited by low participation rates which may be due to selective bias as those with depressive disorders could perhaps be more apathetic about study engagement, therefore underestimating prevalence rates. This was likely to be particularly exacerbated by those studies reliant on postal questionnaires rather than in-person assessments perhaps explaining the significant difference in the pooled prevalence rates. The methods, and therefore the high participation rate, of the Oxford Vascular Study made it less vulnerable to the selective attrition that could be associated with longitudinal studies of depression. Furthermore, the Oxford Vascular Study population had fewer exclusions and as such the results are perhaps more generalisable, than the other studies in the analysis.

In the general population, the duration of a depressive episode is estimated to last 20 weeks on average with up to 70% recovering within 12-months. [37,38] However, in the Oxford Vascular Study whilst there was a general improvement in the prevalence rate of depression over half of the patients that had been depressed at 1-month still remained depressed at 12-months. What is not clear from this study, and the systematic review, is whether the persistence is due to a brain lesion effect (e.g. DWI positive cerebrovascular events) or due to other unknown factors (such as the impact of chronic illnesses of persistence of depression).

There were some shared susceptibility factors for depression after a TIA compared with after a minor stroke: pre-morbid depression and self-reporting feeling sad at baseline. However, for the TIA population alone socio-economic deprivation was associated. In contrast to other studies in the review, the Oxford Vascular Study results did not find an association between

age and depression after an event. Whilst other studies have found that younger age is associated with depression after a TIA, in the general population there are two peaks in the prevalence rates – the first between the second and third decade and the second in the fifth and sixth decades.[39] Furthermore, the Global Burden of Disease survey in 2017 found the prevalence of depressive disorders in those under 70 years to be 3.4% but 6.2% in those over 70 years.[40]

In the Oxford Vascular Study population the presence of premorbid depression was strongly associated with depression after a TIA. However, in the meta-analysis less than half the studies took pre-morbid symptoms into account. By including those with pre-morbid depression in this study it was not subsequently possible to say whether the psychological impairment was new onset related to the TIA or whether it was ongoing premorbid distress. However, studies that excluded patients with recent or current depression whilst they may be able to deduce the risk associated with the TIA itself, will underestimate the prevalence in an unselected population and not be able to describe the potential impact of pre-morbid psychological disorders on the risk of post event depression.

In the Oxford Vascular Study the rate of prescription of antidepressants after a minor stroke / TIA was low. Similarly, El Husseini et al found in their secondary analysis of the AVAIL study that only 30% of TIA patients with persistent depression (at 3 and 12 months) were prescribed an antidepressant.[13] However, this does not take into account any potential sign-posting towards psychological therapies, such as cognitive behavioural therapy, which are first line for mild to moderate episodes of depression.[41]

A limitation of the results in the Oxford Vascular Study population, and indeed many studies in the meta-analysis, is that the non-completers of follow-up were not matched with those that did complete and had higher rates of some baseline variables subsequently found to be associated with post-event anxiety and / or depression. The selective attrition of more depressed patients after 1-month may mean that potentially the study is at risk of under-estimating the 12-month prevalence rate (though this would impact less on the TIA versus

minor stroke analysis). The loss of the more depressed subset from a study is particularly of concern clinically especially given the complex interplay of psychological disorders and risk of further vascular events potentially increasing that subsets' morbidity and mortality.[42-43] Furthermore, the low rate of recurrent events between the two assessments in the Oxford Vascular Study population limited the ability to assess of the impact of these on the prevalence rate of depression. A larger study is required to answer this question.

2.6 Conclusion

The early prevalence of depression after a TIA is similar to that after a minor stroke suggesting psychological resources should be equally focused on both populations, particularly in those with pre-morbid depression. However, reassuringly by 12-months there do appear to be lower rates of post-event depression in the TIA population. Whilst there are some shared susceptibility factors for depression after a TIA compared with a minor stroke the additional predictive factors in TIA patients (e.g. socio-economic deprivation) and its diverging 12-month prevalence rate may suggest a differing underlying pathophysiology.

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Reason	Reason for not completing 1-month assessment % (n)	Reason for not completing 12-month assessment % (n)
Reason not given	33.0% (34)	39.3% (39)
Patient refused	15.5% (16)	6.1% (6)
Withdrew from study	10.7% (11)	27.2% (27)
Time constraints	10.7% (11)	1.0% (1)
Felt to be inappropriate	10.7% (11)	3.0% (3)
Lost contact	7.8% (8)	8.1% (8)
Language issue	6.8% (7)	1.0% (1)
Other (e.g. recent bereavement)	3.9% (4)	2.0% (2)
Aphasia	1.0% (1)	0
Died prior to follow-up	0	11.1% (11)
Advanced dementia	0	1.0% (1)
Total	**103**	**99**

Table 2.1 Reasons for the 103 patients who did not complete the 1-month assessment and the 99 patients that completed the 1-month but not the 12-month assessment.

	Completed at least 1 month of follow up	Did not complete 1 month of f/u	p value*	Completed 12 months of follow-up	Completed 1 but not 12 months of follow-up	p value**
Overall, n (%) of total eligible	558 (84.4)	103 (15.6)		459 (69.4)	99 (15.0)	
TIA alone	354 (87.0)	53 (13.0)	n/a	295 (72.4)	59 (14.5)	n/a
Minor stroke alone	204 (80.3)	50 (19.7)		164 (64.5)	40 (15.7)	
Age at event, mean (s.d)	69.5 (14.1)	73.0 (14.5)	**0.021**	69.4 (13.6)	70.0 (16.2)	0.690
TIA alone	70.0 (14.5)	73.0 (14.6)	0.133	70.2 (12.7)	69.1 (16.2)	0.619
Minor stroke alone	68.7 (15.3)	73.1 (14.5)	0.067	68.0 (15.0)	71.5 (16.3)	0.203
Female sex, n (%)	278 (49.8)	67 (65.0)	**0.005**	224 (48.8)	54 (54.5)	0.304
TIA alone	179 (50.6)	33 (62.3)	0.112	148 (50.2)	31 (52.5)	0.747
Minor stroke alone	99 (48.5)	34 (68.0)	**0.014**	76 (46.3)	23 (57.5)	0.205
Pre-morbid depression, n (%)[$]	147 (26.4)	35 (34.0)	0.113	120(26.2)	27 (27.3)	0.822
TIA alone	92 (26.0)	16 (30.2)	0.519	77 (26.1)	15 (25.4)	0.911
Minor stroke alone	55 (27.1)	19 (38.0)	0.130	43 (26.4)	12 (30.0)	0.908
SED, mean IMD (s.d)	10.7 (7.2)	11.1 (7.3)	0.656	10.6 (6.7)	11.6 (9.1)	0.175
TIA alone	10.6 (6.9)	11.6 (8.0)	0.307	10.3 (6.1)	12.0 (9.9)	0.088
Minor stroke alone	11.1 (7.7)	10.5 (6.5)	0.653	11.0 (7.7)	11.2 (7.8)	0.925
Hypertension, n (%)	307 (55.0)	65 (63.1)	0.128	250 (54.5)	57 (57.6)	0.573
TIA alone	165 (46.6)	35 (66.0)	0.103	156 (52.9)	33 (55.9)	0.668
Minor stroke alone	118 (57.8)	30 (60.0)	0.873	94 (57.3)	24 (60.0)	0.758
Hyperlipidaemia, n (%)	190 (34.1)	36 (35.0)	0.859	153 (33.3)	37 (37.4)	0.442
TIA alone	116 (32.0)	20 (37.7)	0.533	95 (32.2)	21 (35.6)	0.613
Minor stroke alone	74 (36.3)	16 (32.0)	0.623	58 (35.4)	16 (40.0)	0.585
Atrial fibrillation, n (%)	64 (11.5)	16 (15.5)	0.245	45 (9.8)	19 (19.2)	**0.008**
TIA alone	39 (11.0)	6 (11.3)	1.00	28 (9.5)	11 (18.6)	**0.040**
Minor stroke alone	25 (12.3)	10 (20.0)	0.171	17 (10.4)	8 (20.0)	0.096
Previous TIA / stroke, n (%)	6 (1.1)	3 (2.9)	0.139	6 (1.3)	0 (0)	0.253
TIA alone	4 (1.1)	2 (3.8)	0.177	4 (1.4)	0 (0)	0.368
Minor stroke alone	2 (1.0)	1 (2.0)	0.483	2 (1.2)	0 (0)	0.483
Diabetes mellitus, n (%)	83 (14.9)	15 (14.6)	0.935	61 (13.3)	22 (22.2)	**0.029**
TIA alone	44 (12.4)	8 (15.1)	0.658	34 (11.5)	10 (16.9)	0.249
Minor stroke alone	39 (19.1)	7 (14.0)	0.539	27 (16.5)	12 (30.0)	0.051
Peripheral vascular disease, n (%)	25 (4.5)	4 (3.9)	0.786	18 (3.9)	7 (7.1)	0.170
TIA alone	12 (3.4)	3 (5.7)	0.427	10 (3.4)	2 (3.4)	1.000
Minor stroke alone	13 (6.4)	1 (2.0)	0.315	8 (4.9)	5 (12.5)	0.077
IHD/ angina, n (%)	67 (12.0)	22 (21.4)	**0.011**	52 (11.3)	15 (15.2)	0.306
TIA alone	42 (11.9)	13 (24.5)	**0.017**	34 (11.5)	8 (13.6)	0.659
Minor stroke alone	25 (12.3)	9 (18.0)	0.352	18 (11.0)	7 (17.5)	0.259
Current / prior smoking, n (%)	287 (51.4)	59 (57.3)	0.271	239 (52.1)	48 (48.5)	0.516
TIA alone	176 (49.7)	33 (62.3)	0.087	146 (49.5)	30 (50.8)	0.856
Minor stroke alone	111 (54.4)	26 (52.0)	0.761	93 (56.7)	18 (45.0)	0.184
Education <12 years, n (%)[$]	292 (52.4)	51 (50.5)	0.725	233 (50.8)	59 (60.2)	0.091
TIA alone	174 (49.3)	27 (51.9)	0.727	140 (47.5)	34 (58.6)	0.123
Minor stroke alone	118 (57.8)	24 (49.0)	0.266	93 (56.7)	25 (62.5)	0.506
TIA (ABCD2 score≥4), n (%)	189 (54.0)	26 (51.0)	0.689	158 (53.6)	31 (54.4)	0.912
Minor stroke (NIHSS) mean, s.d	1.1 (1.2)	1.4 (1.3)	0.120	1.1 (1.2)	1.1 (1.2)	0.875
Depression at 1 month, n (%)	117 (21.0)			84 (18.3)	33 (33.3)	**0.001**
TIA alone	69 (19.5)	n/a	n/a	54 (18.3)	15 (25.4)	0.209
Minor stroke alone	48 (23.5)			30 (18.3)	18 (45.0)	**0.004**

Table 2.2 Comparison of the patients that completed no follow-up versus at least 1 month of follow up, and those that completed 12 months versus those that completed 1 but not 12 months of follow up. p value for difference between completing *1 month of follow up and no follow-up and **all follow up and only 1 month of follow-up. [$]Missing data (1 x pre-morbid depression history, 3 x education history, 3 x ABCD2 scores, 4 x NIHSS). SED=socio-economic deprivation, IMD=indices of multiple deprivation IHD=ischaemic heart disease NIHSS= National Institutes of Health Stroke Scale.

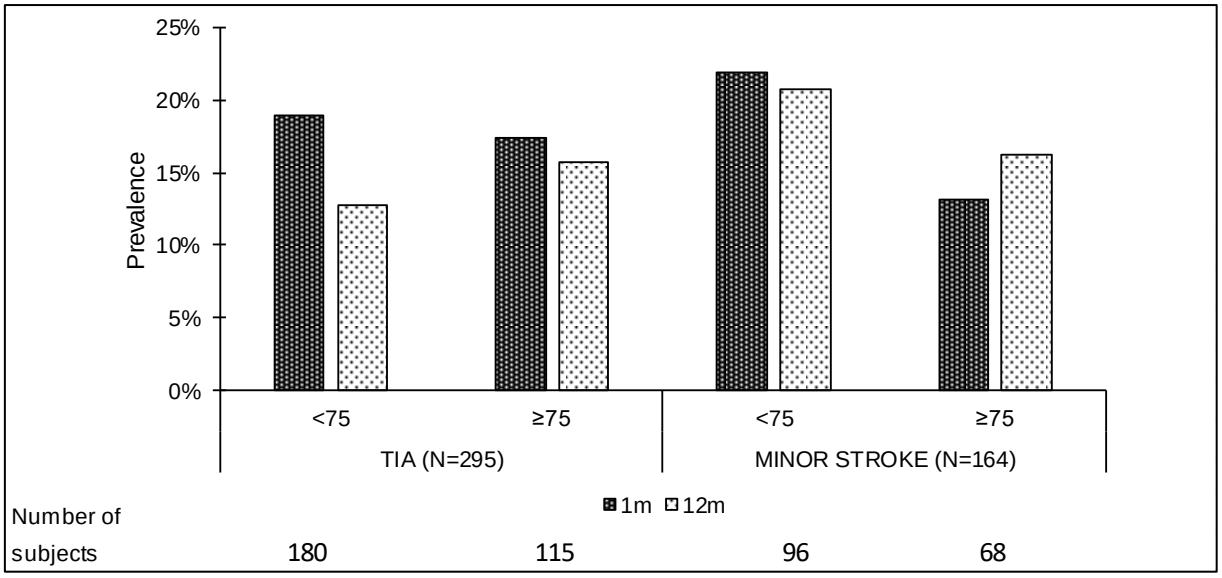

Figure 2.1 Prevalence of depression in the first year after a TIA / minor stroke stratified by age cohorts (<75 years, ≥75 years). Data for the 459 patients that completed both the 1 month and 12 month assessments presented. The difference between the prevalence rates at 1-month compared with 12-months were not significant for all the subsets (all p>0.05).

Baseline variable	All	Depression at 1 month	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	278 (49.8)	64 (54.7)	214 (48.5)	1.28 (0.85-1.93)	0.236	1.30 (0.86-1.97)	0.209	1.06 (0.68-1.67)	0.796
Mean age at event (s.d)	69.5 (14.1)	69.0 (16.2)	69.7 (13.5)	1.00 (0.98-1.01)	0.662	1.00 (0.98-1.01)	0.546	1.00 (0.98-1.02)	0.938
Sad at baseline (%)*	98 (18.1)	42 (37.8)	56 (13.0)	4.08 (2.53-6.56)	**<0.001**	4.04 (2.50-6.50)	**<0.001**	3.24 (1.96-5.36)	**<0.001**
Premorbid depression (%)	147 (26.4)	51 (43.6)	96 (21.8)	2.77 (1.80-4.26)	**<0.001**	2.71 (1.76-4.20)	**<0.001**	2.29 (1.42-3.69)	**0.001**
$ABCD2 ≥ 4 (%)*	189 (53.7)	36 (52.2)	153 (54.1)	0.93 (0.55-1.57)	0.778	0.95 (0.54-1.65)	0.848	-	
$Symptoms > 1 hour (%)*	149 (42.2)	27 (39.1)	122 (43.0)	0.85 (0.50-1.44)	0.534	0.88 (0.51-1.50)	0.630	-	
$Isolated speech symptoms (%)	88 (24.9)	21 (30.4)	67 (23.5)	1.42 (0.80-2.55)	0.234	1.45 (0.80-2.62)	0.218	-	
$Weakness symptoms (%)	98 (27.7)	19 (27.5)	79 (27.7)	0.99 (0.55-1.79)	0.976	1.02 (0.56-1.84)	0.950	-	
%Mean NIHSS (s.d)	1.1 (1.2)	1.4 (1.2)	1.1 (1.2)	1.28 (0.80-3.00)	0.200	1.28 (0.98-1.67)	0.072	-	
Smoking – current/prior (%)	287 (51.4)	63 (53.8)	224 (50.8)	1.13 (0.75-1.70)	0.557	1.21 (0.79-1.84)	0.382	-	
Hypertension	307 (55.0)	62 (53.0)	245 (55.6)	0.90 (0.60-1.36)	0.620	0.93 (0.60-1.44)	0.742	-	
Hyperlipidaemia	190 (34.1)	36 (30.8)	154 (34.9)	0.83 (0.53-1.28)	0.400	0.87 (0.56-1.37)	0.553	-	
Atrial fibrillation	64 (11.5)	15 (12.8)	49 (11.1)	1.18 (0.63-2.18)	0.606	1.25 (0.66-2.37)	0.490	-	
Diabetes mellitus	83 (14.9)	20 (17.1)	63 (14.3)	1.24 (0.71-2.15)	0.449	1.29 (0.74-2.25)	0.369	-	
Peripheral vascular disease	25 (4.5)	9 (7.7)	16 (3.6)	2.21 (0.95-5.15)	0.065	2.46 (1.04-5.80)	**0.041**	2.56 (1.03-6.36)	**0.044**
IHD / angina	67 (12.0)	14 (12.0)	53 (12.0)	1.00 (0.53-1.86)	0.988	1.08 (0.57-2.07)	0.806	-	
Past history of TIA / stroke	6 (1.1)	2 (1.7)	4 (0.9)	1.90 (0.34-10.50)	0.462	1.90 (0.34-10.62)	0.463	-	
Low education (%)*	292 (52.4)	65 (55.6)	227 (51.5)	1.17 (0.78-1.77)	0.446	1.20 (0.79-1.81)	0.398	-	
Socio-economic deprivation (%)	75 (13.4)	23 (19.7)	52 (11.8)	1.83 (1.07-3.14)	**0.028**	1.81 (1.04-3.12)	**0.033**	1.71 (0.94-3.09)	0.077

Table 2.3 Baseline characteristics of TIA / minor stroke patients stratified by their subsequent 1-month (n=558) presence or absence of depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 1 month also included. (*missing data = 16 baseline feeling sad, 2 ABCD2 scores, 1 TIA symptom duration, 3 NIHSS, 1 pre-morbid depression history and 1 education history). $For TIA patients only. %For minor stroke patients only.

Baseline variable	All	Depression at 1 month	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	179 (50.6)	41 (59.4)	138 (48.4)	1.56 (0.92-2.66)	0.103	1.59 (0.93-2.72)	0.092	1.41 (0.81-2.46)	0.995
Mean age at event (s.d)	70.0 (13.4)	69.6 (16.3)	70.1 (12.6)	1.00 (0.98-1.02)	0.761	1.00 (0.98-1.02)	0.599	1.00 (0.81-2.46)	0.228
Sad at baseline (%)*	59 (17.0)	25 (37.9)	34 (12.1)	4.43 (2.40-8.18)	**<0.001**	4.47 (2.41-8.30)	**<0.001**	1.26 (1.06-1.50)	**0.009**
Premorbid depression (%)	92 (26.0)	27 (39.1)	65 (22.8)	2.18 (1.25-3.80)	**0.006**	2.07 (1.18-3.64)	**0.011**	1.99 (1.12-3.54)	**0.019**
ABCD2 ≥ 4 (%)*	189 (53.7)	36 (52.2)	153 (54.1)	0.93 (0.55-1.57)	0.778	0.95 (0.54-1.65)	0.848	-	-
Symptoms > 1 hour (%)*	149 (42.2)	27 (39.1)	122 (43.0)	0.85 (0.50-1.44)	0.534	0.88 (0.51-1.50)	0.876	-	-
Isolated speech symptoms (%)	88 (24.9)	21 (30.4)	67 (23.5)	1.42 (0.80-2.55)	0.234	1.45 (0.80-2.62)	0.218	-	-
Weakness symptoms (%)	98 (27.7)	19 (27.5)	79 (27.7)	0.99 (0.55-1.79)	0.976	1.02 (0.56-1.84)	0.950	-	-
Smoking – current/prior (%)	176 (49.7)	33 (47.8)	143 (50.2)	0.91 (0.54-1.54)	0.726	1.01 (0.58-1.74)	0.977	-	-
Hypertension	189 (53.4)	33 (47.8)	156 (54.7)	0.76 (0.45-1.28)	0.303	0.76 (0.43-1.35)	0.351	-	-
Hyperlipidaemia	116 (32.8)	22 (31.9)	94 (33.0)	0.95 (0.54-1.67)	0.862	1.04 (0.58-1.84)	0.908	-	-
Atrial fibrillation	39 (11.0)	10 (14.5)	29 (10.2)	1.50 (0.69-3.24)	0.307	1.64 (0.74-3.64)	0.223	-	-
Diabetes mellitus	44 (12.4)	8 (11.6)	36 (12.6)	0.91 (0.40-2.05)	0.815	0.97 (0.42-2.20)	0.936	-	-
Peripheral vascular disease	12 (3.4)	3 (4.3)	9 (3.2)	1.39 (0.37-5.29)	0.626	1.65 (0.42-6.46)	0.476	-	-
IHD / angina	42 (11.9)	9 (13.0)	33 (11.6)	1.15 (0.52-2.52)	0.736	1.35 (0.60-3.08)	0.470	-	-
Past history of TIA / stroke	4 (1.1)	1 (1.4)	3 (1.1)	1.38 (0.14-13.50)	0.781	1.30 (0.13-12.89)	0.823	-	-
Low education (%)*	174 (49.3)	34 (49.3)	140 (49.3)	1.00 (0.59-1.69)	0.998	1.01 (0.59-1.72)	0.967	-	-
Socio-economic deprivation (%)	41 (11.6)	14 (20.3)	27 (9.5)	2.43 (1.20-4.94)	**0.014**	2.33 (1.14-4.78)	**0.021**	2.49 (1.20-5.17)	**0.015**

Table 2.4 Baseline characteristics of TIA patients stratified by their subsequent 1-month (n=354) presence or absence of depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 1-month also included. (*Missing data: 7 baseline feeling sad, 2 ABCD2 scores, 1 TIA symptom duration, and 1 education history).

Baseline variable	All	Depression at 1 month	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	99 (48.5)	23 (47.9)	76 (48.7)	0.97 (0.51-1.85)	0.923	0.98 (0.51-1.88)	0.949	0.53 (0.25-1.15)	0.110
Mean age at event (s.d)	68.7 (15.3)	68.2 (16.3)	68.8 (15.0)	1.00 (0.98-1.02)	0.810	1.00 (0.98-1.02)	0.819	1.01 (0.99-1.04)	0.279
Sad at baseline (%)*	39 (20.0)	17 (37.8)	22 (14.7)	3.53 (1.66-7.51)	**0.001**	3.91 (1.79-8.53)	**0.001**	2.59 (1.12-5.99)	**0.027**
Premorbid depression (%)*	55 (27.8)	24 (50.0)	31 (20.0)	4.00 (2.01-7.97)	**<0.001**	4.30 (2.10-8.79)	**<0.001**	3.61 (1.64-7.95)	**0.001**
Mean NIHSS (s.d)	1.1 (1.2)	1.4 (1.2)	1.1 (1.2)	1.28 (0.98-1.67)	0.075	1.21 (0.93-1.58)	0.153	-	-
Smoking – current/prior (%)	111 (54.4)	30 (62.5)	81 (51.9)	1.54 (0.80-3.00)	0.200	1.57 (0.79-3.09)	0.196	-	-
Hypertension	118 (57.8)	29 (60.4)	89 (57.1)	1.15 (0.59-2.22)	0.680	1.19 (0.60-2.35)	0.625	-	-
Hyperlipidaemia	74 (36.3)	14 (29.2)	60 (38.5)	0.66 (0.33-1.33)	0.243	0.65 (0.31-1.34)	0.240	-	-
Atrial fibrillation	25 (12.3)	5 (10.4)	20 (12.8)	0.79 (0.28-2.23)	0.658	0.80 (0.27-2.37)	0.693	-	-
Diabetes mellitus	39 (19.1)	12 (25.0)	27 (17.3)	1.59 (0.74-3.45)	0.239	1.60 (0.74-3.49)	0.236	-	-
Peripheral vascular disease	13 (6.4)	6 (12.5)	7 (4.5)	3.04 (0.97-9.54)	0.057	3.15 (0.99-9.99)	0.052	-	-
IHD / angina	25 (12.3)	5 (10.4)	20 (12.8)	0.79 (0.28-2.23)	0.658	0.80 (0.28-2.30)	0.676	-	-
Past history of TIA / stroke	2 (1.0)	1 (2.1)	1 (0.6)	3.30 (0.20-53.74)	0.402	3.41 (0.21-56.09)	0.391	-	-
Low education (%)	118 (57.8)	31 (64.6)	87 (55.8)	1.45 (0.75-2.83)	0.281	1.48 (0.75-2.92)	0.259	-	-
Socio-economic deprivation (%)	34 (16.7)	9 (18.8)	25 (16.0)	1.21 (0.52-2.81)	0.658	1.20 (0.51-2.79)	0.675	-	-

Table 2.5 Baseline characteristics of minor stroke patients stratified by their subsequent 1-month (n=204) presence or absence of depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 1-month also included. (*Missing data: 1 month = 9 baseline feeling sad and 1 pre-morbid depression history).

Baseline variable	All	Depression at 12 months	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	224 (48.8)	34 (47.2)	190 (49.1)	0.93 (0.56-1.54)	0.770	0.94 (0.57-1.56)	0.811	0.74 (0.40-1.38)	0.347
Mean age at event (s.d)	69.4 (13.6)	68.6 (16.6)	69.6 (13.0)	1.00 (0.98-1.01)	0.561	1.00 (0.98-1.01)	0.578	1.00 (0.98-1.02)	0.946
Sad at baseline (%)*	75 (16.7)	23 (33.3)	52 (13.7)	3.14 (1.76-5.62)	**<0.001**	3.17 (1.77-5.68)	**<0.001**	1.84 (0.89-3.82)	0.100
Premorbid depression (%)*	120 (26.2)	28 (38.9)	92 (23.8)	2.03 (1.20-3.45)	**0.008**	2.06 (1.21-3.52)	**0.008**	1.13 (0.57-2.24)	0.718
$ABCD2 ≥ 4 (%)	158 (53.6)	26 (63.4)	132 (52.0)	1.60 (0.81-3.17)	0.175	1.77 (0.86-3.66)	0.121	-	
$Symptoms > 1 hour (%)	130 (44.1)	21 (51.2)	109 (42.9)	1.36 (0.71-2.60)	0.352	1.41 (0.73-2.74)	0.307	-	
$Isolated speech symptoms (%)	71 (24.1)	13 (31.7)	58 (22.8)	1.57 (0.76-3.22)	0.220	1.61 (0.78-3.33)	0.200	-	
$Weakness symptoms (%)	82 (27.8)	14 (34.1)	68 (26.8)	1.42 (0.70-2.86)	0.330	1.44 (0.71-2.90)	0.315	-	
%Mean NIHSS (s.d)	1.1 (1.2)	1.4 (1.4)	1.1 (1.1)	1.25 (0.91-1.74)	0.173	1.29 (0.93-1.80)	0.132	-	
Smoking – current/prior (%)	239 (52.1)	41 (56.9)	198 (51.2)	1.26 (0.76-2.10)	0.368	1.25 (0.75-2.10)	0.392	-	
Hypertension	250 (54.5)	42 (58.3)	208 (53.7)	1.21 (0.72-2.01)	0.473	1.30 (0.76-2.22)	0.344	-	
Hyperlipidaemia	153 (33.3)	23 (31.9)	130 (33.6)	0.93 (0.54-1.59)	0.785	0.94 (0.54-1.63)	0.828	-	
Atrial fibrillation	45 (9.8)	7 (9.7)	38 (9.8)	0.99 (0.42-2.31)	0.980	1.02 (0.43-2.43)	0.958	-	
Diabetes mellitus	61 (13.3)	8 (11.1)	53 (13.7)	0.79 (0.36-1.74)	0.554	0.78 (0.35-1.72)	0.539	-	
Peripheral vascular disease	18 (3.9)	3 (4.2)	15 (3.9)	1.08 (0.30-3.82)	0.907	1.10 (0.31-3.96)	0.880	-	
IHD / angina	52 (11.3)	8 (11.1)	44 (11.4)	0.97 (0.44-2.17)	0.949	1.00 (0.44-2.27)	0.997	-	
Past history of TIA / stroke	6 (1.3)	3 (4.2)	3 (0.8)	5.57 (1.10-28.14)	**0.038**	6.05 (1.18-31.01)	**0.031**	6.42 (0.85-48.47)	0.072
Low education (%)	233 (50.8)	42 (58.3)	191 (49.4)	1.44 (0.86-2.39)	0.163	1.47 (0.88-2.45)	0.144	-	
Socio-economic deprivation (%)	60 (13.1)	17 (23.6)	43 (11.1)	2.47 (1.32-4.64)	**0.005**	2.46 (1.30-4.66)	**0.006**	1.98 (0.91-4.28)	0.083
Depression at 1 month	84 (18.3)	46 (63.9)	38 (9.8)	16.25 (9.04-29.20)	**<0.001**	16.37 (9.09-29.49)	**<0.001**	13.07 (7.01-24.34)	**<0.001**
Recurrent event between 1-12 months	25 (5.4)	7 (9.7)	18 (4.7)	2.01 (0.89-5.50)	0.089	2.22 (0.89-5.54)	0.088	-	

Table 2.6 Baseline characteristics of TIA / minor stroke patients stratified by their subsequent 12-month (n=459) presence or absence of depression. Depression at 1-month and recurrent events between the one and 12-month assessments also included. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 12-months also included. (*12 month missing data = 11 baseline feeling sad, 1 pre-morbid depression history). $For TIA patients only. %For minor stroke patients only.

Baseline variable	All	Depression at 12 months	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	148 (50.2)	21 (51.2)	127 (50.0)	0.95 (0.49-1.84)	0.885	1.06 (0.55-2.06)	0.858	0.73 (0.32-1.67)	0.456
Mean age at event (s.d)	70.1 (12.7)	69.5 (16.9)	70.3 (12.0)	1.00 (0.97-1.02)	0.722	1.00 (0.97-1.02)	0.711	1.00 (0.97-1.03)	0.876
Sad at baseline (%)*	46 (15.9)	13 (33.3)	33 (13.1)	3.30 (1.55-7.06)	**0.002**	3.27 (1.53-6.99)	**0.002**	1.61 (0.62-4.21)	0.328
Premorbid depression (%)	77 (26.1)	16 (39.0)	61 (24.0)	2.03 (1.02-4.04)	**0.045**	2.02 (1.01-4.05)	**0.048**	1.34 (0.56-3.19)	0.513
ABCD2 ≥ 4 (%)	158 (53.6)	26 (63.4)	132 (52.0)	1.60 (0.81-3.17)	0.175	1.77 (0.86-3.66)	0.121	-	-
Symptoms > 1 hour (%)	130 (44.1)	21 (51.2)	109 (42.9)	1.36 (0.71-2.60)	0.352	1.41 (0.73-2.74)	0.307	-	-
Isolated speech symptoms (%)	71 (24.1)	13 (31.7)	58 (22.8)	1.57 (0.76-3.22)	0.220	1.61 (0.78-3.23)	0.200	-	-
Weakness symptoms (%)	82 (27.8)	14 (34.1)	68 (26.8)	1.42 (0.70-2.86)	0.330	1.44 (0.71-2.90)	0.315	-	-
Smoking – current/prior (%)	146 (14.5)	23 (53.1)	123 (48.4)	1.36 (0.70-2.64)	0.363	1.39 (0.70-2.76)	0.341	-	-
Hypertension	156 (52.9)	22 (53.7)	134 (52.8)	1.04 (0.54-2.01)	0.914	1.10 (0.54-2.25)	0.796	-	-
Hyperlipidaemia	95 (32.2)	11 (26.8)	84 (33.1)	0.74 (0.36-1.55)	0.429	0.75 (0.36-1.59)	0.460	-	-
Atrial fibrillation	28 (9.5)	4 (9.8)	24 (9.4)	1.04 (0.34-3.16)	0.950	1.07 (0.35-3.31)	0.904	-	-
Diabetes mellitus	34 (11.5)	4 (9.8)	30 (11.8)	0.81 (0.27-2.42)	0.703	0.82 (0.27-2.47)	0.721	-	-
Peripheral vascular disease	10 (3.4)	2 (4.9)	8 (3.1)	1.58 (0.32-7.70)	0.573	1.72 (0.34-8.67)	0.514	-	-
IHD / angina	34 (11.5)	6 (14.6)	28 (11.0)	1.38 (0.54-3.58)	0.503	1.49 (0.56-4.00)	0.427	-	-
Past history of TIA / stroke	4 (1.4)	2 (4.9)	2 (0.8)	6.46 (0.88-47.21)	0.066	6.82 (0.92-50.85)	0.061	-	-
Low education (%)	140 (47.5)	24 (58.5)	116 (45.7)	1.68 (0.86-3.28)	0.129	1.71 (0.87-3.34)	0.121	-	-
Socio-economic deprivation (%)	32 (10.8)	10 (24.4)	22 (8.7)	3.40 (1.47-7.85)	**0.004**	3.44 (1.46-8.10)	**0.005**	0.88 (0.29-2.72)	0.835
Depression at 1 month	54 (18.3)	28 (68.3)	26 (10.2)	18.89 (8.72-40.91)	**<0.001**	19.35 (8.85-42.29)	**<0.001**	14.33 (6.23-32.96)	**<0.001**
Recurrent event between 1-12months	15 (5.1)	2 (4.9)	13 (5.1)	0.95 (0.21-4.38)	0.948	0.94 (0.21-4.35)	0.941	-	-

Table 2.7 Baseline characteristics of TIA patients stratified by their subsequent 12-month (n=295) presence or absence of depression. Depression at 1-month and recurrent events between the one and 12-month assessments also included. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 12-months also included (*Missing data: 12 months = 5 feeling sad at baseline).

Baseline characteristic	All	Depression at 12 months	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	76 (46.3)	13 (41.9)	63 (47.4)	1.25 (0.57-2.75)	0.585	0.81 (0.37-1.79)	0.603	0.65 (0.24-1.78)	0.404
Mean age at event (s.d)	68.0 (15.0)	67.3 (16.4)	68.2 (14.7)	1.00 (0.97-1.02)	0.756	1.00 (0.97-1.02)	0.793	1.01 (0.97-1.04)	0.769
Sad at baseline (%)*	29 (18.4)	10 (33.3)	19 (14.8)	2.87 (1.16-7.07)	**0.022**	3.20 (1.25-8.14)	**0.015**	2.49 (0.82-7.53)	0.106
Premorbid depression (%)*	43 (26.4)	12 (38.7)	31 (23.5)	2.06 (0.90-4.71)	0.087	2.14 (0.93-5.17)	0.072	-	**-**
Mean NIHSS (s.d)*	1.1 (1.2)	1.4 (1.4)	1.1 (1.1)	1.25 (0.91-1.74)	0.173	1.29 (0.93-1.80)	0.132	-	-
Smoking – current/prior (%)	96 (56.7)	18 (58.1)	75 (56.4)	1.07 (0.49-2.36)	0.866	1.04 (0.47-2.33)	0.915	-	-
Hypertension	94 (57.3)	20 (64.5)	74 (55.6)	1.45 (0.64-3.26)	0.370	1.53 (0.66-3.34)	0.317	-	-
Hyperlipidaemia	58 (35.4)	12 (38.7)	46 (34.6)	1.20 (0.53-2.38)	0.666	1.20 (0.52-2.76)	0.668	-	-
Atrial fibrillation	17 (10.4)	3 (9.7)	14 (10.5)	0.91 (0.25-3.39)	0.889	0.93 (0.24-3.62)	0.921	-	-
Diabetes mellitus	27 (16.5)	4 (12.9)	23 (17.3)	0.71 (0.23-2.22)	0.554	0.68 (0.22-2.15)	0.512	-	-
Peripheral vascular disease	8 (4.9)	1 (3.2)	7 (5.3)	0.60 (0.07-5.06)	0.639	0.57 (0.07-4.89)	0.611	-	-
IHD / angina	18 (11.0)	2 (6.5)	16 (12.0)	0.50 (0.11-2.32)	0.379	0.49 (0.11-2.30)	0.367	-	-
Past history of TIA / stroke	2 (1.2)	1 (3.2)	1 (0.8)	4.40 (0.27-72.36)	0.300	4.70 (0.28-78.84)	0.282	-	-
Low education (%)	96 (56.7)	18 (58.1)	75 (56.4)	1.07 (0.49-2.36)	0.866	1.08 (0.49-2.40)	0.844	-	-
Socio-economic deprivation (%)	28 (17.1)	7 (22.6)	21 (15.8)	1.56 (0.59-4.07)	0.368	1.52 (0.57-4.01)	0.401	-	-
Depression at 1 month	30 (18.3)	18 (58.1)	12 (9.0)	13.96 (5.52-35.31)	**<0.001**	13.88 (5.47-35.17)	**<0.001**	12.21 (4.57-32.58)	**<0.001**
Recurrent event between 1-12months	12 (7.3)	3 (9.7)	9 (6.8)	1.48 (0.38-5.81)	0.577	5.44 (1.42-20.81)	**0.013**	5.57 (1.08-28.75)	**0.040**

Table 2.8 Baseline characteristics of minor stroke patients stratified by their subsequent 12-month (n=164) presence or absence of depression. Depression at 1-month and recurrent events between the one and 12-month assessments also included. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 12-months also included. (*Missing data: 12 month = 6 feeling sad at baseline, 1 pre-morbid depression history and 2 NIHSS).

	1-month depression		12-month depression	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
(a) TIA				
Female	1.41 (0.81-2.46)	0.995	0.72 (0.31-1.66)	0.441
Increasing age	1.00 (0.81-2.46)	0.228	1.00 (0.97-1.03)	0.869
Sad at baseline	1.26 (1.06-1.50)	**0.009**	1.66 (0.64-4.35)	0.299
Premorbid depression	1.99 (1.12-3.54)	**0.019**	1.35 (0.57-3.22)	0.501
Socio-economic deprivation	2.49 (1.20-5.17)	**0.015**	2.68 (0.92-7.76)	0.070
Depression at 1-month	n/a	n/a	14.73 (6.37-34.05)	**<0.001**
Recurrent events between 1 & 12 months	n/a	n/a	0.47 (0.07-3.04)	0.427
(b) Minor stroke				
Female	0.54 (0.25-1.16)	0.113	0.66 (0.24-1.80)	0.415
Increasing age	1.01 (0.99-1.04)	0.277	1.00 (0.97-1.04)	0.790
Sad at baseline	2.57 (1.10-6.01)	**0.030**	2.58 (0.79-8.41)	0.117
Premorbid depression	3.62 (1.64-8.03)	**0.002**	0.92 (0.29-2.88)	0.117
Socio-economic deprivation	1.06 (0.40-2.79)	0.908	1.17 (0.34-4.00)	0.800
Depression at 1-month	n/a	n/a	12.41 (4.53-33.99)	**<0.001**
Recurrent event between 1 & 12 months	n/a	n/a	5.54 (1.07-28.59)	**0.041**
(c) TIA / minor stroke in the absence of a history of premorbid depression				
Female	-	-	0.63 (0.27-1.49)	0.294
Increasing age			1.01 (0.98-1.05)	0.397
Depression at 1-month	n/a	n/a	12.32 (5.26-28.83)	**<0.001**
Recurrent event between 1 & 12 months	n/a	n/a	2.15 (0.77-5.96)	0.142

Table 2.9 Summary multivariate regression analysis for the risk of depression at 1-month and 12-months after a (a) TIA, (b) minor stroke, and a (c) TIA/minor stroke in the absence of a history of premorbid depression. Adjusted for age, sex and variables that were significant (p<0.05) in age/sex adjusted model for either TIA or minor stroke patients. n/a = not applicable for 1 month adjusted model. For further details on the analysis for TIA / minor stroke patients in the absence of a history of premorbid depression refer to Appendix IV.

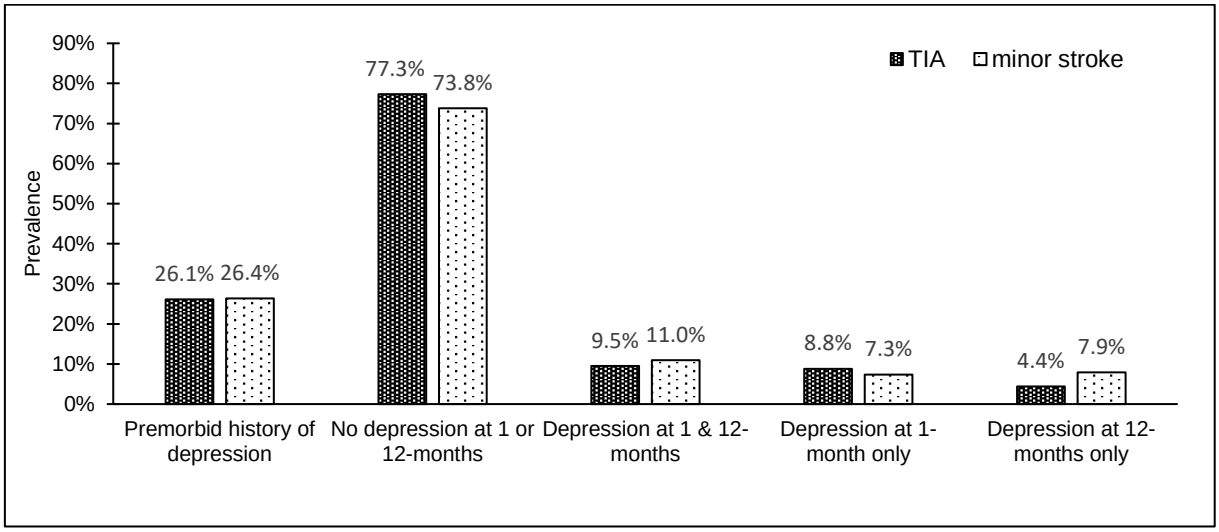

Figure 2.2: Proportion patients with persistent, transient or delayed onset depression after a TIA or minor stroke. Prevalence of patients with premorbid history of depression also included. Patients that completed both the 1-month and 12-month assessments were included. Persistent depression defined as present at both 1-month and 12-months. Transient depression defined as present at 1-month but not 12-months. Delayed onset depression defined as depression present at 12-months but absent at 1-month.

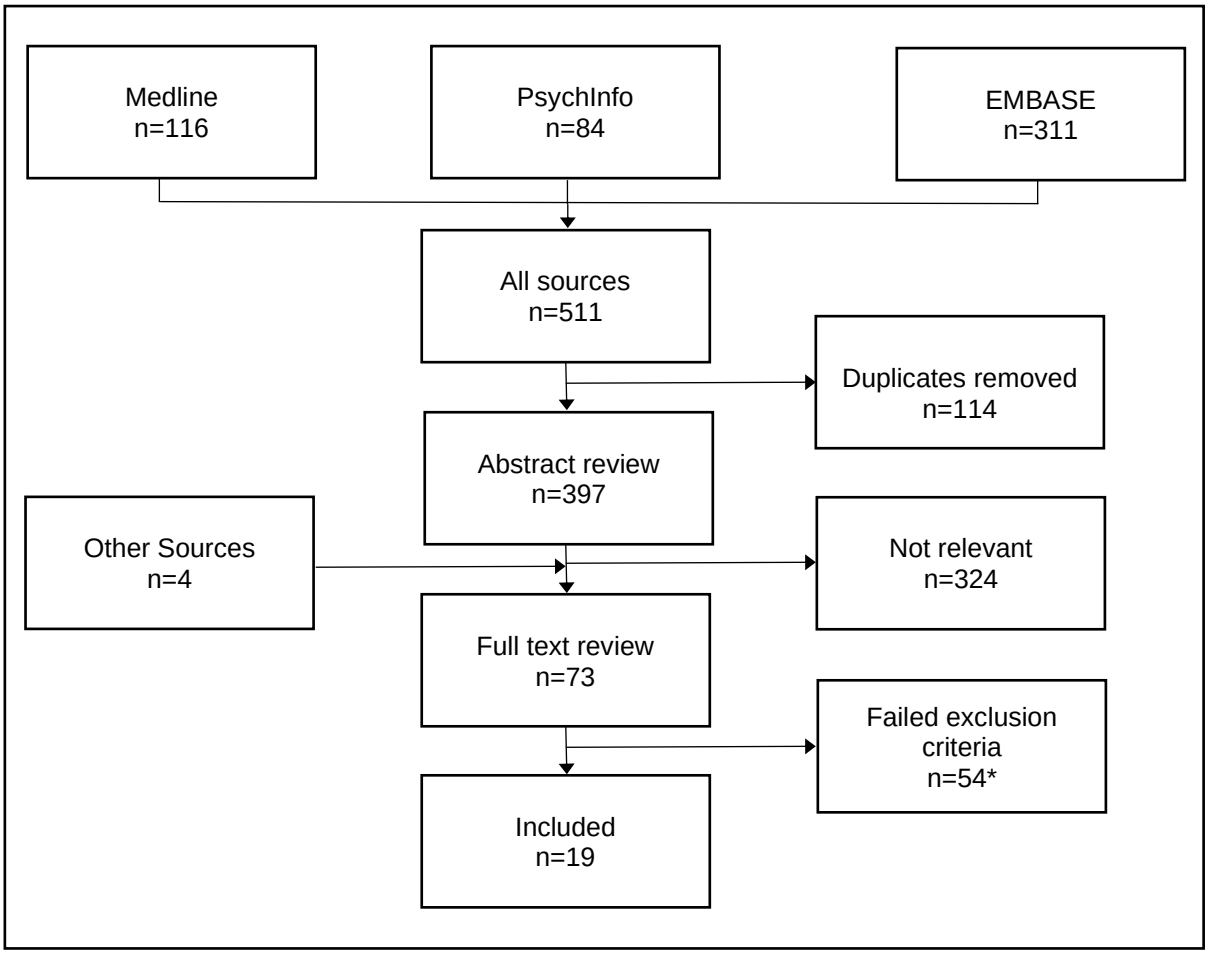

Figure 2.3 Literature search summary. *Reasons for exclusions after full text review presented in Appendix XV.

Study Author, year, location	Number of TIA subjects	Male gender	Age (mean)	Inclusion Criteria	Exclusion Criteria	Follow up time point(s) for which prevalence data presented	Measure. Cut-off	Susceptibility factors
Broomfield NM et al, 2014 UK	1247	52%	Median: 70.8	All living stroke survivors in database 2012-2013	Care home/ house bound (coding)	Cross-sectional	HADS –D. Possible: 8-10. Probable: ≥11	Younger age, socio-economic deprivation, smoking status, COPD
Carnes-Vendrell A et al, 2019 Spain	40	*Overall 72.0%	*Overall, 66.4 (11.0)	aged 18 - 85, TIA or minor stroke (=<4 on NIHSS),	modified Rankin >3, mild cognitive impairment or dementia prior to stroke, life expectancies of < 1 year, language barriers and /or illiteracy	10 days after event and 12 months	BDI-2, MADRS N/S	
El Husseini N et al, 2012 USA	397	45%	68.0	18 or older, hospitalisation with primary diagnosis of TIA or stroke, direct admission or through ED	Missing baseline data, PHQ incomplete, died prior to 12 month review	3 months and 12 months	PHQ-8. Antidepressant use at therapeutic (or higher) dose ≥10	
Hickie I et al, 2003 Australia	16	56%	66.9 (+ 10 years)	TIA in past 10 years, age <75 for men and <80 for women at baseline (10 years prior), community dwelling at baseline	Stroke in past 10 years	Cross-sectional	CES-D N/S	
Kiphuth IC et al, 2014 Germany	108	54.60%	median 70 (17)	Admitted to the stroke unit of a single centre, ABCD2 score >3 or =<2 with hemiparesis, aphasia, amaurosis fugax. Negative brain scan. Fully resolved symptoms. Rankin 0-2 before and after.	N/S	3 months	HADS-D ≥8	
Luijendijk HJ et al, 2011 Netherlands	325	42.3%	*Overall 70.0	Free of depression at baseline, aged >= 55 at enrolment in study, community dwelling at enrolment	Baseline depressive symptoms, loss to follow up, bipolar disorder, dementia, history of stroke or incident stroke after baseline assessment	Cross-sectional	CES-D leading to more detailed assessment, GP record review	Higher number of TIAs
Maaijwee NA et al, 2016 Netherlands	186	44.6%	40.5 at event, 49.2 at assessment	first ever TIA, aged 18-50	N/S	Long-term: mean 8.3 (8.1) years	HADS-D ≥8	
Naess H et al, 2012 Norway	44	65.9%	71.0	TIA	N/S	Long-term: mean 382 days (range 185-756 days)	HADS-D ≥11	
Rao R et al, 2001	25	60.0%	75.7 (7.9)	TIA with carotid artery stenosis of >70% on Doppler	Stroke, Drug or alcohol misuse, Parkinsons / head injury / epilepsy / carcinomatosis / uncontrolled metabolic,	N/S	modified HRSD, 15-GDS	Not associated with laterality or degree of

UK					endocrine or respiratory disorders, too frail, severely cognitively impaired, aphasia, lacked sufficient English.		mHRSD ≥6 GDS: N/S	carotid artery stenosis
Rizos T et al, 2018 Germany	73	63.0%	Median: 69.0	Consecutive TIA admissions to a single centre	N/S	Baseline, 3 months	PHQ-9	
Sackley CM et al, 2019 UK	364	58.8%	69.8 (11.8)	new incident, diagnosed within 14 days of event, able to self-complete postal questionnaire (deemed by stroke physician or neurologist)	history of stroke or TIA	Baseline (median 4 days from event)	HADS-D N/S	Associated with younger age
Snaphaan L et al, 2009 Netherlands	137	66.3%	61.2	acute symptomatic cerebral ischemia	Death prior to ascertainment, not able to visit the hospital 6-8 weeks later due to physical limitations, terminal diseases, chronic diseases (Parkinson's disease, dementia), epilepsy, MI, head trauma. Depressive symptoms within 1 month prior	6-8 weeks post event	HADS-D >8	Not associated with age, gender, education, recurrence, pre-morbid depression, cerebral atrophy, laterality of event.
Tanislav C et al, 2015 European	516	52.7%	N/S for TIA alone. Overall 57.3	15-55 with cerebrovascular disease event <3 months prior, cerebral MRI obtained within 1 month of inclusion	N/S	0-3 months post event	BDI ≥18	
Turner A et al, 2016 Australia	51	67%	69.4	TIA	N/S	Baseline & 3 months	PHQ-9 >9	
van Rooij FG et al, 2017 Netherlands	103 (65 TIA & 38 TNA)	*Overall 60.5%	*Overall 65.8 (9.1)	45 years and older, referred within 7 days after an acute onset neurological symptom lasting <24	Incomplete f/u.	Baseline, 6 months	HADS-D ≥8	Not associated with DWI status
Von Weitzel-Mudersbach P et al, 2011 Denmark	167	N/S	N/S	First ever TIA during last 6 months, residence in Aarhus area.	mRS >2	12 months	MDI or use of antidepressant N/A	
Wilson D et al, 2010 UK	29	47%	69	First ever TIA probable or definite confirmed with a senior stroke physician	N/S	Baseline	CES-D ≥16	

Wong A et al, 2016 China	73	39.7%	69.1	Stroke or TIA. Able to participate in cognitive assessment	Pre-event dementia, significant sensorimotor / language impairment precluding participation in testing.	3-6 months post event	Neuropsychiatric Inventory ≥1 symptom
Wu KY et al, 2010 Taiwan	295	*Overall 51.5%	*Overall 72.8 (5.9)	TIA	fully manifest stroke	Cross-sectional	Taiwanese Depression Questionnaire >19

Table 2.10. Studies reporting on prevalence and associated factors for depression after a TIA Susceptibility factors are those reported in the individual studies to be significantly associated with post TIA depression (in univariate associations). *= Data for TIA participants alone not stated, overall data (for combined TIA/stroke participants) presented where available, [&]median, [†]Van-Rooij additionally includes atypical TIAs. N/S=not specified, COPD=Chronic obstructive pulmonary disease, DWI=Diffusion-weighted imaging. HADS-D= Depression subscale of the Hospital Anxiety and Depression Scale, CES-D= Center for Epidemiologic Studies Depression Scale, HSRD= Hamilton Rating Scale for Depression, GDS= Geriatric Depression Scale, BDI= Beck Depression Inventory, MADRS= Montgomery Asberg Depression Rating Scale, PHQ= Patient Health Questionnaire, MDI= Major Depression Inventory, TDQ= Taiwanese Depression Questionnaire, NPI= Neuropsychiatric Inventory.

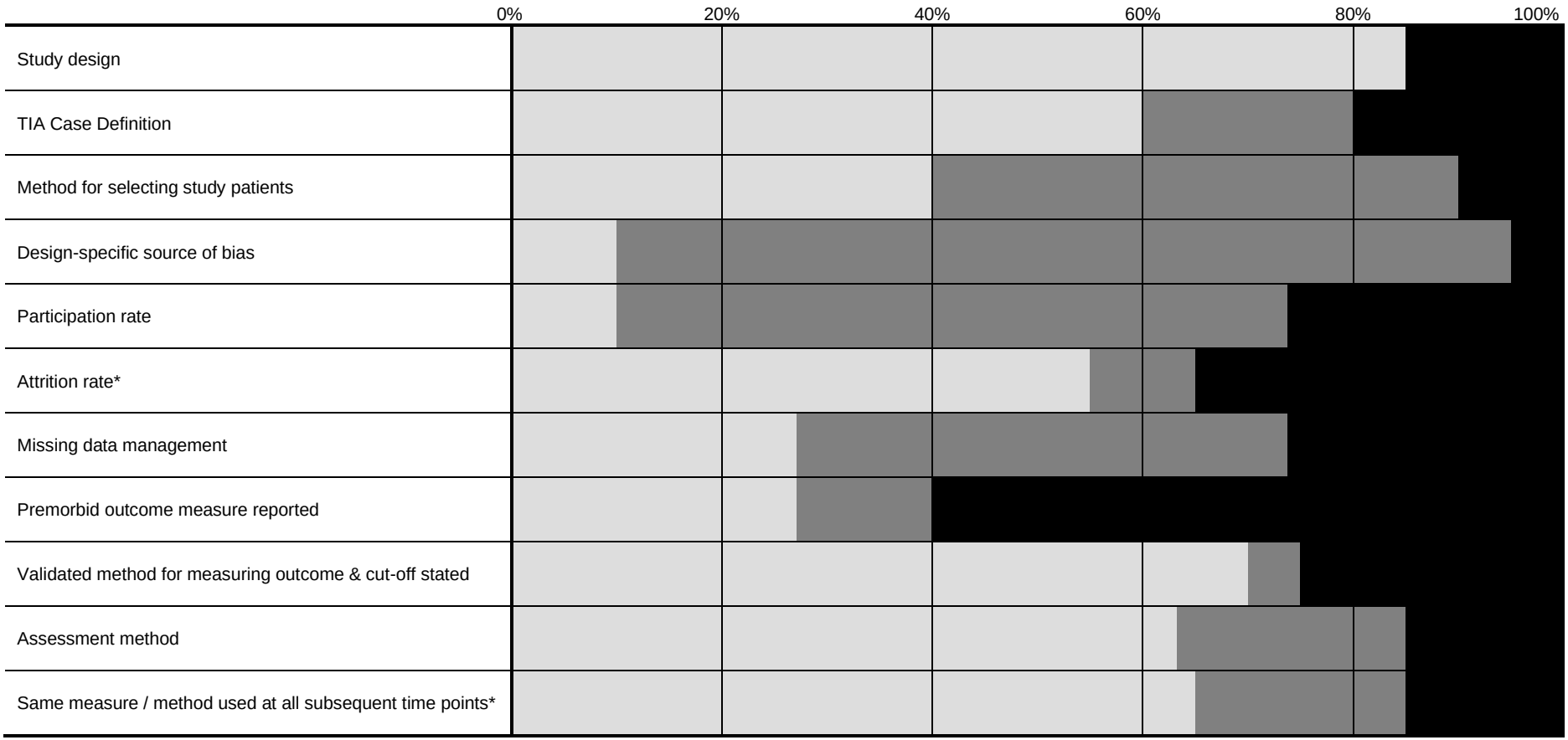

Figure 2.4 Summary figure of risk of bias for the 19 studies on post-TIA depression. Percentages represent proportion of studies with low, insufficient information or high risk of bias for each risk of bias variable. For further details on individual studies refer to Appendix XVI. *includes only studies where data presented for more than one time-point (n=7)

Screening Tool	Study	Cut-off	Sensitivity (%)	Specificity (%)
HADS-D	[6]Prisnie et al, 2016	≥8	64%	89%
	[30]Sagen et al, 2009		58%	94%
	[31]Turner et al, 2012		62%	83%
	[32]Kang et al, 2013		83%	76%
	[33]O'Rouke et al, 1998		45%	85%
	[6]Prisnie et al, 2016	≥11	46%	98%
	[30]Sagen et al, 2009		40%	99%
	[33]O'Rouke et al, 1998		35%	93%
CES-D	[34]Roger et al, 2009	≥16	60%	76%
	[35]Parikh et al, 1988		86%	90%
Modified HSRD (17 item)	No validation studies found (validation studies of other versions of HSRD in stroke patients are available)			
GDS-15	[34]Roger et al, 2009	≥5	46%	90%
	[6]Prisnie et al, 2016	≥6	46%	81%
BDI 2	[31]Turner et al, 2012	≥14*	85%	75%
MADRS	[30]Sagen et al, 2009	>6	90%	39%
	[32]Kang et al, 2013		83%	80%
PHQ - 8	No validation studies found though significant overlap in structure with PHQ-9			
PHQ - 9	[6]Prisnie et al, 2016	≥10	82%	93%
	[31]Turner et al, 2012		69%	78%
MDI	No validation studies found.			
TDQ	No validation studies found.			
NPI	No validation studies found.			

Table 2.11. Assessment tools identified in the systematic review of depression after a TIA with their validation studies (where available). Sensitivity and specificity values are quoted from the referenced validation study. *Cut-off value not stated in study included in systematic review, therefore a validation study on commonly accepted cut-off value included. Table adapted from Burton et al.[33] HADS-D= Depression subscale of the Hospital Anxiety and Depression Scale, CES-D= Center for Epidemiologic Studies Depression Scale, HSRD= Hamilton Rating Scale for Depression, GDS= Geriatric Depression Scale, BDI= Beck Depression Inventory, MADRS= Montgomery Asberg Depression Rating Scale, PHQ= Patient Health Questionnaire, MDI= Major Depression Inventory, TDQ= Taiwanese Depression Questionnaire, NPI= Neuropsychiatric Inventory.

	Number of studies	Depressed / Total	Prev (%)	95% CI (%)	p het
Assessment Method					
Face to face	8	195 / 1222	16.6	12.3-21.4	<0.001
Postal	2	26 / 472	6.0	2.1-11.7	0.064
Definition of TIA					
Time based	7	190 / 1410	15.9	9.5-23.5	<0.001
Tissue based	2	23 / 181	12.6	8.2-17.9	0.905
Pre-morbid depression					
Included	10	215 / 1592	15.2	10.1-21.1	<0.001
Excluded	2	45 / 363	12.5	9.2-16.1	0.339

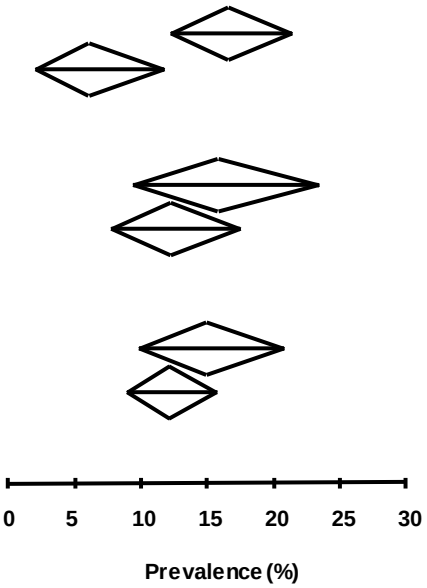

Figure 2.5 Impact of assessment method, definition of TIA and inclusion / exclusion of premorbid depression on the prevalence rate of post-TIA depression (within the first 6 months after the event). Where multiple prevalence rates were present within a study, the prevalence rate of depression was taken from the earliest assessment. Not all studies presented data on the different variables therefore different numbers included for each sub-set. Prev=prevalence. CI= confidence interval. p het= p value for heterogeneity of studies.

	Depression/ Total	Prev (%)	95% CI	p value for heterogeneity	Time	Assessment method	Assessment tool
a) Acute (0-1 months)							
Turner A et al, 2016	7 / 51	13.7	4.3-23.2		Baseline	Face to face	PHQ-9 > 9
Rizos T et al, 2018	12 / 73	16.4	7.9-24.9		Baseline	N/S	PHQ-9 > n/s
Carnes-Vendrell et al, 2019	12 / 40	30.0	15.8-44.2		10 days	Face to face	BDI, MADRS
OxVasc, 2020	69 / 354	19.5	15.4-23.6		1 month	Face to face	GDS > 5
Total:	**100 / 518**	**19.4**	**16.1-22.9**	**0.270**			
b) Sub-acute (3-12 months)							
Turner A et al, 2016	5 / 51	9.8	1.6-18.0		3 months	Telephone	PHQ-9 > 9
Rizos T et al, 2018	7 / 61	11.5	3.5-19.5		3 months	N/S	PHQ-9 > n/s
Carnes-Vendrell et al, 2019	3 / 36	8.3	-0.7-17.4		1 year	Face to face	BDI, MADRS
OxVasc, 2020	41 / 295	13.9	10.0-17.8		1 year	Face to face	GDS > 5
Total:	**56 / 443**	**12.8**	**9.9-16.1**	**0.782**			

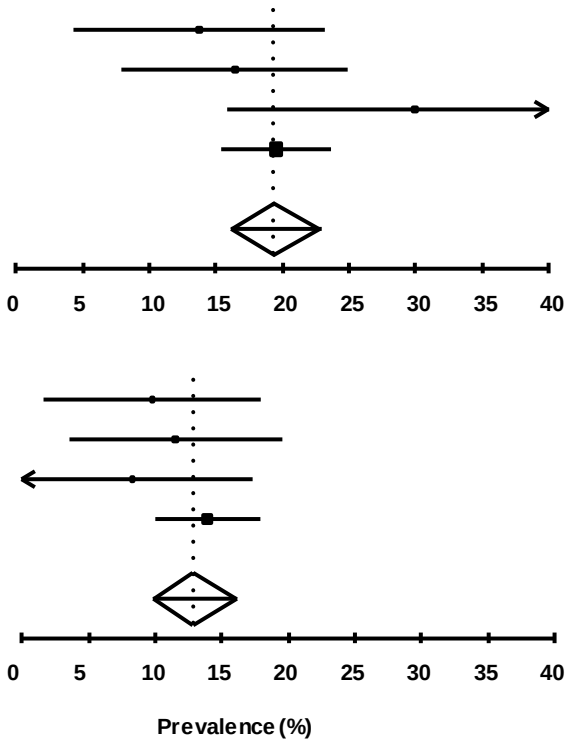

Figure 2.6 Pooled prevalence of depression after a TIA stratified by time. (a) acute: 0 – 1 months, (b) subacute: 3-12 months. Only data from longitudinal cohort studies where prevalence rates reported at multiple time-points within the study is included. Prev= prevalence. CI=confidence interval N/S= not specified. BDI=Beck Depression Inventory MADRS=Montgomery Asberg Depression Rating Scale, GDS=Geriatric Depression Scale, PHQ-9=Patient Health Questionnaire version 9

	Depression/ Total		Prev (%)	95% CI	Prevalence (%)	p value for heterogeneity	Time	Assessment method	Assessment tool
a) At time of event									
Wilson D et al, 2010	11 /	29	37.9	20.3-55.6			Baseline	Face to face	CES-D ≥ 16
Turner A et al, 2016	7 /	51	13.7	4.3-23.2			Baseline	Face to face	PHQ-9 >9
van Rooij FG et al, 2017**	8 /	103	7.8	2.6-12.9			Baseline	Face to face	HADS-D ≥8
OxVasc, 2020	73 /	392	18.6	14.8-22.5			Baseline	Face to face	Single question
Sackley CM et al, 2019	16 /	364	4.4	2.3-6.5			Baseline	Postal	HADS-D n/s
Rizos T et al, 2018	12 /	73	16.4	7.9-24.9			Baseline	Not stated	PHQ-9 n/s
Carnes-Vendrell A et al, 2019	12 /	40	30.0	15.8-44.2			10 days	Face to face	BDI, MADRS
Total	**139 /**	**1052**	**16.0**	**25.3**		**<0.001**			
b) 1 – 6 months									
OxVasc, 2020	69 /	354	19.5	15.4-23.6			1 month	Face to face	GDS>5
Snaphaan L et al, 2009*	14 /	137	10.2	5.1-15.3			6-8 weeks	Face to face	HADS-D ≥8
El Husseini N et al, 2012	57 /	397	14.4	10.9-17.8			3 months	Face to face	PHQ-8 ≥ 10 only
Turner A et al, 2016	5 /	51	9.8	1.6-18.0			3 months	Telephone	PHQ-9 >9
Kiphuth IC et al, 2014	10 /	108	9.3	3.8-14.7			3 months	Postal	HADS-D ≥8
Rizos T et al, 2018	7 /	61	11.5	3.5-19.5			3 months	Not stated	PHQ-9 n/s
Wong A et al, 2016	13 /	73	17.8	9.0-26.6			3-6 months	Face to face	NPI
van Rooij FG et al, 2017**	9 /	103	8.7	3.3-14.2			6 months	Face to face	HADS-D ≥8
Total	**184 /**	**1284**	**13.3**	**10.4-16.4**		**0.029**			
c) 12-months									
Carnes-Vendrell A et al, 2019	3 /	36	8.3	-0.7-17.4			1 year	Face to face	BDI, MADRS
Von Weitzel-M et al, 2011	14 /	167	8.4	4.2-12.6			1 year	Not stated	MDI, antidepressants
El Husseini N et al, 2012	51 /	397	12.8	9.6-16.1			1 year	Face to face	PHQ-8 ≥ 10 only
OxVasc, 2020	41 /	295	13.9	10.0-17.8			1 year	Face to face	GDS>5
Total	**109 /**	**895**	**12.2**	**10.2-14.5**		**0.301**			

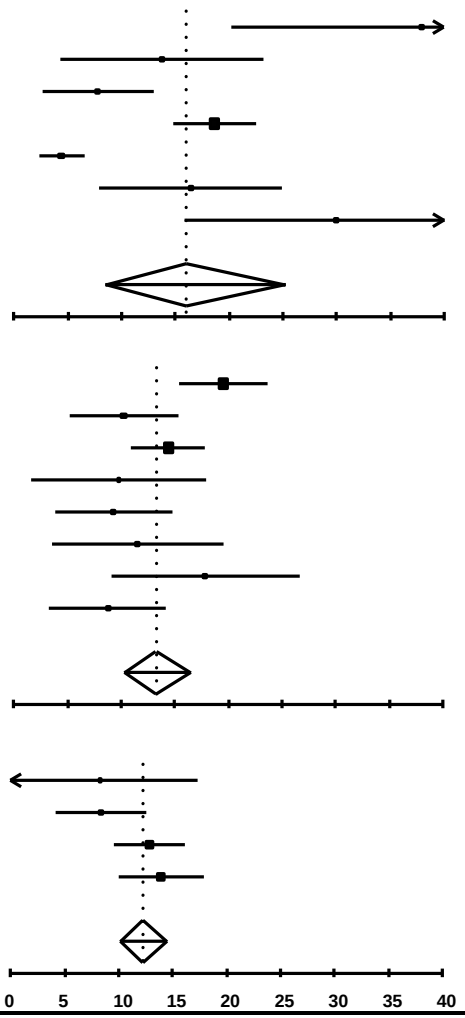

Figure 2.7: Pooled prevalence of depression across all studies stratified by time after a TIA: (a) at baseline, (b) 1 – 6 months and (c) 12-months. Both point prevalence and longitudinal cohort studies included to calculate pooled rates. *Excluded patients if depressive symptoms within the previous month prior to the event. **Included transient neurological attack patients as well as TIA patients. Prev= prevalence. CI=confidence interval N/S= not specified. HADS-D= Depression subscale of the Hospital Anxiety and Depression Scale, CES-D= Center for Epidemiologic Studies Depression Scale, GDS= Geriatric Depression Scale, BDI= Beck Depression Inventory, MADRS= Montgomery Asberg Depression Rating Scale, PHQ= Patient Health Questionnaire, MDI= Major Depression Inventory, NPI= Neuropsychiatric Inventory.

Study	TIA Depression/ Total	Minor stroke Depression/ Total	Odds ratio (95% CI)
(a) 0 – 1 months			
Carnes-Vendrell A et al, 2019	12 / 40	17 / 42	0.63 (0.25-1.57)
Sackley CM et al, 2019	16 / 364	12 / 183	0.66 (0.30-1.42)
OxVasc, 2020	69 / 354	48 / 204	0.79 (0.52-119)
Total	**97 / 758**	**77 / 429**	**0.74 (0.52-1.03)**
		p value:	**0.078**
		p het:	**0.862**
(b) 12-months			
Von Weitzel-M et al, 2011	14 / 167	30 / 114	0.26 (0.13-0.51)
Carnes-Vendrell A et al, 2019	2 / 36	6 / 34	0.27 (0.05-1.47)
OxVasc, 2020	41 / 295	31 / 164	0.69 (0.42-1.15)
Total	**57 / 498**	**67 / 312**	**0.46 (0.31-0.68)**
		p value:	**<0.001**
		p het:	**0.061**

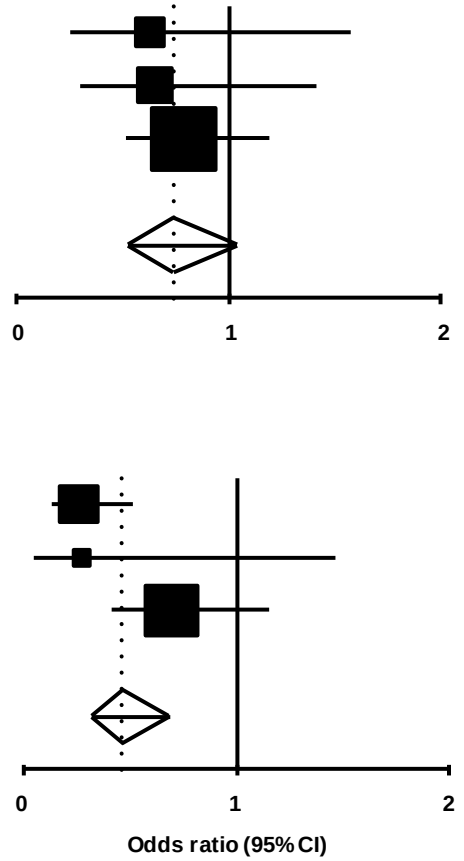

Figure 2.8 Pooled odds ratios of depression after a TIA compared with minor stroke from studies that provided data on both cohorts using the same method for assessment in both. (a) At 0 – 1 months. (b) At 12-months. p het=p value for heterogeneity of studies

CHAPTER 3

PREVALENCE, TEMPORAL TREND AND SUSCEPTIBILITY FACTORS ASSOCIATED WITH DEPRESSIVE AND ANXIETY SYMPTOMS AFTER A TRANSIENT ISCHAEMIC ATTACK VERSUS A MINOR STROKE: A POPULATION-BASED STUDY AND SYSTEMATIC REVIEW

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3.1 Abstract

Introduction: Anxiety disorders and depression both commonly occur after a major stroke and often co-exist. However, little is known about the prevalence and risk factors for anxiety after a Transient Ischaemic Attack (TIA) or minor stroke nor the relationship of anxiety with depression. Given this, I aim to assess what the prevalence of anxiety / depression symptoms is and whether there is a difference in the rates after a TIA compared with a minor stroke?

Methods: I assessed the prevalence of, and associated factors for, moderate to severe symptoms of anxiety and/or depression one-month and 12-months after a TIA and minor stroke in a longitudinal population-based study (OxVasc) using the Euro-Qol 5D. A systematic review was then undertaken of the prevalence rates of anxiety, post-traumatic stress disorder and comorbid anxiety and/or depression after a TIA with the results collated into a meta-analysis.

Results: Among 2137 TIA / minor stroke patients the prevalence of anxiety and/or depression symptoms was 29.9% at one-month and 22.9% (in 1822 patients) at 12-months. The prevalence rate of symptoms at one-month was similar in the TIA and minor stroke patients (TIA: 28.7%, minor stroke: 31.3%, p=0.191), but differed by one year (TIA: 20.9%, minor stroke: 25.5%, p=0.020). Risk factors for anxiety and/or depression symptoms at one-month included premorbid anxiety or depression (adjusted OR=1.96, 95% CI 1.57-2.45, p<0.001), reporting often feeling sad at baseline (3.27,2.61-4.09, p<0.001), and for the TIA patients alone, female sex (1.69, 1.26-2.26, p<0.001) and younger age (0.99 per year, 0.98-1.00, p=0.010). The presence of anxiety and/or depression symptoms at one-month was the strongest predictor of symptoms at 12-months (4.38, 3.39-5.64, p<0.001). Additionally, in the minor stroke patients, a greater severity of initial stroke was a risk factor for 12-month anxiety and/or depression symptoms (1.16 per point increase in NIHSS, 1.01-1.34, p=0.011). Eleven studies on anxiety after a TIA were identified in the systematic review and overall the pooled prevalence was 11.6% at baseline and 9.7% at three-to-six months.

Conclusion: Whilst both TIA and minor stroke patients have a high rate of anxiety and/or depression symptoms one-month after their event, the subsequent temporal trends and diverging risk factor profiles suggest differing underlying mechanisms.

3.2 Introduction

In the previous chapter (Chapter 2) I demonstrated that depression after a TIA appeared to be more transient than after a minor stroke. However, depression is but one facet of post-stroke psychological distress with 29% of stroke patients experiencing anxiety disorders and 11% experiencing post-traumatic stress disorder (PTSD) in the first year after their stroke.[1,2] The prevalence rates of anxiety disorders and PTSD after a TIA are not known with the single systematic review identifying only one study on the prevalence of anxiety after a TIA and none for PTSD.[3,4] In a previous OxVasc study, no significant difference was found in the presence of anxiety and/or depression symptoms at one-month compared with six-months or between TIA and minor stroke patients, though, the study was limited by small numbers (n=149).[5]

The co-existence, and inter-dependency, of anxiety disorders with depression is well described.[6] In the primary care general population, more than 50% of patients with depression or anxiety also have a second anxiety or depressive disorder.[7] Additionally there is a great degree of overlap in their management strategies and a shared association with a lower quality of life. In a post-stroke population between 57%-73% of patients with anxiety were found to have comorbid depression.[8] Yet, many studies assess the prevalence rates of the conditions independently of each other. Furthermore, as the assessment and ongoing care of TIA and minor stroke patients is often undertaken by the primary care team there is a need for a brief but accurate screening tool. Whilst a previous meta-analysis on ultra-short screening instruments found that a single question was poorly sensitive (32%) in detecting depression none of the included studies included the anxiety / depression question of the widely used EuroQol-5D.[9]

Given this, I aim to answer the following questions. Firstly, is there a difference in prevalence of anxiety / depression symptoms after a TIA compared with a minor stroke? Secondly, are the susceptibility factors for anxiety / depression symptoms after a TIA or minor stroke similar to those for just depressive disorders alone? Thirdly, what is the

prevalence, and temporal trend, of anxiety alone after a TIA? Finally, what is the sensitivity of the EuroQol-5D for detection of anxiety disorders or depression after a TIA or minor stroke?

3.3 Methods

3.3.1 Population-Based Study

The Oxford Vascular Study (OxVasc) is a longitudinal, prospective population-based study of the incidence and outcomes of all acute vascular events in Oxfordshire, UK. The study population comprises 92,728 individuals registered with nine General Practices in Oxfordshire. As described in Chapter Two, ascertainment of patients is through both 'hot' and 'cold' methods which have been demonstrated to achieve near complete ascertainment of all acute vascular events. Recruitment began 1st April 2002 and is ongoing.

All patients with TIA, ischaemic or haemorrhagic stroke were reviewed by a study physician as soon as possible after their initial presentation either on a hospital ward or in an outpatient neurovascular clinic. A structured interview and examination (including the National Institutes of Health Stroke Scale (NIHSS)) were completed and the primary care record reviewed. Patients are additionally asked at baseline if they "often feel sad or depressed." If capacitous, patients gave informed consent to participate, otherwise assent was gained from a relative.

A TIA was defined, according to the World Health Organisation (WHO) criteria, as focal neurological symptoms lasting less than 24 hours with a stroke defined as symptoms lasting more than 24 hours and the probability of the event being defined according to National Institute of Neurological and Communicative Disorders and Stroke (NINDS) criteria.[10] The senior study neurologist (PMR) subsequently reviewed all cases to confirm diagnosis and management. For the purposes of this study I included consecutive patients with first (in study) probable or definite TIA or minor ischaemic stroke (defined as NIHSS < 5) who were

recruited into OxVasc from its inception (1st April 2002) until 30 September 2018. There were no exclusion criteria applied.

Patients were subsequently further reviewed face-to-face at one-month and 12-months by a study nurse or physician with a structured interview .This included the EuroQol-5D Visual Assessment Scale (VAS) and Anxiety / Depression question where patients are asked to self-rate whether they have no, moderate or extreme symptoms of anxiety and / or depression. From 2014 onwards patients also completed the Geriatric Depression Scale (GDS) at one and 12-months with depression defined as a score of greater than five.[11] To minimise attrition, if a subject was unable to attend hospital for their follow-up then a home visit or telephone assessment was completed instead.

I defined pre-morbid anxiety and / or depression as a composite of self-reported history from the structured interview, GP coding in their primary care record or pre-event use of anti-anxiety or antidepressant medication (defined as that prescribed at a therapeutic dose according to Maudsley Prescribing Guidelines).[12] Socio-economic deprivation was defined by the indices of multiple deprivation (IMD) for the subject's baseline post-code and treated as binary (greater deprivation equating to an IMD score >17.398). Low education was defined as leaving school aged 16 or less without any further subsequent formal education. Vascular risk factors were defined as either self-reporting at baseline, from primary care records, or for hyperlipidaemia the prescription of a lipid-lowering agent in the baseline medication history. A recurrent cerebrovascular event was defined as a TIA, ischaemic stroke, subarachnoid haemorrhage or intracerebral haemorrhage occurring prior to the 12-month assessment.

3.3.2 Systematic Review and Meta-Analysis

To identify studies on post-TIA anxiety, PTSD and comorbid anxiety and depression I searched Ovid Medline, EMBASE and PsychInfo using a comprehensive search strategy for any form of psychological distress after a TIA (Appendix XIII). Relevant review articles were hand-searched for further studies. The review was completed according to PRISMA

(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Studies were included if they reported on the prevalence of anxiety, PTSD and co-existing anxiety / depression at any time point after a probable or definite TIA in a series of consecutively recruited eligible patients. Both journal articles and conference abstracts were eligible. For prevalence rates of anxiety disorders and PTSD, studies were required to use a validated measure in order to quantify frequencies, though to maximise yield, the measure did not have to have been validated specifically in a stroke or TIA population. However, due to the paucity of studies on comorbid anxiety and depressive disorders the search was broadened to include self-reporting symptoms and primary care records. Studies on only sub-sets of a TIA population (e.g. post carotid endarterectomy) were included in the review but the prevalence data were not included in the meta-analysis. Studies were excluded if the data relevant to the TIA population could not be isolated from the data of a mixed population of stroke and TIA, if the full text of the paper was unavailable or if a translation of a non-English study was unavailable. Where multiple studies used a subset or the whole of the same data set, the duplicate studies were only included if frequencies at different time points were reported, otherwise the study of the largest patient series was included. Susceptibility to bias was assessed for each study using principles from Cochrane and a systematic review of tools for assessing quality and susceptibility to bias in observational studies in epidemiology.[13-14]

From the included studies, information was extracted on the study characteristics (type, follow-up duration, recruitment method, proportion of eligible assessed, assessment method, tools used and their cut-off values) and participant characteristics (mean age, gender, proportion with psychological symptoms and associated factors). If provided, data on control (non-TIA/stroke) and minor stroke (defined according to the individual paper) patients were also extracted.

3.3.3 Statistical Analysis

For the OxVasc data, the EuroQol 5D Anxiety / Depression assessment was treated as a binary variable with no symptoms being compared with moderate or extreme symptoms. I calculated the prevalence rate of moderate / extreme symptoms of anxiety / depression after a TIA and after a minor stroke at one month and at 12 months. I compared continuous variables by Students T-test and categorical variables by X^2 test. Statistical significance was defined as $p < 0.05$. Patients who completed one month and then also 12 months of follow-up were compared with those with incomplete follow-up. Univariate associations between baseline characteristics and subsequent post-event moderate / extreme symptoms were determined by binary logistic regression and subsequently with age / sex adjustments. The results of the latter analysis were used to inform the variables to include in the multivariate regression analysis ($p<0.05$ in age/sex adjusted analysis). Age and sex were forced (if necessary) into the multivariate regression analysis as they have been found to be associated with anxiety / depression in prior studies. A sensitivity analysis was performed excluding patients who had either a pre-morbid history of anxiety or depression or had reported often feeling sad at baseline. The Kappa correlation coefficient for the EuroQol-5D anxiety / depression question with the Geriatric Depression Scale (GDS) was undertaken in the subset of patients that had both assessments performed one month after their event. The cut-off for depression for the GDS was defined as >5 (as per Chapter 2)

In the meta-analysis I calculated pooled prevalence rates (and 95% confidence intervals) for anxiety disorders according to pre-specified time frames after a TIA. Firstly, in all studies that reported a prevalence rate at either baseline or at 1-6 months after a TIA. Then only in longitudinal cohort studies that reported prevalence rates at baseline and at 3-6 months for the same cohort. An analysis of prevalence of anxiety one year after a TIA was planned but no studies were found. The 95% confidence intervals of the pooled prevalences were calculated to allow for extra-binomial variation because standard methods of calculating confidence intervals produce artificially narrow intervals if there is heterogeneity of risk

between different studies.[15] Analyses of heterogeneity of prevalence across studies were done with X^2 tests. A pooled analysis of the relative prevalence of anxiety after a TIA compared with after a minor stroke was planned but insufficient studies were found. An insufficient number of studies were identified on the prevalence rates of PTSD and comorbid anxiety / depressive symptoms therefore pooled estimates were not attempted. Statistical analyses were performed using SPSS Statistics 26.

3.4 Results

3.4.1 Population-Based Study (OxVasc)

There were 2744 (1304 minor stroke, 1440 TIA) patients with their first in study event recruited between 2002 and 2018. Of these, 77.9% (n=2137) completed at least one-month of assessment and 66.4% (n=1822) completed the 12-months assessments. The one-year participation rate for TIA patients was higher than for minor stroke patients (70.1% vs 62.3%). The most common reasons for lack of completion fof follow-up were death, uncontactable, recurrent stroke, dementia or declining follow-up. In general, patients who did not complete any assessment, compared with those that completed at least one-month, were older (75.6 vs 71.1, p<0.001), more likely to be female (53.0% vs 48.2%, p=0.037), have a higher proportion of vascular risk factors (e.g. atrial fibrillation: 20.5% vs 14.6%, p<0.001) and have had a prior cerebrovascular event (19.7% vs 12.4%, p<0.001). TIA patients who did not complete follow up had higher rates of ABCD2 scores above four (68.3% vs 57.1%, p<0.001) and minor stroke patients who did not complete had higher baseline NIHSS scores (mean (s.d) = 1.6(1.4) vs 1.4(1.3), p0.013). However, there were no differences in rates of pre-morbid anxiety or depression (28.6% vs 26.3%, p=0.267). Rates of anxiety and/or depression symptoms reported at one-month were similar in patients who subsequently failed to complete the 12-month assessment and those who did complete it (30.5% vs 29.8%, p=0.802). Baseline characteristics of patients that completed one-month and 12-months of assessments can be found in table 3.1 with details of non-completers in Appendix XVII.

Moderate to extreme symptoms of anxiety and/or depression were reported by 29.9% of the 2137 patients at one-month and 22.9% of the 1822 patients at 12-months (p<0.001). At one-month the prevalence rate of symptoms in 1162 TIA patients was similar to that found in 975 minor stroke patients (28.7% vs 31.3%, p=0.191). However, by 12-months the rates had diverged with a lower prevalence of symptoms in 1010 TIA patients than in 812 minor stroke patients (20.9% vs 25.5%, p=0.020). Limiting the analysis to only those 1822 patients that completed both the one-month and the 12-month assessments did not impact the one-month prevalence rates (overall: 29.8%, TIA 28.7%, minor stroke: 31.2%) nor the trends (overall 12 month vs 1 month: p<0.001, 1-month TIA vs 1-month minor stroke: 0.191). Stratifying the 1822 patients (that completed both the one and 12-month assessments) by event type and, for the minor strokes, NIHSS score also found a trend to increasing 12-month prevalence rates of anxiety and/or depression symptoms as the score increased from TIA through NIHSS 0 to NIHSS 4 (figure 3.1).

When stratified by event / age the highest prevalence of moderate to extreme symptoms of anxiety and/or depression at one-month was in minor stroke patients aged 75 years and older (32.5%) and at 12-months in minor stroke patients aged below 75 years (27.2%). In TIA patients there was a significant decrease in prevalence rates over the first year (17.4% vs 29.6%, p<0.001) in those aged under 75 years but not in those aged over 75 years (27.6% vs 25.3%, p=0.439) (figure 3.2).

Overall, the presence of symptoms of anxiety and/or depression at one-month was associated with being female (crude OR 1.66 95% CI 1.38-2.01, p<0.001), younger age (0.99, 0.99-1.00, p=0.032), reporting often feeling sad (OR 4.07, 3.29-5.04, p<0.001), pre-morbid anxiety or depression (2.78, 2.27-3.41, p<0.001) and greater socio-economic deprivation (1.50, 1.15-1.95, p=0.003) (Table 3.2 (a)). The associations were similar for the TIA patients and minor stroke patients when analysed separately. A prior cerebrovascular event was additionally associated with anxiety and/or depression symptoms after a minor stroke (1.57, 1.06-2.31, p=0.024) but not after a TIA (Tables 3.2 (c), (e)). In a multivariate

model, younger age and female sex remained associated with one-month symptoms for the TIA patients but neither remained associated for minor stroke patients (Tables 3.2 (c), (e), table 3.3). For TIA patients the duration of symptoms, character of TIA symptoms, vascular risk factors, vascular history and ABCD2 score at baseline were not associated with the presence of symptoms at one-month.

Twelve-months after a TIA or minor stroke, anxiety and/or depression symptoms were again associated with female sex, premorbid anxiety or depression, often feeling sad and greater socioeconomic deprivation. The presence of symptoms at one-month were also associated with the presence of symptoms at 12-months (crude OR 5.89, 4.55-7.30, p<0.001) (table 3.2 (b)). In an unadjusted model, recurrent cerebrovascular events between the one-month and 12-month assessments were associated with symptoms for the minor stroke patients (1.99, 1.17-3.38, p=0.011) but not for the TIA patients (table 3.2 (d), (f)). Overall, in a multivariate model, only anxiety and/or depression symptoms at 1-month, pre-morbid anxiety or depression and reporting often feeling sad at baseline remained associated with symptoms at 12-months (Table 3.2 (b), table 3.3). For TIA patients, a past history of ischaemic heart disease was also associated with 12-month symptoms (adjusted OR 1.72, 1.09-2.71, p=0.019) (table 3.2 (d), table 3.3).

The presence of moderate to extreme anxiety and/or depression symptoms at either 1-month or 12-months was associated with lower EQ Visual Analogue Scale (VAS) scores for both the TIA patients and minor stroke patients (table 3.4).

Excluding patients with premorbid anxiety or depression and those that had reported feeling sad at baseline found prevalence rates of moderate to extreme anxiety and/or depression symptoms to be 19.4% in 1277 patients at one-month and 12.4% in 1104 patients at 12-months (p<0.001). The prevalence rate at 12-months was significantly different from that at one-month for the TIA patients (11.6% vs 19.0%, p<0.001) but not the minor stroke patients (15.6% vs 19.9%, p=0.069). In a multivariate analysis for the TIA and minor stroke patients together only the presence of a prior TIA or stroke was associated with symptoms at one-

month (adjusted OR 1.52, 1.00-2.29, p=0.048). This remained associated in a multivariate analysis with symptoms at 12-months (1.65, 1.01-2.71, p=0.047) but additionally ischaemic heart disease or angina (1.78, 1.13-2.81, p=0.013) and the presence of anxiety and/or depression symptoms at 1-month were associated (5.35, 3.70-7.71, p<0.001). For minor stroke patients a higher baseline NIHSS was associated with anxiety and/or depression symptoms at 12-months (1.22, 1.00-1.48, p=0.046) but not at 1-month (age / sex adjusted OR 0.79, 0.53-1.20, p=0.274) (Appendix XVIII).

Comparison of the one-month EuroQol-5D anxiety / depression score with the 351 TIA patients and 204 minor stroke patients that additionally were assessed at the same time for depression (using the GDS, Chapter 2) found that it had a sensitivity of 65.7% and 59.6% in TIA and minor stroke patients respectively. The specificity of the EuroQol-5D for depression was 78.9% and 80.7% for TIA and minor stroke patients respectively. Correlation between depression symptoms identified by the GDS and the EuroQol-5D was moderate (kappa correlation coefficients: TIA/minor stroke= 0.370, TIA alone= 0.377, minor stroke= 0.358, all p<0.001).

3.4.2 Systematic Review and Meta-Analysis

The search of electronic databases and hand-searching of relevant review articles identified 515 articles (including 114 duplicates) of which 15 were eligible for inclusion (figure 3.3, tables 3.5-3.7). Reasons for exclusion after full text review are described in further detail in Appendix XV .Of the 15 studies included 11 reported prevalence rates for anxiety disorders after a TIA, 4 for PTSD and 4 for comorbid anxiety / depression symptoms.

Anxiety Disorders

Eleven studies that reported on the prevalence of an anxiety disorder after a TIA were identified (table 3.5).[16-25,27] The majority of studies (n=9/11) were single centre (neurovascular clinic referrals or stroke ward admissions) with participant numbers ranging from 24 to 186.[17-18,20-25,27] There was one multi-centre study and one on primary care

coding.[19,16] The proportion of eligible patients assessed was often not reported for TIA patients alone but where presented participation ranged from 35% to 51%.[16,20] Seven of the studies used a face-to-face interview[17-18,21-23,25,27] for their assessment, two used postal questionnaires,[19-20] one used a telephone interview[24] and one used primary care coding.[16]

Five of the eleven studies used the Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), which has been validated in a stroke population, in order to assess for anxiety with an agreed cut-off of ≥ 8 to define possible cases of anxiety disorders.[16,18-21] Other assessment tools used including Structured Clinical Interview for DSM-IV disorders (SCID),[24] Generalised Anxiety Disorder 7 (GAD-7)[17,25,23,27] and the Neuropsychiatric Inventory (NPI)[22] none of which have currently been validated in a stroke population. Further details regarding the validation of anxiety assessment tools in a stroke population are in table 3.8.

In terms of generalisability of the participant population, three studies excluded patients with prior history of TIA/stroke[18,19,24] and two of the studies excluded patients with pre-morbid functional dependency (defined as modified Rankin ≥ 3, housebound or a care home resident).[16,20] No study stated that they excluded patients due to pre-morbid anxiety disorders but only two of the studies reported pre-morbid prevalence rates of anxiety disorders.[24,27]

After a TIA the pooled prevalence rate for an anxiety disorder at the time of the event was 13.1% (p het=0.506) and 14.3% (p het=0.001) one-to-six months later (figure 3.4 (a)). The pooled prevalence rates when the analysis was restricted to only studies reporting at multiple time points in the same cohort found rates of anxiety of 11.6% at the time of the event (p het=0.432) and 9.7% (p het=0.296) at three-to-six months with no significant difference between the rates (p=0.520) (figure 3.4 (b)). There were no studies reporting the prevalence rate of anxiety disorders 12-months after the TIA though a study reported the long-term prevalence (mean 8.3 years from the event) to be 23%.[18]

One study reported no difference in the the prevalence rate of anxiety disorders at baseline in TIA patients compared with minor stroke (TIA: 13.2%, minor stroke: 14.8%, p=0.608).[19] However, by 12-months they found a significant improvement in anxiety scores in the TIA patients but not in the minor stroke patients.

Two studies reported on the prevalence rates of anxiety disorders in TIA patients compared to a matched control population.[18,19] One reported a prevalence rate of 6.2% in controls compared with 14% in TIA patients (2 weeks after their event) and found that TIA patients scored a mean 1.31 points higher on the HADS-A scale (out of 21) at baseline and 0.78 points higher at 12-months.[19] The other, reporting on a young population (aged 18-50), found prevalence rates of anxiety of 12% in controls compared to 23% in patients long-term after a TIA.[18]

Overall there was a general agreement that younger age was associated with a higher risk of an anxiety disorder after a TIA but limited, and conflicting, information on other variables.

Post-Traumatic Stress Disorder

Three studies that reported the prevalence of PTSD after a TIA were identified (table 3.6) but with two of the studies reporting on the same cohort at different time points.[20,26-27] All the studies were single centre studies with participation rates of 48% to 61% where stated.[20,27] The largest study (n=108 at 3 months and n=84 at 12 months) reported rates of PTSD of 30% at 3 months and 8% at 12 months and assessed patients by a postal questionnaire using the Post-traumatic stress Diagnostic Scale (PDS) with a requirement for patients to fulfil the DSM-IV-TR criteria for PTSD.[20,27] The smaller study (n=73) reported rates of 25% at 3 months.[27] Similar to anxiety disorders the studies suggested that a younger age was associated with increased risk of developing PTSD after a TIA. There were no studies providing prevalence rates on a matched control population identified by this review.

Comorbid Anxiety and Depressive Disorders

Four studies reported on the presence of comorbid anxiety and depressive disorders after a TIA (table 3.7). The largest study (n=9240 patients) was a cross-sectional review of primary care coding and prescriptions and reported a prevalence of anxiety and/or depressive disorders of 34%.[28] Two other studies utilised the anxiety / depression question of the EuroQol.[5,29] The larger study (n=748) relied on a postal questionnaire (though with telephone follow up if required) reporting a prevalence of 36% three-to-six months after a TIA.[29] The smaller study, from OxVasc, found rates of 26% at 1-month and 27% at 6-months.[5] This cohort has now been expanded and is included within the current population-based study reported earlier. Three months after a TIA, a study of 175 patients, using a detailed psychiatric interview, found that 10% had an anxiety disorder alone, 4% had a depressive disorder alone but 11% had comorbid anxiety and depression.[24]

3.5 Discussion

Anxiety disorders cover a range of conditions including generalised anxiety disorder, panic disorders, social anxiety, and phobias all of which share a theme of the disproportionate fear of a perceived threat. After a TIA or minor stroke a degree of anxiety regarding its recurrence is a normal response which is why the Diagnostic and Statistical manual of Mental Disorders – 5th edition (DSM-5) criteria for anxiety disorders specifies that the anxiety should be excessive to the threat.[31] The definition of disproportionality requires an understanding of the patient's actual risk of recurrence compared with their perceived risk. Furthermore, the DSM-5 criteria requires that the anxiety symptoms be present for six-months or more.[31] Yet, in the systematic review on anxiety prevalence I found that the majority of studies assessed on a single occasion, cross-sectionally within six-months of the event and without assessment of duration of symptoms. Despite this limitation, in the meta-analysis I found that the prevalence of anxiety disorders was 11.6% at the time of the event and 9.7% at three-to-six months. These rates were lower than the prevalence rate found in a previous review of 52% at 14 days though that review included only one study

for TIA patients and it had a considerably lower cut-off score for the HADS-A.[3,4] Given the lack of studies assessing beyond six-months it was not possible to conclusively assess the temporal trend in anxiety disorders after a TIA.

Only one study reported comparisons in the prevalence rates of anxiety disorders between minor stroke and TIA populations and found no difference at baseline but perhaps a greater improvement in the TIA population at 12-months (though scores, not prevalence rates were reported).[18] Likewise, in the Oxford Vascular Study I found that at one-month the prevalence rates of moderate-to-extreme symptoms of anxiety and/or depression were similar in the TIA (28.7%) and minor stroke patients (31.3%). However, parallel to the trend in depression prevalence after a TIA, there was a greater improvement in anxiety and/or depression symptoms in the TIA patients at 12-months than in the minor stroke patients.

A premorbid history of an anxiety disorder or depression along with reporting feeling often sad at the time of the event were associated with the presence of anxiety and/or depressive symptoms at one-month in both the minor stroke and TIA patients. Similarly both characteristics were found to be associated with the presence of depression one-month after a TIA / minor stroke in the previous chapter. However, in this current study, additionally younger age and female sex were found to be associated with anxiety and/or depressive symptoms in the TIA population. The association between female sex, younger age and anxiety symptoms has been found in prior studies on anxiety after stroke and also in the general population.[1,32] In the Global Burden of Disease survey in 2017 females aged 45 to 49 had the highest prevalence of anxiety disorders in the general population (6.1%) compared with males aged 45 to 49 (3.6%) and females aged 70 years and over (5.1%).[33]

In the longer term, it was the presence of symptoms (either anxiety / depression symptoms or a depressive disorder) at one-month that was most strongly associated with the presence of symptoms at 12-months. Additionally a higher baseline NIHSS score was associated with an increased risk of anxiety and/or depression symptoms but for the minor stroke population alone. Ischaemic heart disease was found to be associated with an increased

risk of anxiety and/or depressive symptoms in the TIA patients. This may be due to its impact on the patient's perceived risk of future recurrent events and therefore the associated fear. A review in 2017 found that the factors associated with a higher perceived risk of recurrent stroke were the risk factors associated with stroke itself such as hypertension, diabetes, ischaemic heart disease, high cholesterol and prior stroke.[34]

The diverging 12-month temporal trends and non-congruent risk factors for anxiety and depression after a TIA compared to a minor stroke suggest differing underlying mechanisms. TIA and minor stroke patients share many similarities in their investigations and management but differ in the higher probability of the presence of a persisting cerebral insult in the minor stroke patients. Risk factors for anxiety and/or depression after a TIA are in common with many risk factors seen for these conditions in the general population: younger age, female sex, socio-economic deprivation.[32] Yet for minor stroke patients risk factors such as a greater severity of initial stroke was found to be associated with anxiety / depression symptoms and, as seen in Chapter 2, a recurrent cerebrovascular event with depression itself. This may suggest a direct impact of the lesion itself on mood or a different cerebrovascular susceptibility to both stroke and depression / anxiety disorders.

One of the limitations of this study, particularly for answering that question, was that TIA patients with an acute lesion on imaging were not analysed separately from the imaging negative TIA patients. In practice, and certainly historically, not all patients who have a TIA undergo brain imaging so a pragmatic approach to the assessment of risk of subsequent anxiety / depression was completed. In the previous chapter I demonstrated that for post TIA depression whilst the definition of a TIA (time based vs tissue based) did not significantly impact on the prevalence rate there was still a trend to a lower level in imaging negative TIAs (12.6% vs 15.9%). Furthermore, as imaging markers were not taken into account in this study it was not possible to comment on the impact of small vessel disease, which has been found to be an independent predictor for both post stroke depression and stroke recurrence.[35,36]

A further limitation of this study was the lack of co-assessment for an anxiety disorder with a validated tool in order to assess the sensitivity of the EuroQol-5D. However, a study on anxiety and depression in patients with acute lung injury found that the anxiety / depression question of the EuroQol-5D correlated moderately well both with the HADS-A (Spearman correlation = 0.54, $p<0.005$) and HAD-D (Spearman correlation = 0.41, $p<0.005$).[37] Likewise in 152 post stroke patients the EuroQol was moderately correlated with HADS-A (0.56, $p<0.001$) and the HADS-D (0.35, $p<0.001$).[38] Whilst limited by a lack of assessment for anxiety disorders, in this study I similarly found a moderate correlation (Kappa=0.370, $p<0.001$) between depression identified by the Geriatric Depression Score and the EuroQol-5D single question supporting its usefulness as a brief and pragmatic screening tool.

3.6 Conclusion

Symptoms of anxiety and depression are moderately high acutely after either a TIA or a minor stroke but show a greater improvement by 12-months in the TIA population with the EuroQol 5D offering a simple pragmatic approach to screening. The different temporal trajectories along with the varying risk factors for anxiety / depression symptoms between the TIA and minor stroke patients suggest a different underlying basis which requires further study.

3.7 References

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	Completed at least 1 month of follow up	Completed 12 months of follow-up
Overall, n (%) of total eligible	2137 (77.9)	1822 (85.3)
TIA alone	1162 (80.7)	1010 (86.9)
Minor stroke alone	975 (74.8)	812 (83.3)
Age at event, mean (s.d)	71.1 (13.2)	70.6 (12.9)
TIA alone	71.3 (13.0)	70.9 (12.6)
Minor stroke alone	71.0 (13.4)	70.3 (13.3)
Female sex, n (%)	1031 (48.2)	872 (47.9)
TIA alone	586 (50.4)	501 (49.6)
Minor stroke alone	445 (45.6)	371 (45.7)
Pre-morbid anxiety/depression, n (%)*	558 (26.3)	472 (26.0)
TIA alone	306 (26.5)	262 (26.0)
Minor stroke alone	252 (26.0)	210 (26.0)
Deprivation, mean IMD (s.d)*	10.8 (7.2)	10.6 (7.1)
TIA alone	10.6 (6.9)	10.4 (6.7)
Minor stroke alone	11.0 (7.5)	10.8 (7.5)
Hypertension, n (%)*	1230 (57.6)	1034 (56.8)
TIA alone	643 (55.3)	549 (54.4)
Minor stroke alone	587 (60.2)	485 (59.7)
Hyperlipidaemia, n (%)*	710 (33.2)	607 (33.3)
TIA alone	388 (33.4)	344 (34.1)
Minor stroke alone	322 (33.0)	263 (32.4)
Atrial fibrillation, n (%)*	311 (14.6)	247 (13.6)
TIA alone	160 (13.8)	134 (13.3)
Minor stroke alone	151 (15.5)	113 (13.9)
Previous TIA / stroke, n (%)*	264 (12.4)	219 (12.0)
TIA alone	142 (12.2)	122 (12.1)
Minor stroke alone	122 (12.5)	97 (11.9)
Diabetes mellitus, n (%)*	299 (14.0)	238 (13.1)
TIA alone	148 (12.7)	118 (11.7)
Minor stroke alone	151 (15.5)	120 (14.8)
Peripheral vascular disease, n (%)*	143 (6.7)	93 (5.1)
TIA alone	51 (4.4)	41 (4.1)
Minor stroke alone	92 (6.4)	52 (6.4)
IHD/ angina, n (%)*	367 (17.2)	299 (16.4)
TIA alone	183 (15.7)	152 (15.0)
Minor stroke alone	184 (18.9)	147 (18.1)
Current / prior smoking, n (%)*	1198 (56.1)	1010 (55.4)
TIA alone	622 (53.5)	526 (52.1)
Minor stroke alone	576 (59.1)	484 (59.6)
Education <12 years, n (%)*	1305 (61.9)	1101 (61.1)
TIA alone	673 (58.7)	585 (58.5)
Minor stroke alone	632 (65.8)	516 (64.3)
TIA (ABCD2 score≥4), n (%)*	661 (57.1)	567 (63.5)
Minor stroke (NIHSS) mean, s.d*	1.4 (1.3)	1.4 (1.3)

Table 3.1 Baseline characteristics of the 2137 patients who completed at least 1 month of follow up and the 1822 patients who completed 12 months of follow up. Baseline characteristics for the patients that did not complete follow up and comparisons are in Appendix XVII *Missing data overall: 36 x pre-morbid anxiety/depression, 2 x socio-economic deprivation status, 22 x smoking history, 193 x education level, 24 x ABCD2 scores, 2 x NIHSS scores, 8 x vascular history/risk factors (hypertension, hyperlipidaemia, previous TIA/stroke, diabetes mellitus, peripheral vascular disease, IHD/angina). IHD=ischaemic heart disease, NIHSS=National Institutes of Health Stroke Scale, IMD=indices of multiple deprivation.

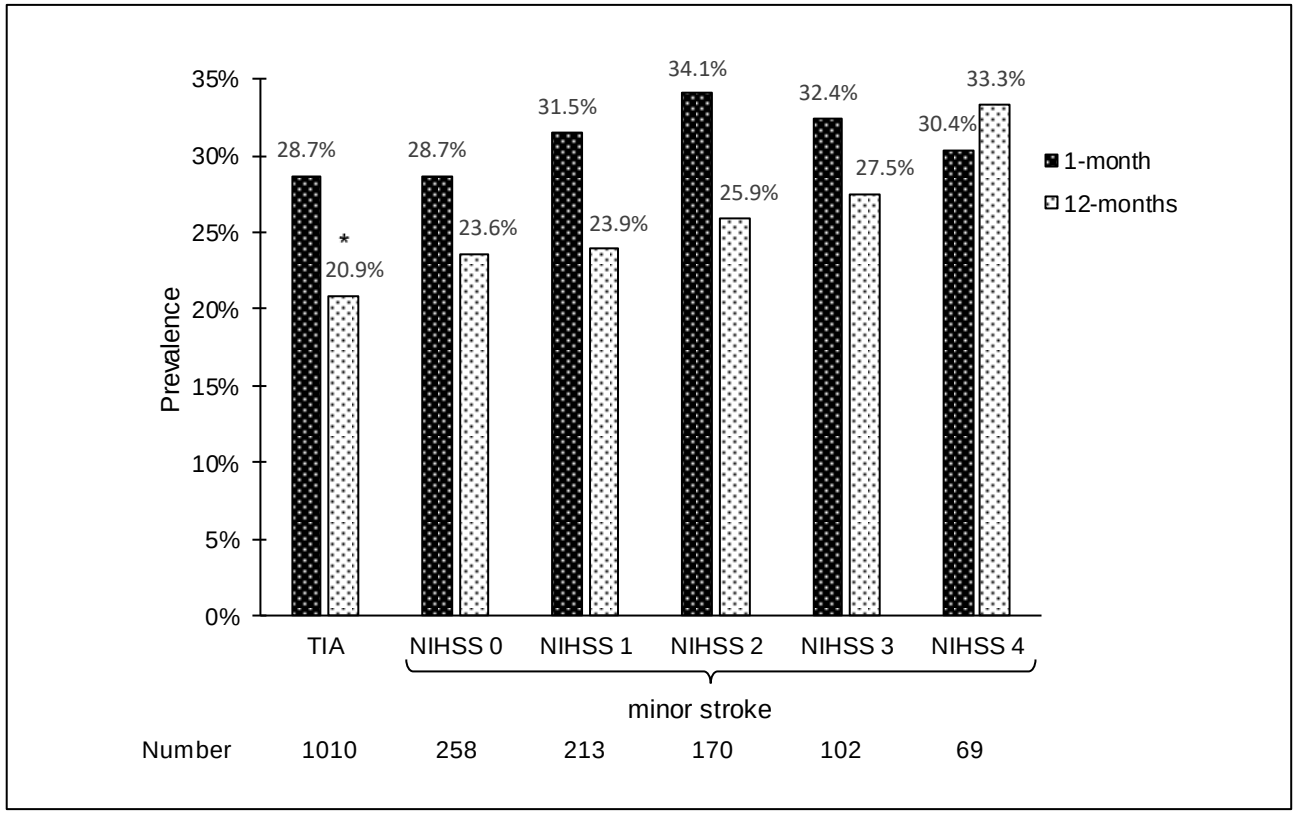

Figure 3.1 Prevalence of moderate-to-extreme symptoms of anxiety and/or depression at 1-month and 12-months after a TIA or minor stroke stratified by initial NIHSS score. Only patients who completed both the 1-month and 12-month assessments are included. Prevalence rates for symptoms of anxiety and/or depression at 12 months compared with those at 1 month with significance: * $p<0.001$

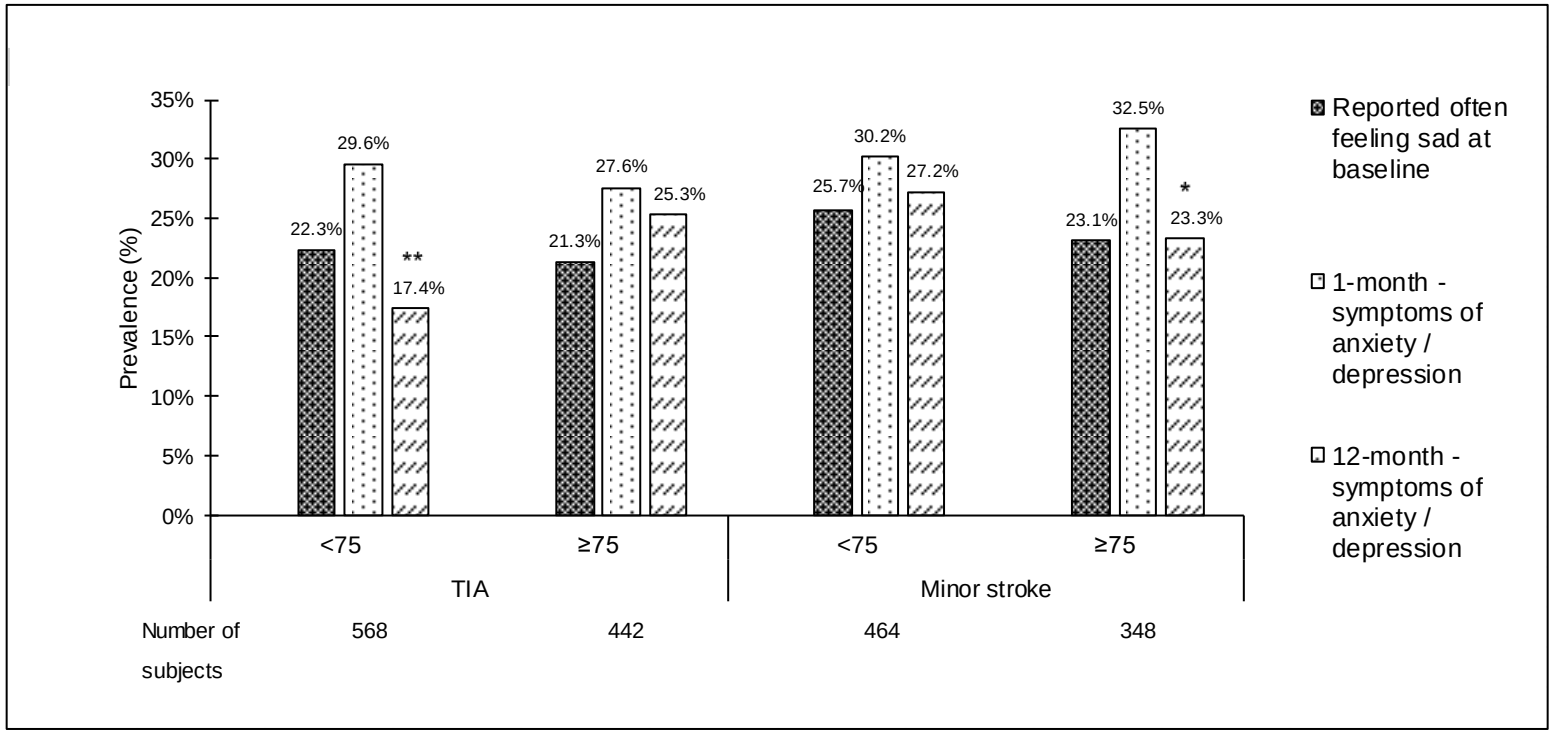

Figure 3.2 Prevalence of moderate-to-extreme symptoms of anxiety and/or depression at 1-month and 12-months after a TIA / minor stroke stratified by age cohorts. Prevalence of reporting feeling sad at the time of the event also included. Prevalence rates for symptoms of anxiety and/or depression at 12 months compared with those at 1 month with significance: * p<0.01 and **<0.001.

Baseline variable	All	Anxiety / depressive symptoms at 1-month	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	1031 (48.2)	365 (57.1)	666 (44.5)	1.66 (1.38-2.01)	**<0.001**	1.72 (1.42-2.08)	**<0.001**	1.48 (1.20-1.83)	**<0.001**
Mean age at event (s.d)	71.1 (13.2)	70.2 (13.5)	71.6 (13.0)	0.99 (0.99-1.00)	**0.032**	0.99 (0.98-1.00)	**0.005**	0.99 (0.98-1.00)	0.061
Sad at baseline (%)*	558 (26.3)	262 (42.1)	221 (15.1)	4.07 (3.29-5.04)	**<0.001**	3.90 (3.14-4.84)	**<0.001**	3.27 (2.61-4.09)	**<0.001**
Premorbid anxiety/depression (%)	483 (23.2)	260 (41.0)	298 (20.0)	2.78 (2.27-3.41)	**<0.001**	2.58 (2.10-3.17)	**<0.001**	1.96 (1.57-2.45)	**<0.001**
$ABCD2 ≥ 4 (%)*	661 (57.3)	195 (58.4)	466 (56.6)	1.08 (0.83-1.39)	0.583	1.23 (0.93-1.62)	0.140	-	-
$Symptoms > 1 hour (%)*	490 (42.8)	139 (41.6)	351 (42.6)	0.96 (0.74-1.24)	0.760	0.98 (0.75-1.27)	0.856	-	-
$Isolated speech symptoms (%)*	296 (25.5)	89 (26.6)	207 (25.1)	1.00 (0.78-1.30)	0.986	1.02 (0.78-1.32)	0.901	-	-
$Weakness symptoms (%)*	385 (33.2)	107 (32.0)	278 (33.7)	0.96 (0.78-1.19)	0.716	0.96 (0.77-1.19)	0.715	-	-
%Mean NIHSS (s.d)	1.4 (1.3)	1.5 (1.3)	1.4 (1.3)	1.03-0.93-1.14)	0.624	1.04 (0.93-1.15)	0.510	-	-
Smoking – current/prior (%)	1198 (56.1)	377 (59.0)	821 (54.8)	1.19 (0.98-1.43)	0.074	1.37 (1.13-1.67)	**0.002**	1.16 (0.93-1.43)	0.184
Hypertension	1230 (57.6)	384 (60.1)	846 (56.5)	1.16 (0.96-1.40)	0.121	1.25 (1.02-1.52)	**0.030**	1.13 (0.91-1.41)	0.282
Hyperlipidaemia	710 (33.2)	223 (34.9)	487 (32.5)	1.11 (0.92-1.35)	0.283	0.99 (0.98-1.00)	**0.003**	1.05 (0.84-1.31)	0.674
Atrial fibrillation	311 (14.6)	91 (14.2)	220 (14.7)	0.97 (0.74-1.26)	0.789	1.03 (0.79-1.35)	0.833	-	-
Diabetes mellitus	299 (14.0)	86 (13.5)	213 (14.2)	0.84 (0.72-1.23)	0.643	0.99 (0.75-1.30)	0.942	-	-
Peripheral vascular disease	113 (5.3)	29 (4.5)	84 (5.6)	0.80 (0.52-1.23)	0.313	0.88 (0.57-1.37)	0.579	-	-
IHD / angina	367 (17.2)	110 (17.2)	257 (17.2)	1.00 (0.79-1.29)	0.974	1.16 (0.90-1.50)	0.252	-	-
Past history of TIA / stroke	264 (12.4)	98 (15.3)	166 (11.1)	1.45 (1.11-1.90)	0.006	0.99 (0.98-1.00)	**0.001**	1.37 (1.02-1.85)	**0.039**
Low education (%)*	1305 (61.9)	410 (64.5)	895 (60.7)	0.99 (0.97-1.01)	0.217	0.99 (0.97-1.01)	0.234	-	-
Socio-economic deprivation (%)	276 (12.9)	104 (16.3)	172 (11.5)	1.50 (1.15-1.95)	**0.003**	0.99 (0.98-1.00)	**0.009**	1.29 (0.97-1.72)	0.082

Table 3.2 (a) Baseline characteristics of TIA / minor stroke stratified by the subsequent 1-month (n=2137) presence or absence of moderate-to-extreme symptoms of anxiety and/or depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of anxiety / depression symptoms at 1 month also included. (*missing data = 53 baseline feeling sad, 5 ABCD2 scores, 4 TIA symptom duration, 2 speech/weakness symptoms, 13 pre-morbid anxiety or depression history and 30 education history). $For TIA patients only. %For minor stroke patients only. IHD=ischaemic heart disease, NIHSS=National Institutes of Health Stroke Scale.

Baseline variable	All	Anxiety / depressive symptoms at 12-months	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	872 (47.9)	227 (54.3)	645 (45.9)	1.40 (1.12-1.74)	0.003	1.43 (1.14-1.78)	**0.002**	1.11 (0.86-1.44)	0.404
Mean age at event (s.d)	70.6 (12.9)	70.0 (13.9)	70.8 (12.6)	1.00 (0.99-1.00)	0.258	0.99 (0.99-1.00)	0.138	1.00 (0.99-1.01)	0.456
Sad at baseline (%)*	413 (23.1)	181 (44.3)	232 (16.8)	3.93 (3.09-5.00)	**<0.001**	3.82 (3.00-4.86)	**<0.001**	2.18 (1.66-2.86)	**<0.001**
Premorbid depression (%)*	472 (26.0)	173 (41.9)	299 (21.3)	2.66 (2.10-3.36)	**<0.001**	2.55 (2.01-3.24)	**<0.001**	1.66 (1.27-2.17)	**<0.001**
$ABCD2 ≥ 4 (%)*	567 (56.1)	210 (58.6)	444 (55.6)	1.13 (0.83-1.54)	0.435	1.07 (0.77-1.48)	0.685	-	-
$Symptoms > 1 hour (%)	424 (42.0)	98 (46.4)	326 (40.8)	1.26 (0.93-1.71)	0.140	1.24 (0.91-1.68)	0.172	-	-
$Isolated speech symptoms (%)*	258 (25.6)	58 (27.6)	200 (25.0)	1.14 (0.81-1.61)	0.445	1.01 (0.99-1.02)	0.307	-	-
$Weakness symptoms (%)*	323 (32.0)	67 (31.9)	256 (32.0)	0.99 (0.71-1.38)	0.970	0.98 (0.71-1.67)	0.925	-	-
%Mean NIHSS (s.d)	1.4 (1.3)	1.5 (1.3)	1.4 (1.3)	1.10 (0.98-1.24)	0.122	1.13 (1.00-1.28)	0.046	-	-
Smoking – current/prior (%)	1010 (55.4)	242 (57.9)	768 (54.7)	1.14 (0.91-1.42)	0.249	1.25 (0.99-1.47)	0.058	-	-
Hypertension	1034 (56.8)	241 (57.7)	793 (56.5)	1.05 (0.84-1.31)	0.671	0.99 (0.98-1.00)	0.102	-	-
Hyperlipidaemia	607 (33.3)	154 (36.8)	453 (32.3)	1.23 (0.98-1.54)	0.082	1.29 (1.03-1.63)	**0.030**	1.06 (0.80-1.39)	0.702
Atrial fibrillation	247 (13.6)	56 (13.4)	191 (13.6)	0.98 (0.71-1.35)	0.914	1.03 (0.74-1.43)	0.856	-	-
Diabetes mellitus	238 (13.1)	60 (14.4)	178 (12.7)	1.15 (0.84-1.58)	0.372	1.21 (0.88-1.66)	0.250	-	-
Peripheral vascular disease	93 (5.1)	18 (4.3)	75 (5.3)	0.80 (0.47-1.35)	0.399	0.86 (0.50-1.45)	0.561	-	-
IHD / angina	299 (16.4)	84 (20.1)	215 (15.3)	1.39 (1.05-1.84)	0.021	1.56 (1.17-2.08)	**0.003**	1.37 (0.97-1.93)	0.074
Past history of TIA / stroke	219 (12.0)	64 (15.3)	155 (11.0)	1.46 (1.06-2.00)	**0.019**	1.54 (1.12-2.12)	**0.008**	1.27 (0.88-1.83)	0.196
Low education (%)*	1101 (60.5)	266 (64.1)	835 (60.2)	1.18 (0.94-1.48)	0.154	1.19 (0.94-1.49)	0.146	-	-
Socio-economic deprivation (%)	229 (12.6)	65 (15.6)	164 (11.7)	1.39 (1.02-1.90)	**0.037**	1.40 (1.02-1.91)	**0.035**	1.10 (0.77-1.58)	0.588
Anxiety/Dep symptoms at 1-month	543 (29.8)	253 (60.5)	290 (20.7)	5.89 (4.66-7.45)	**<0.001**	5.77 (4.55-7.30)	**<0.001**	4.38 (3.39-5.64)	**<0.001**
Recurrent event between 1-12months	149 (8.2)	46 (11.0)	103 (7.3)	1.56 (1.08-2.25)	0.017	1.55 (1.07-2.23)	**0.020**	1.19 (0.78-1.81)	0.423

Table 3.2 (b) Baseline characteristics of TIA / minor stroke stratified by their subsequent 12-month (n=1822) presence or absence of moderate-to-extreme symptoms of anxiety and/or depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of anxiety / depression symptoms 12 months also included. (*12 month missing data = 33 baseline feeling sad, 8 pre-morbid anxiety or depression history, 20 education history, 1 ABCD2 score, 1 TIA speech/weakness symptoms). $For TIA patients only. %For minor stroke patients only. IHD=ischaemic heart disease, NIHSS=National Institutes of Health Stroke Scale, Anxiety/Dep = anxiety / depression.

Baseline characteristic	All	Anxiety / depressive symptoms at 1-month	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	586 (50.4)	202 (60.5)	384 (46.4)	1.77 (1.37-2.29)	**<0.001**	1.87 (1.44-2.43)	**<0.001**	1.69 (1.26-2.26)	**<0.001**
Mean age at event (s.d)	71.3 (13.0)	69.9 (13.3)	71.2 (12.8)	0.99 (0.98-1.00)	**0.017**	0.99 (0.98-1.00)	**0.003**	0.99 (0.98-1.00)	**0.010**
Sad at baseline (%)*	251 (22.0)	136 (41.2)	115 (14.2)	4.24 (3.16-5.70)	**<0.001**	4.14 (3.07-5.58)	**<0.001**	3.47 (2.55-4.73)	**<0.001**
Premorbid anxiety/depression (%)*	306 (26.5)	139 (41.7)	167 (20.3)	2.81 (2.13-3.70)	**<0.001**	2.55 (1.93-3.38)	**<0.001**	1.98 (1.46-2.68)	**<0.001**
ABCD2 ≥ 4 (%)*	661 (57.3)	195 (58.4)	466 (56.6)	1.08 (0.83-1.39)	0.583	1.23 (0.93-1.62)	0.140	-	-
Symptoms > 1 hour (%)*	490 (42.8)	139 (41.6)	351 (42.6)	0.96 (0.74-1.24)	0.760	0.98 (0.75-1.27)	0.856	-	-
Isolated speech symptoms (%)*	296 (25.5)	89 (26.6)	207 (25.1)	1.00 (0.78-1.30)	0.986	1.02 (0.78-1.32)	0.901	-	-
Weakness symptoms (%)*	385 (33.2)	107 (32.0)	278 (33.7)	0.96 (0.78-1.19)	0.716	0.96 (0.77-1.19)	0.715	-	-
Smoking – current/prior (%)	622 (53.5)	193 (57.8)	429 (51.8)	1.27 (0.99-1.65)	0.065	1.50 (1.15-1.97)	**0.003**	1.22 (0.91-1.62)	0.182
Hypertension	643 (55.3)	187 (56.0)	456 (55.1)	1.04 (0.80-1.34)	0.776	1.15 (0.87-1.51)	0.324	-	-
Hyperlipidaemia	388 (33.4)	110 (32.9)	278 (33.6)	0.97 (0.74-1.27)	0.834	1.08 (0.82-1.42)	0.610	-	-
Atrial fibrillation	160 (13.8)	49 (14.7)	111 (13.4)	1.11 (0.77-1.60)	0.571	1.26 (0.86-1.82)	0.233	-	-
Diabetes mellitus	148 (12.7)	42 (12.6)	106 (12.8)	0.98 (0.67-1.44)	0.916	1.03 (0.70-1.51)	0.900	-	-
Peripheral vascular disease	51 (4.4)	40 (4.8)	11 (3.3)	0.67 (0.34-1.32)	0.250	0.78 (0.39-1.55)	0.480	-	-
IHD / angina	183 (15.7)	141 (17.0)	42 (12.6)	0.70 (0.48-1.02)	0.060	0.83 (0.57-1.22)	0.351	-	-
Past history of TIA / stroke	142 (12.2)	49 (14.7)	93 (11.2)	1.36 (0.94-1.97)	0.103	1.49 (1.02-2.18)	**0.039**	1.39 (0.92-2.09)	0.119
Low education (%)*	673 (58.7)	205 (61.7)	468 (57.4)	1.20 (0.92-1.55)	0.178	1.23 (0.94-1.61)	0.126	-	-
Socio-economic deprivation (%)	141 (12.1)	51 (15.3)	90 (10.9)	1.48 (1.02-2.14)	**0.038**	1.48 (1.02-2.15)	**0.041**	1.32 (0.88-1.97)	0.179

Table 3.2 (c) Baseline characteristics of 1162 patients with a TIA stratified by their subsequent 1-month presence or absence of moderate-to-extreme symptoms of anxiety and/or depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 1 month also included. (*Missing data: 1 month =21 baseline feeling sad, 7 pre-morbid depression or anxiety history, 5 ABCD2 scores, 4 TIA symptom duration, 2 speech/weakness symptoms, 15 education histories). IHD=ischaemic heart disease.

Baseline characteristic	All	Anxiety / depression symptoms at 12-months	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	501 (49.6)	119 (56.4)	382 (47.8)	1.41 (1.04-1.92)	**0.027**	1.38 (1.02-1.88)	**0.039**	1.12 (0.79-1.58)	0.533
Mean age at event (s.d)	70.9 (12.6)	71.9 (13.2)	70.6 (12.4)	1.01 (1.00-1.02)	0.169	1.01 (1.00-1.02)	0.265	1.01 (1.00-1.03)	0.090
Sad at baseline (%)*	218 (21.9)	85 (41.3)	133 (16.9)	3.46 (2.45-4.83)	**<0.001**	3.41 (2.44-4.78)	**<0.001**	1.93 (1.32-2.81)	**0.001**
Premorbid anxiety / depression (%)*	262 (26.0)	86 (41.1)	176 (22.1)	2.47 (1.79-3.41)	**<0.001**	2.44 (1.75-3.39)	**<0.001**	1.69 (1.16-2.44)	**0.006**
ABCD2 ≥ 4 (%)	567 (56.1)	123 (58.3)	444 (55.6)	1.13 (0.83-1.54)	0.435	1.07 (0.77-1.48)	0.685	-	-
Symptoms > 1 hour (%)	424 (42.0)	98 (46.4)	326 (40.8)	1.27 (0.94-1.72)	0.126	1.24 (0.91-1.68)	0.172	-	-
Isolated speech symptoms (%)*	258 (25.5)	58 (27.5)	200 (25.0)	1.14 (0.81-1.61)	0.445	1.12 (0.79-1.58)	0.532	-	-
Weakness symptoms (%)*	323 (32.0)	67 (31.8)	256 (32.0)	0.99 (0.72-1.34)	0.970	0.98 (0.71-1.37)	0.984	-	-
Smoking – current/prior (%)	526 (52.1)	112 (53.1)	414 (51.8)	1.05 (0.78-1.43)	0.743	1.16 (0.85-1.60)	0.347	-	-
Hypertension	549 (54.4)	120 (56.9)	429 (43.7)	1.14 (0.84-1.54)	0.410	1.07 (0.78-1.48)	0.674	-	-
Hyperlipidaemia	344 (34.1)	77 (36.5)	267 (33.4)	1.15 (0.83-1.57)	0.402	1.16 (0.84-1.60)	0.368	-	-
Atrial fibrillation	134 (13.3)	29 (13.7)	105 (13.1)	1.05 (0.68-1.64)	0.818	1.03 (0.66-1.62)	0.886	-	-
Diabetes mellitus	118 (11.7)	24 (11.4)	94 (11.8)	0.86 (0.60-1.55)	0.875	0.97 (0.60-1.56)	0.891	-	-
Peripheral vascular disease	41 (4.1)	8 (3.8)	33 (4.1)	0.92 (0.42-2.01)	0.825	0.93 (0.42-2.05)	0.847	-	-
IHD / angina	152 (15.0)	42 (19.9)	110 (13.8)	1.56 (1.05-2.31)	**0.027**	1.58 (1.05-2.38)	**0.028**	1.72 (1.09-2.71)	**0.019**
Past history of TIA / stroke	122 (12.1)	32 (15.2)	90 (11.3)	1.41 (0.91-2.18)	0.123	1.39 (0.90-2.16)	0.142	-	-
Low education (%)*	585 (58.5)	134 (64.1)	451 (57.0)	1.07 (0.92-1.23)	0.383	1.30 (0.95-1.79)	0.105	-	-
Socio-economic deprivation (%)	114 (11.3)	31 (14.7)	83 (10.4)	1.49 (0.95-2.32)	0.080	1.51 (0.97-2.35)	0.071	-	-
Anxiety/Dep symptoms at 1-month	290 (28.7)	125 (59.2)	165 (20.7)	5.59 (4.04-7.72)	**<0.001**	5.63 (4.05-7.82)	**<0.001**	4.70 (3.30-6.70)	**<0.001**
Recurrent event between 1-12months	85 (8.4)	21 (10.0)	64 (8.0)	1.27 (0.76-2.13)	0.367	1.26 (0.75-2.12)	0.384	-	-

Table 3.2 (d) Baseline characteristics of 1010 patients with a TIA stratified by their subsequent 12-month presence or absence of moderate-to-extreme symptoms of anxiety and/or depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 12-months also included. (*Missing data: 12 months = 5 feeling sad at baseline, 4 pre-morbid anxiety / depression histories, 1 speech / weakness symptoms, 10 education histories) IHD=ischaemic heart disease, Anxiety/Dep = anxiety / depression.

Baseline characteristic	All	Anxiety / depression symptoms at 1 month	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	445 (45.6)	163 (53.4)	282 (42.1)	1.58 (1.20-2.07)	**0.001**	1.60 (1.22-2.11)	0.**001**	1.28 (0.95-1.73)	0.111
Mean age at event (s.d)	71.0 (13.4)	70.6 (13.6)	71.1 (13.4)	1.00 (0.99-1.01)	0.549	1.00 (0.99-1.01)	0.333	1.00 (0.99-1.01)	0.893
Sad at baseline (%)*	232 (24.6)	126 (43.0)	106 (16.3)	3.87 (2.84-5.29)	**<0.001**	3.72 (2.72-5.09)	**<0.001**	3.09 (2.22-4.29)	**<0.001**
Premorbid anxiety /depression (%)*	252 (26.0)	121 (40.2)	131 (19.6)	2.76 (2.04-3.72)	**<0.001**	2.63 (1.94-3.56)	**<0.001**	1.96 (1.41-2.72)	**<0.001**
Mean NIHSS (s.d)	1.4 (1.3)	1.5 (1.3)	1.4 (1.3)	1.03 (0.93-1.14)	0.624	1.04 (0.93-1.15)	0.510	-	-
Smoking – current/prior (%)	576 (59.1)	184 (60.3)	392 (58.5)	1.08 (0.82-1.42)	0.592	1.23 (0.92-1.65)	0.159	-	-
Hypertension	587 (60.2)	197 (64.6)	390 (58.2)	1.31 (0.99-1.73)	0.059	1.36 (1.02-1.82)	**0.038**	1.20 (0.87-1.66)	0.274
Hyperlipidaemia	322 (33.0)	113 (37.0)	209 (31.21)	1.30 (0.98-1.73)	0.072	1.37 (1.03-1.83)	**0.033**	1.16 (0.83-1.63)	0.381
Atrial fibrillation	151 (15.5)	42 (13.8)	109 (16.3)	0.82 (0.56-1.21)	0.318	0.83 (0.56-1.22)	0.337	-	-
Diabetes mellitus	151 (15.5)	44 (14.4)	107 (16.0)	0.89 (0.61-1.30)	0.537	0.95 (0.64-1.39)	0.773	-	-
Peripheral vascular disease	62 (6.4)	18 (5.9)	44 (6.6)	0.89 (0.51-1.57)	0.693	0.95 (0.54-1.37)	0.849	-	-
IHD / angina	184 (18.9)	68 (22.3)	116 (17.3)	1.37 (0.98-1.92)	0.066	1.53 (1.08-2.17)	**0.016**	1.15 (0.77-1.71)	0.510
Past history of TIA / stroke	122 (12.5)	49 (16.1)	73 (10.9)	1.57 (1.06-2.31)	**0.024**	1.68 (1.12-2.50)	**0.011**	1.32 (0.85-2.04)	0.212
Low education (%)*	632 (65.8)	205 (68.3)	427 (64.7)	1.18 (0.88-1.58)	0.271	1.18 (0.88-1.59)	0.268	-	-
Socio-economic deprivation (%)	135 (13.8)	53 (17.4)	82 (12.2)	1.51 (1.04-2.20)	**0.032**	1.49 (1.02-2.17)	**0.040**	1.27 (0.84-1.92)	0.259

Table 3.2 (e) Baseline characteristics of 975 patients with a minor stroke stratified by their subsequent 1-month presence or absence of moderate-to-extreme symptoms of anxiety and/or depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 1 month also included. (*Missing data: 1 month = 32 baseline feeling sad, 6 premorbid anxiety or depression histories, 15 education histories). IHD=ischaemic heart disease, NIHSS=National Institutes of Health Stroke Scale.

Baseline characteristic	All	Anxiety / depression symptoms at 12-months	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	371 (45.7)	108 (52.2)	263 (43.5)	1.42 (1.03-1.95)	**0.030**	1.49 (1.09-2.06)	**0.014**	1.10 (0.76-1.60)	0.620
Mean age at event (s.d)	70.3 (13.3)	68.0 (14.2)	71.1 (12.9)	0.98 (0.97-1.00)	**0.004**	0.98 (0.97-0.99)	**0.002**	0.98 (0.97-1.00)	**0.010**
Sad at baseline (%)*	195 (24.5)	96 (47.3)	99 (16.7)	4.47 (3.15-6.34)	**<0.001**	4.26 (2.99-6.07)	**<0.001**	2.55 (1.71-3.81)	**<0.001**
Premorbid anxiety / depression (%)*	210 (26.0)	87 (42.6)	123 (20.4)	2.91 (2.07-4.09)	**<0.001**	2.68 (1.90-3.80)	**<0.001**	1.69 (1.13-2.53)	**0.011**
Mean NIHSS (s.d)	1.4 (1.3)	1.5 (1.3)	1.4 (1.3)	1.10 (0.98-1.24)	0.112	1.13 (1.00-1.28)	**0.046**	1.16 (1.01-1.34)	**0.011**
Smoking – current/prior (%)	484 (59.6)	130 (62.8)	354 (58.5)	1.20 (0.87-1.66)	0.278	1.29 (0.92-1.81)	0.140	-	-
Hypertension	485 (59.7)	121 (58.5)	364 (60.2)	0.93 (0.68-1.28)	0.932	1.06 (0.75-1.48)	0.755	-	-
Hyperlipidaemia	263 (32.4)	77 (37.2)	186 (30.7)	1.33 (0.96-1.86)	0.087	1.44 (1.03-2.02)	**0.034**	1.15 (0.78-1.70)	0.491
Atrial fibrillation	113 (13.9)	27 (13.0)	86 (14.2)	0.91 (0.57-1.44)	0.674	1.02 (0.63-1.34)	0.940	-	
Diabetes mellitus	120 (14.8)	36 (17.4)	84 (13.9)	1.31 (0.82-2.00)	0.221	1.40 (0.91-2.16)	0.128	-	
Peripheral vascular disease	52 (6.4)	10 (4.8)	42 (6.9)	0.68 (0.34-1.38)	0.680	0.76 (0.37-1.55)	0.443	-	
IHD / angina	147 (18.1)	42 (20.3)	105 (17.4)	1.21 (0.81-1.81)	0.344	1.47 (0.97-2.22)	0.070	-	
Past history of TIA / stroke	97 (11.9)	32 (15.5)	65 (10.7)	1.52 (0.96-2.40)	0.072	1.78 (1.12-2.85)	**0.016**	1.29 (0.75-2.22)	0.365
Low education (%)*	516 (64.3)	132 (64.1)	384 (64.4)	0.91 (0.76-1.09)	0.302	1.04 (0.74-1.46)	0.817	-	
Socio-economic deprivation (%)	115 (14.2)	34 (16.4)	81 (13.4)	1.27 (0.82-1.97)	0.280	1.23 (0.79-1.92)	0.355	-	
Anxiety/Dep symptoms at 1-month	253 (31.2)	128 (61.8)	125 (20.7)	6.22 (4.42-8.77)	**<0.001**	6.20 (4.38-8.78)	**<0.001**	4.37 (3.01-6.35)	**<0.001**
Recurrent event between 1-12months	64 (7.9%)	25 (12.1)	39 (6.4)	1.99 (1.17-3.38)	**0.011**	1.85 (1.08-3.17)	**0.025**	1.51 (0.80-2.84)	0.208

Table 3.2 (f) Baseline characteristics of 812 patients with a minor stroke stratified by their subsequent 12-month presence or absence of moderate-to-extreme symptoms of anxiety and/or depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of moderate / extreme symptoms of anxiety / depression at 12-months also included. (*Missing data: 12 month = 17 feeling sad at baseline, 4 pre-morbid anxiety or depression histories, 10 education histories). IHD=ischaemic heart disease, NIHSS=National Institutes of Health Stroke Scale, Anxiety/Dep=anxiety/depression.

	TIA / minor stroke		TIA		Minor stroke	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
(a) 1-month						
Female sex	1.41 (1.15-1.73)	**<0.001**	1.69 (1.26-2.26)	**<0.001**	1.23 (0.91-1.65)	0.482
Younger age (per year)	0.99 (0.99-1.00)	0.069	0.99 (0.98-1.00)	**0.010**	1.00 (0.99-1.01)	0.182
Reporting often feeling sad at baseline	3.33 (2.67-4.17)	**<0.001**	3.47 (2.55-4.73)	**<0.001**	3.23 (2.32-4.47)	**<0.001**
Premorbid anxiety / depression	1.43 (1.06-1.91)	**<0.001**	1.98 (1.46-2.68)	**<0.001**	2.01 (1.45-2.79)	**<0.001**
Past history of TIA / stroke	1.43 (1.06-1.91)	**0.019**	**-**	**-**	-	**-**
(b) 12-months (not including 1-month symptoms)						
Female sex	1.18 (0.93-1.50)	0.169	1.27 (0.91-1.77)	0.159	1.16 (0.82-1.65)	0.408
Younger age (per year)	1.00 (0.99-1.01)	0.735	1.01 (1.00-1.02)	0.214	0.99 (0.97-1.00)	**0.031**
Reporting often feeling sad at baseline	3.25 (2.53-4.18)	**<0.001**	2.87 (2.02-4.07)	**<0.001**	3.73 (2.57-5.41)	**<0.001**
Premorbid anxiety / depression	2.00 (1.55-2.58)	**<0.001**	2.05 (1.45-2.91)	**<0.001**	2.02 (1.38-2.96)	**<0.001**
Past history of IHD/angina	-	**-**	1.54 (1.00-2.38)	**0.049**	-	**-**
Higher NIHSS (per 1 point increase)*	-	**-**	**-**	**-**	1.18 (1.03-1.34)	**0.016**
(c) 12 months (including 1-month symptoms)						
Female sex	1.06 (0.83-1.36)	0.639	1.12 (0.79-1.58)	0.533	1.08 (0.75-1.56)	0.682
Younger age (per year)	1.00 (0.99-1.01)	0.848	1.01 (1.00-1.03)	0.090	0.98 (0.97-1.00)	**0.012**
Reporting often feeling sad at baseline	2.23 (1.70-2.93)	**<0.001**	1.93 (1.32-2.81)	**0.001**	2.60 (1.71-3.87)	**<0.001**
Premorbid anxiety / depression	1.68 (1.28-2.20)	**<0.001**	1.69 (1.16-2.44)	**0.006**	1.71 (1.14-2.55)	**0.009**
Anxiety / depression symptoms at 1 month	4.43 (3.44-5.71)	**<0.001**	4.70 (1.09-2.71)	**<0.001**	4.50 (3.10-6.52)	**<0.001**
Past history of IHD/angina	-	**-**	1.72 (1.09-2.71)	**0.019**	-	**-**
Higher NIHSS (per 1 point increase)*	-	-	-	-	1.17 (1.01-1.34)	**0.031**

Table 3.3 Summary of characteristics associated with moderate-to-extreme symptoms of anxiety and/or depression at (a) 1-month and (b,c) 12-months after a multivariate analysis for all patients, TIA patients and minor stroke patients alone. Only variables that were found to be significantly ($p<0.05$) associated with symptoms in the multivariate analysis were included in each model. Age/sex were included in all models as have been found to be associated with anxiety and depression in other studies. - = not significant in multivariate analysis so not included in model. Separate models for 12-month symptoms are presented with (b) only including baseline variables and (c) also including 1-month symptoms of anxiety / depression. NIHSS score included in models of minor stroke only. See Tables 3.2 (a) – (f) for further details. IHD=ischaemic heart disease, NIHSS=National Institutes of Health Stroke Scale.

	Mean VAS score (s.d)		p value
	Anxiety / depression symptoms	No anxiety / depression symptoms	
TIA / minor stroke			
At 1 month	65.6 (19.7)	78.1 (15.9)	<0.001
At 12 months	65.0 (18.9)	79.8 (16.2)	<0.001
TIA patients only			
At 1 month	68.0 (18.4)	79.1 (15.4)	<0.001
At 12 months	65.1 (18.4)	81.0 (15.2)	<0.001
Minor stroke patients only			
At 1 month	62.9 (20.8)	76.9 (16.4)	<0.001
At 12 months	64.8 (78.3)	78.3 (17.3)	<0.001

Table 3.4 EQ Visual Analogue Scale (VAS) scores for those with and without moderate / extreme anxiety / depression symptoms stratified by time after event and event type. Mean (standard deviation) VAS scores are presented for all patients, TIA patients and minor stroke patients at both 1 month and 12 month with a comparison of the scores in those reporting and not anxiety / depression symptoms at each time point.

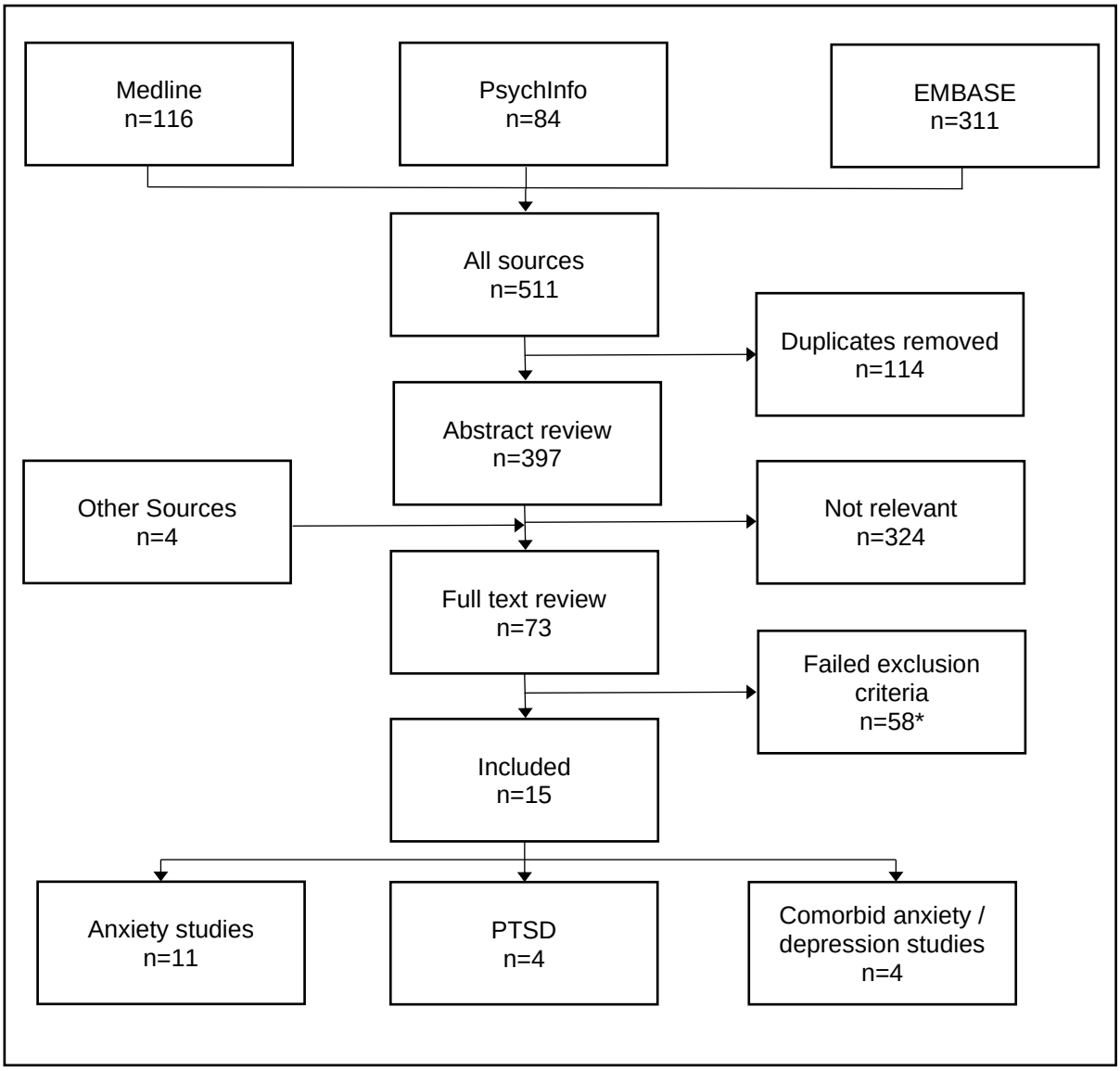

Figure 3.3 Literature search summary. *Reasons for failing full text review presented in Appendix XV

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Study Author, year, location	N. of TIA patients	Male gender	Mean age (yrs)	Recruitment method	Participation rate	Review Method	Inclusion Criteria	Exclusion Criteria	Follow up time point(s) for which prevalence data presented	Measure & cut-off	Associated factors
Broomfield NM et al, 2014, UK	1247	52%	[&]71	Enhanced primary care coding data	35%	Annual Local Enhanced Services primary care reviews	All living stroke survivors in database 2012-2013	Care home, house bound (coding)	Cross-sectional	HADS-A: 8-10 possible ≥11 definite.	Female, younger age, socioeconomic deprivation, COPD
Chun HY et al, 2018, UK	61	*60%	*70	Consecutive admissions to a single centre	N/S	Telephone (or face-to-face if unable)	Aged ≥18 years, new clinical diagnosis of stroke or definite /probable TIA, able to give informed consent, able to communicate in English on the telephone	SAH, subdural and extradural haematoma, ocular TIA, patients at terminal stage of life, or who were difficult to follow up (e.g no fixed abode)	3 months	SCID	*Younger age, premorbid anxiety / depression
Kapoor A et al, 2019, Canada	133	*50%	[*,&]65	Consecutive referrals to a stroke prevention clinic	N/S	Face to face	Probable / definite diagnosis of ischaemic stroke or TIA by a neurologist.	Severe aphasia, severe motor dysfunction, non-fluent English	At first follow up (median 54.5 days)	GAD-7≥10	Younger age, depression
Maaijwee NA et al, 2016, The Netherlands	186	45%	41	FUTURE study - consecutive patients with TIA, stroke or ICH aged 18-50 years	71% of original cohort	Face to face	First ever TIA, aged 18-50	N/S	Mean 8.3 years	HADS-A≥8	*Lower risk in 'rarer' causes
Sackley CM et al, 2019, UK	364	59%	70	Patients attending one of 30 TIA clinics across 4 regions of England	N/S	Postal questionnaires	Diagnosed within 14 days of event, able to self-complete postal questionnaire	History of stroke or TIA	Baseline	HADS-A>N/S	Younger age
Kiphuth IC et al, 2017, Germany	108	55%	[&]70	Consecutive admissions to a single centre stroke unit	51%	Postal questionnaires	TIA with ABCD2 score >3 or ≤2 with hemiparesis, aphasia, amaurosis fugax. Negative brain scan. Rankin 0-2 before and after event.	N/S	3 months	HADS-A≥8	N/S
Sanner Beauchamp JE et al, 2020, USA	24	*56%	*60	Convenience sampling of secondary data from outpatient stroke follow up clinic	* 68%	Face to face	Aged ≥18 years, completed follow up assessments.	Incomplete data, lacked consent to participate	1-3 months	GAD-7≥10	*non-married, fatigue, depression
[†]van Rooij FG et al, 2017, The Netherlands	103	*61%	*66	Consecutive stroke-free patients referred to outpatient TIA clinic (CONNECT) study	N/S	Face to face	45 years and older, referred within 7 days after an acute onset neurological symptom lasting <24	Incomplete f/u.	Baseline and 6 months	HADS-A≥8	Not associated with DWI status
Wong A et al, 2016, China	73	40%	69	Consecutive admissions to an acute stroke unit recruited to STRIDE (parent study)	51% of STRIDE	Face to face	Stroke or TIA (symptoms <24 hours and negative imaging). Able to participate in cognitive assessment	Pre-event dementia, significant sensorimotor and language impairment precluding participation in cognitive testing.	3 to 6 months	NPI≥ 1 symptom	N/S
Turner A et al, 2016, Australia	51	67%	69	Outpatient stroke nurse practitioner follow up clinic at a single centre	N/S	Baseline: face to face. 3 month: telephone	Diagnosed with TIA	N/S	Baseline and 3 months	GAD-7≥10	N/S
Rizos T et al, 2018, Germany	73	63%	[&]69	Consecutive TIA admissions to a single centre	N/S	N/S	N/S	N/S	Baseline and 3 months	GAD-7> N/S	N/S

Table 3.5 Studies reporting on prevalence and associated factors for anxiety disorders after a TIA. *= Data for TIA patients alone not stated, overall data (for combined TIA/stroke patients) presented where available, [&]median, [†]Van-Rooij additionally includes atypical TIAs. HADS-A=Hospital Anxiety and Depression Scale-Anxiety, GAD-7=Generalised Anxiety Disorder-7, NPI=Neuropsychiatric Inventory, SCID=Structured Clinical Interview for DSM-IV disorders N/S=not specified, FUTURE=Follow-up of transient ischaemic attack and stroke patients and unelucidated risk factor evaluation, CONNECT=Cohort study ON Neuroimaging, Etiology, an Cognitive consequences of Transient neurological attacks, STRIDE=Stroke Registry investigating cognitive Decline, COPD=Chronic obstructive pulmonary disease, DWI=Diffusion-weighted imaging.

Study Author, year, location	N. of TIA patients	Male gender	Median age (years)	Recruitment method	Participation rate	Review Method	Inclusion Criteria	Exclusion Criteria	Follow up time point(s) for which prevalence data presented	Measure & cut-off	Associated factors
*Kiphuth IC et al, 2014 and Utz KS et al, 2019, Germany	108 at 3 months, 84 at 12 months	3 months: 55% 12 months: 54%	3 months: 70 12 months: 69	Consecutive admissions to a single centre stroke unit	3 months: 51% 12 months:48%	Postal questionnaire	ABCD2 score >3 or ≤2 with hemiparesis, aphasia, amaurosis fugax. Negative brain scan. Rankin 0-2 before and after event.	For 12 month assessment: excluded if recurrent stroke/TIA after first event	3 months and 12 months	German version of PDS	Younger age, subjectively rated stroke risk, maladaptive coping strategies
Rizos T et al, 2018, Germany	73	63%	69	Consecutive hospitalised TIA patients	N/S	N/S	TIA	N/S	3 months	PDS	Psychiatric history

Table 3.6 Studies reporting on prevalence and associated factors for PTSD after a TIA. *Two papers reported on the same population but at different time points so have been collated for the purpose of this review. N/S = not stated. PDS=Post-traumatic stress assessment.

Study Author, year, location	N. of TIA patients	Male gender	Median age (years)	Recruitment method	Participation rate	Review Method	Inclusion Criteria	Exclusion Criteria	Follow up time point(s) for which prevalence data presented	Measure & cut-off	Associated factors
Turner GM et al, 2016, UK	9240	48%	74	Retrospective study of first-ever TIA patients from primary care coding	N/A (review of coding data only)	Primary care coding	≥18 years, first-ever TIA, registered at their GP for ≥ 1 year prior to event, survive ≥ 1 month after event	Baseline psychological impairment, prior TIA/stroke	Cross-sectional (median length of follow up was 11.2 months)	Clinical codes or first prescription of an anti-depressant or anti-anxiety drug	N/S
Thayabaranathan T et al, 2018, Australia	748	*52.8%	74	Prospective multi-centre observational cohort study of all patients admitted with TIA or stroke.	*71%	Postal questionnaire with follow up telephone call if required	Diagnosis of ischaemic stroke, intracerebral haemorrhage, TIA or stroke of unknown cause. 18 years or older, provided responses to EQ-5D-5L questionnaire	Incomplete data (0.7% excluded)	90-180 days	EuroQol anxiety/ depression question	Pre-morbid mental health problem, dementia, discharge home with support, socioeconomic deprivation
Winward C et al, 2009, UK	76	53%	73	Population based study of all acute vascular events with near complete case ascertainment	100%	Face to face interview	TIA, functionally independent at 6 month follow, Barthel index ≥18	Recurrent stroke during the first 6 months, major non-stroke disorder (e.g. cancer, ACS) during first 6 months	1 month and 6 month	EuroQol anxiety/ depression question	N/S

Table 3.7 Studies reporting on prevalence and associated factors for comorbid anxiety / depression after a TIA. *Data for TIA patients alone not stated, overall data (for combined TIA/stroke patients) presented where available. N/S=not stated. Chun HY et al also presented data on patients with combined anxiety and depression (see Table 2.10 and 3.5) for details of the study assessments for each mood disorder.

Screening Tool	Study	Cut-off	Sensitivity (%)	Specificity (%)
Anxiety screening tools:				
HADS-A	[39]Sagen et al, 2009	≥8	52%	90%
	[40]O'Rouke et al, 1998		50%	87%
GAD-7	No validation studies found.			
SCID	No validation studies found.			
NPI	No validation studies found.			
PTSD screening tools:				
PDS	No validation studies found.			
Comorbid anxiety/depression:				
Euroqol Anxiety/Depression	No validation studies found			

Table 3.8 Assessment tools identified in the systematic review of anxiety, PTSD and comorbid anxiety / depression after a TIA with their validation studies (where available). Sensitivity and specificity values are quoted from the referenced validation study. * Table adapted from Burton et al.[41] HADS-A= Anxiety subscale of the Hospital Anxiety and Depression Scale, NPI= Neuropsychiatric Inventory, SCID= Structured Clinical Interview, PDS= Post-traumatic stress assessment.

	Anxiety/ Total	Prev (%)	95% CI	p value for heterogeneity	Time	Assessment method	Assessment tool
Baseline							
Rizos T et al, 2014	6 / 73	8.2	1.9-15.5		Baseline	N/S	HADS-A>n/s
Turner A et al, 2016	5 / 51	9.8	1.6-18.0		Baseline	Face to face	GAD-7>n/s
van Rooij FG et al, 2017	15 / 105	14.3	7.6-21.0		10 days	Face to face	HADS-A ≥8
Sackley CM et al, 2019	51 / 364	14.0	10.4-17.6		Baseline	Postal	HADS-A>n/s
Total	**77 / 593**	**13.1**	**10.5-16.0**	**0.506**			
1 – 6 months							
Kiphuth IC et al, 2014	21 / 108	19.4	12.0-26.9		3 months	Postal	HADS-A ≥8
Rizos T et al, 2014	3 / 61	4.9	-0.5-10.3		3 months	N/S	GAD-7>n/s
Turner A et al, 2016	6 / 46	11.8	2.9-20.6		3 months	Telephone	GAD-7 >9
Wong A et al, 2016	3 / 73	4.1	-0.4-8.7		3-6 months	Face to face	NPI
van Rooij FG et al, 2017	11 / 103	10.7	4.7-16.6		6 months	Face to face	HADS-A ≥8
Chun HY et al, 2018	11 / 61	18.0	8.4-27.7		3 months	Telephone	SCID n/s
Beauchamp S et al, 2020	8 / 24	33.3	14.5-52.2		1-3 months	Face to face	GAD-7 >9
Total	**60 / 420**	**14.3**	**8.1-20.4**	**0.001**			

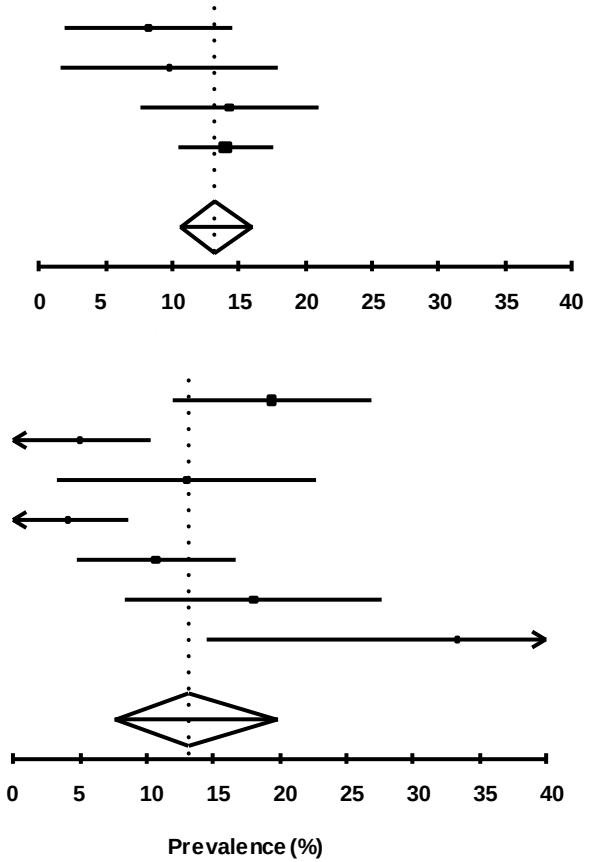

Figure 3.4 (a) Pooled prevalence of anxiety stratified by time (baseline, 1-6 months) after a TIA in all studies where a prevalence rate was reported.
Prev=prevalence, HADS-A=Hospital Anxiety and Depression Scale-Anxiety, GAD-7=Generalised Anxiety Disorder-7, NPI=Neuropsychiatric Inventory, SCID=Structured Clinical Interview for DSM-IV disorders, N/S=not specified.

	Anxiety/ Total	Prev (%)	95% CI	p value for heterogeneity	Time	Assessment method	Assessment tool
Baseline							
Rizos T et al, 2014	6 / 73	8.2	1.9-15.5		Baseline	N/S	HADS-A>n/s
Turner A et al, 2016	5 / 51	9.8	1.6-18.0		Baseline	Face to face	GAD-7>n/s
van Rooij FG et al, 2017	15 / 105	14.3	7.6-21.0		10 days	Face to face	HADS-A ≥8
Total	**26 / 229**	**11.6**	**7.8-16.2**	**0.432**			
3 – 6 months							
Rizos T et al, 2014	3 / 61	4.9	-0.5-10.3		3 months	N/S	GAD-7>n/s
Turner A et al, 2016	6 / 46	11.8	2.9-20.6		3 months	Telephone	GAD-7 >9
van Rooij FG et al, 2017	11 / 103	10.7	4.7-16.6		6 months	Face to face	HADS-A ≥8
Total	**20 / 210**	**9.7**	**6.0-14.0**	**0.296**			

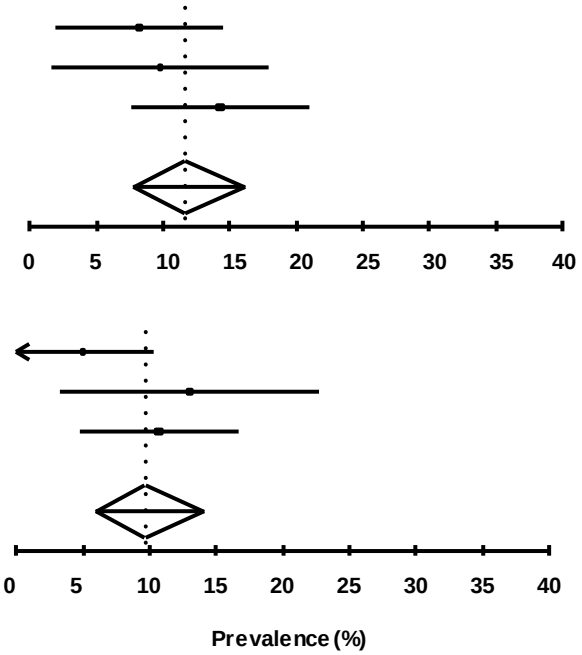

Figure 3.4 (b) Pooled prevalence of anxiety stratified by time (baseline, 3-6 months) after a TIA in only the longitudinal studies where prevalence rates at multiple time points for the same cohort were reported. Prev=prevalence, HADS-A=Hospital Anxiety and Depression Scale-Anxiety, GAD-7= Generalised Anxiety Disorder-7, N/S=not specified.

CHAPTER 4

PRELIMINARY ANALYSIS OF IMAGING PREDICTORS AND PROGNOSIS OF SYMPTOMS OF ANXIETY AND DEPRESSION AFTER A TIA OR MINOR STROKE

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4.1 Abstract

Introduction: Brain imaging markers acquired at the time of a stroke have been demonstrated to have prognostic value for assessing the risk of subsequent anxiety and depression disorders, but studies are often limited to MRI-imaging and in major stroke patients with little known about their predictive ability in Transient Ischaemic Attack (TIA) patients. Furthermore, whilst there is increasing literature on the outcomes associated with post-stroke depression and anxiety, this has not been explored in the TIA population.

Methods: In a prospective longitudinal population-based study, TIA and minor stroke patients who had baseline brain imaging (CT or MRI) were subsequently interviewed at one and 12-months after their event to detect anxiety and/or depression symptoms. Baseline brain imaging was assessed for the presence (none-to-mild vs moderate-to-severe) of white matter disease and the presence / absence of an acute brain lesion. Patients were then followed (up to death, 10 years or 30 November 2019, whichever came first) to detect any recurrent stroke, recurrent acute vascular event and death. Cox regression analyses were used to estimate the associations between anxiety and / or depression symptoms and subsequent events, in age/sex adjusted models.

Results: Among 2098 TIA and minor stroke patients who had baseline brain imaging (1224 MRI, 874 CT) and at least one-month of follow-up there were 28.5% (n=597) with acute stroke lesions on imaging. The presence of an acute lesion was not associated with subsequent anxiety and/or depression symptoms at one-month (adjusted OR 0.83, 95% CI 0.71-1.12, p=0.332) or 12-months (0.94, 0.72-1.23, p=0.673), with similar results when restricted to the 1224 patients with MRI-based imaging. Among the 2098 patients moderate-to-severe white matter disease on brain imaging (28.5%) was not associated with symptoms of anxiety and/or depression at one-month (1.00, 0.79-1.27, p=0.985) or 12-months (1.18, 0.90-1.55, p=0.242). However, restricting the analysis to MRI-imaging and depression alone did find associations, particularly for TIA patients (one-month: 3.32, 1.39-7.95, p=0.007, 12-months: 2.71, 1.01-7.31, p=0.049).

During a follow up of 10,796 person-years for 2137 TIA / minor stroke patients there were 412 recurrent vascular events and 619 deaths. Although no association was seen between subsequent recurrent vascular event and anxiety and/or depression symptoms at one-month (age/sex adjusted HR 1.20, 95% CI 0.95-1.51, p=0.135) or 12-months (1.28, 0.94-1.74, p=0.119), mortality was increased (one-month: 1.35, 1.13-1.60, p=0.001, 12-months: 1.44, 1.17-1.76, p=0.001) particularly for males and TIA patients.

Conclusion: White matter disease, but not an acute brain lesion, may be weakly associated with subsequent depression after a TIA. Further studies on the location of the brain pathology and subsequent risk of symptoms are required. No relationship between anxiety and depression and subsequent risk of recurrent of stroke was demonstrated but a strong relationship with mortality was demonstrated.

4.2 Introduction

In the previous chapters I have demonstrated that anxiety and depression symptoms are prevalent after transient ischaemic attacks (TIA) and minor strokes. A question remained as to whether transient ischaemic attacks with an acute lesion on brain imaging had different psychological outcomes to those who were imaging negative. In the meta-analysis (Chapter 2) those studies with a strict tissue-based (imaging-negative) definition of a TIA reported lower rates of post-event depression, albeit the difference was not significant. Yet, in recent studies no association has been found between DWI status and subsequent post-TIA depression, though these have been limited to MRI-based imaging.[1,2] Other neuroimaging markers, such as white matter disease, global atrophy and lesion location have all been demonstrated to be associated with risk of subsequent depression and anxiety disorders after a stroke.[3-5] However the evidence is heterogeneous particularly in the acute phase and there are limited studies in the TIA population.[1-2, 6,7]

After a TIA or stroke, patients remain at risk of further acute vascular events with numerous studies suggesting that post-stroke depression amplifies the risk.[8,9] Furthermore, depression is associated with increased all-cause mortality including in a post-stroke population.[10,11] The relationship between anxiety, stroke and mortality is less clear as both negative (smoking, physical inactivity, increased hypertension), and positive (earlier medical attention, faster rate of blood pressure control, improved HbA1c) factors are associated with anxiety disorders confounding the impact.[10,12-15] Overall, a meta-analysis on anxiety disorders and all-cause mortality found no association, though this was not limited to a post-stroke population.[16] No study, to my knowledge, has addressed the relevance of anxiety and / or depression symptoms to risk of recurrence or mortality in a TIA population.

In this preliminary study I aim to firstly, assess whether simple imaging markers are predictive of subsequent anxiety and depression symptoms after a TIA or minor stroke. Secondly, are symptoms of anxiety and / or depression after a TIA predictive of subsequent

cerebrovascular or cardiovascular events? Finally, are symptoms of anxiety and / or depression after a TIA associated with increased mortality?

4.3 Methods

4.3.1 Population-Based Study

The Oxford Vascular Study is a longitudinal population-based study of the incidence and outcomes of all acute cerebrovascular, cardiovascular and peripheral vascular events occurring in Oxfordshire UK. The study population comprises 92,728 individuals registered with nine General Practices in Oxfordshire. As described in Chapter Two, ascertainment of patients is through both 'hot' and 'cold' methods which together achieve near complete ascertainment of all acute vascular events. Recruitment began 1st April 2002 and is ongoing.

All patients with a TIA, ischaemic or haemorrhage stroke were reviewed by a study physician as soon as possible after their initial presentation either on a hospital ward or in an outpatient neurovascular clinic. A structured interview and examination were completed and the primary care record reviewed. As part of the interview patients were asked at the time of their event if they "often feel sad or depressed." The single screening question has been demonstrated to have moderate sensitivity (62% - 90%) and specificity (74% - 82%) for detecting depression in patients presenting with acute coronary syndrome.[17]

Patients with an acute cerebrovascular event underwent routine brain imaging (CT or MRI) as soon as feasible after their event. At study commencement CT brain was the first line imaging modality but was superseded by 1.5T MRI Brain imaging from 1st April 2008 and by 3T MRI Brain imaging from 1st April 2011 onwards. Further details on the imaging parameters are described in Chapter One. A small proportion of patients did not have available brain imaging either due to death prior to hospital attendance, events occurring out of area or ocular ischaemic events. They have been excluded from this study.

The senior study neurologist (PMR) reviewed all cases to confirm the diagnosis and the management. For the purposes of this study I included consecutive patients with first (in study) probable or definite TIA or minor ischaemic stroke (defined as National Institutes of Health Stroke Scale (NIHSS) <5) who were recruited from study commencement up until 30 September 2018 and who had completed at least 1 month of follow-up. A TIA was defined, according to the World Health Organisation (WHO) criteria, as focal neurological symptoms lasting less than 24 hours with a stroke defined as symptoms lasting more than 24 hours and the probability of the event being defined according to National Institute of Neurological and Communicative Disorders and Stroke (NINDS) criteria.[18]

All patients were followed up face-to-face at 1 month, 6 months, 12 months, 5 years and 10 years by a study nurse or physician with a structured interview. These interviews include the EuroQol-5D Anxiety and Depression question (as per Chapter 4) where the patients are asked to self-rate whether they have no, moderate or extreme symptoms of anxiety and / or depression. From 2014 onwards patients also completed the Geriatric Depression Scale (GDS) at one and 12 months with depression defined as >5.[19]

Pre-morbid anxiety and/or depression, baseline vascular risk factors, socio-economic deprivation and low education were defined as per Chapter 3.

Imaging Markers Assessment

White matter disease was defined according to a modified Fazekas scale (for MRI) and ARWMC scale (for CT).[21,22] The details of the methods applied in OxVasc, and in particular the harmonisation for comparability across the two modalities, have been published previously.[23] The modified Fazekas scale took into account periventricular and deep white matter lesions with severity of white matter changes defined as absent, mild, moderate or severe. The ARWMC scale rates 5 different regions in both hemispheres with a 0 to 3 score defining severity according to overall score as absent (0), mild (1 – 5), moderate (6 – 10) and severe (>10). The assessments were completed prospectively by a neuroradiologist, a

neurologist and a previous clinical fellow (LL) who were all blinded to the clinical data. Where multiple imaging modalities were available for the same event the assessment of white matter severity on MRI imaging was chosen over CT imaging. For the purposes of this analysis scores were subsequently dichotomised into none-to-mild and moderate-to-severe white matter disease.

Acute lesions on brain imaging were identified by the senior study neuroradiologist (WK) blinded to the clinical data. For MRI imaging these were identified through diffusion-weighted imaging (DWI) with restricted diffusion (DWI-positive) defined as hyperintensity on DWI with decreased signal on apparent diffusion coefficient images. For CT imaging an acute lesion was defined as the presence of focal swelling or parenchymal hypoattenuation. For the purposes of this study I included any acute lesion irrespective of whether it directly correlated with the presenting symptoms. Again, where multiple imaging modalities were available for the same event the assessment of the MRI imaging was chosen over CT imaging. Further details of the imaging protocol is described in Chapter One.

Case Definition of Recurrent Events and Death

Through the follow-up assessments, and 'hot' and 'cold' case-ascertainment within OxVasc, all recurrent vascular events were identified. These included recurrent strokes (ischaemic or haemorrhagic), acute myocardial infarction (ST elevation myocardial infarction, non-ST elevation myocardial infarction), and acute peripheral vascular disease events (including aortic aneurysm dissections / rupture, and acute limb / bowel ischaemia). Any recurrent vascular event was defined as a composite of any of the above.

Deaths occurring within follow up were identified through daily searches of in-hospital death records via the Bereavement Office, and monthly searches of GP coding and death certificates. The cause of death was to be determined through correlation between coroner's reports, death certificates and coding from the Office for National Statistics

National Health Service Central Register. However, a pre-planned analysis of the cause of death was not completed due to a delay in data transfer from NHS digital.

4.3.2 Statistical Analysis

As per Chapter 3 the EuroQol 5D Anxiety / Depression assessment was treated as a binary variable with no symptoms or moderate-to-extreme symptoms.

The baseline characteristics of patients with an acute lesion and with moderate-to-severe white matter disease on brain imaging were compared with those without using Students T-test for continuous variables and X^2 test for categorical variables. Statistical significance was defined as $p<0.005$. The prevalence of anxiety and/or depression symptoms at one-month and 12-month were stratified by the presence of an acute lesion and by severity of white matter disease. The association between post TIA / minor stroke anxiety and/or depression symptoms and acute lesion or moderate-to-severe white matter disease were determined by binary logistic regression and subsequently with age / sex adjustments. A multivariate regression analysis was performed using the variables associated with post TIA and post minor stroke anxiety and/or depression identified in Chapter 3: 1-month - sex, premorbid history of anxiety and/or depression, reporting often feeling sad at baseline and past history of TIA / stroke, 12-month - age, sex, premorbid history of anxiety / depression, reporting often feeling sad at baseline, NIHSS (for minor strokes), ischaemic heart disease (for TIA).

For analysis of the risk of recurrent events and death after a TIA / minor stroke the data was censored at the first recurrent event after their index event, at death, or at 10 years up until 30 November 2019. Kaplan-Meier survival analysis were used to determine the risk of recurrent stroke, acute myocardial infarction, any acute vascular event and death for those with and without one-month and 12-month symptoms of anxiety and/or depression. Patients with a recurrent event prior to the one-month or the 12-month assessments were excluded from the respective analyses. Cox regression analysis, both crude and adjusted for age and sex, were performed for the risk of recurrent events and death. I also assessed the risk of

death associated with symptoms of anxiety and/or depression after a TIA / minor in pre-defined subgroups: TIA, minor stroke, sex, age cohorts.

The analyses were repeated for the cohort that had completed the GDS assessments at one and 12-months with the data censored at five years.

All analyses were performed using SPSS version Statistics 26.

4.4 Results

4.4.1 Imaging Predictors

There were 2098 patients who had a first (in study) TIA or minor stroke, baseline brain imaging and completed at least one-month of follow-up. This included 1129 TIA (MRI imaging: 709, CT imaging only: 420) and 969 minor stroke (MRI imaging: 515, CT imaging only: 454) patients. Overall the mean age (s.d) was 71.1 (13.2) years and 48.2% were female.

Acute brain lesions on imaging were present for 14.0% (158) of TIA patients and 45.3% (439) of minor stroke patients. Patients with an acute lesion were more likely to be male (57.6% vs 49.4%, $p<0.001$) and have a lower premorbid history of anxiety and/or depression (21.3% vs 28.3%, $p=0.001$). TIA patients with an acute lesion had a higher proportion of high risk TIAs defined as an ABCD2≥ 4 (68.8% vs 55.1%, $p=0.001$). Minor stroke patients with an acute lesion had a higher baseline NIHSS (mean (s.d) = 1.7(1.3) vs 1.3(1.2), $p<0.001$) (table 4.1).

There was no significant difference between the prevalence of anxiety and/or depression symptoms at one-month after a TIA / minor stroke in patients with or without an acute lesion on brain imaging (27.5% vs 31.0%, $p=0.115$). When analysed separately, no difference in one-month symptoms were seen in TIA patients (acute lesion: 25.9%, no lesion: 29.6%, $p=0.343$) but difference was noted in minor stroke patients (acute lesion: 28.0%, no lesion: 33.8%, $p=0.053$) (figure 4.1). An acute lesion on brain imaging after a TIA / minor stroke was not associated with subsequent one month anxiety and/or depression in unadjusted,

age / sex adjusted or in a multivariate model (adjusted OR 0.83, 95% CI 0.71-1.12, p=0.332). Again, comparable findings were seen in both TIA patients (0.87, 0.54-1.31, p=0.496) and minor stroke patients (0.85, 0.63-1.14, p=0.275) separately.

Similarly, there was no significant difference between the prevalence of anxiety and/or depression symptoms at 12-months after a TIA / minor stroke in patients with or without an acute lesion on brain imaging (21.1% vs 23.5%, p=0.275). In a univariate analysis, for the minor stroke patients alone, an acute lesion was inversely related with subsequent 12-month anxiety and/or depression symptoms (crude OR 0.72, 0.82-1.00, p=0.047). However, after adjusting for age/sex and in a multivariate analysis no association between an acute lesion on brain imaging and subsequent 12-month anxiety and/or depression symptoms after a TIA / minor stroke, a TIA, or a minor stroke was seen (table 4.2).

Restricting the analysis to the 1224 patients with MRI-imaging produced similar results. A non-significant trend to lower one and 12-month prevalence rates of anxiety and/or depression symptoms was seen in those with a DWI positive lesion but ultimately no association found in multivariate models (table 4.2). Furthermore, when the analysis was performed on the sub-group of 542 TIA / minor patients (TIA: 270 MRI, 76 CT, minor stroke: 197 MRI, 59 CT) who additionally had GDS assessments no association was seen between an acute brain lesion and subsequent one or 12-month depression (table 4.3)

Of the 2098 patients with a TIA / minor stroke 28.5% had moderate-to-severe white matter disease on their baseline brain imaging. Overall, patients with moderate-to-severe white matter disease were older (mean age (s.d) = 77.9 (9.4) vs 68.4 (13.5), p<0.001), more likely to have hypertension (69.7% vs 52.6%, p<0.001), have had a prior TIA or stroke (16.2% vs 10.5%, p<0.001) or have a history of ischaemic heart disease (19.9% vs 14.1%, p=0.028). TIA patients with moderate-to-severe white matter disease had a higher proportion of high risk TIAs defined as an ABCD2≥ 4 (73.4% vs 51.1%, p<0.001). There was no difference in the prevalence of pre-morbid history of anxiety and/or depression between those with

moderate-to-severe and those with none-to-mild white matter disease (26.6% vs 26.2%, p=0.852) (table 4.4).

Overall, the presence of moderate-to-severe white matter disease was not associated with symptoms of anxiety and/or depression at one-month after a TIA / minor stroke (adjusted OR 1.00, 0.79-1.27, p=0.985) or at 12-months (aOR 1.18, 0.90-1.55, p=0.242) (figure 4.2, table 4.5). Restricting the analysis to the MRI-imaging only similarly found no association. However, analysing the 542 TIA / minor strokes who had completed the more detailed GDS assessment found an association between moderate-to-severe white matter disease and depression, particularly for the TIA patients with MRI-based imaging (1 month: aOR 3.32, 1.39-7.95, p=0.007, 12 month: 2.71, 1.01-7.31, p=0.049) (table 4.6).

4.4.2 Recurrent Events

There were 2137 patients with a TIA or a minor stroke (TIA: 1162, minor stroke: 975) who completed at least one-month of assessments of anxiety and/or depression symptoms. Overall the mean age (s.d) was 71.1 (13.2) years and 48.2% were female. Further baseline characteristics were previously shown in table 3.1 in Chapter 3.

During a follow up of 10,796 person-years there were 412 recurrent acute vascular events (4 per 100 person-years) with 328 recurrent strokes, 82 acute myocardial infarctions and 46 acute peripheral vascular events. The risk of a recurrent stroke or any recurrent acute vascular event (up to 10-years) was not associated with either one-month or 12-month symptoms of anxiety and/or depression after a TIA or minor stroke (figures 4.3-4.6). One-month anxiety and/or depression symptoms were not associated with an increased risk of recurrent stroke after a TIA / minor stroke (age/sex adjusted HR 1.14, 95% CI 0.87-1.49, p=0.356) and nor for TIA patients (1.17, 0.74-1.85, p=0.501) or the minor stroke patients (1.08, 0.77-1.51, p=0.654) alone. Similarly, anxiety and/or depression symptoms at one-month were not associated with an increased risk of any recurrent acute vascular event (up to 10 years) for the TIA / minor stroke patients (1.20, 0.95-1.51, p=0.135), TIA patients (1.12, 0.76-1.66, p=0.564) or the minor stroke patients (1.21, 0.90-1.62, p=0.207) alone

(figures 4.3-4.4, table 4.7). Similar results were seen for the 12-month symptoms of anxiety and/or depression and risk of recurrent stroke or any recurrent acute vascular event (figures 4.5-4.6, table 4.8).

For the 555 TIA / minor stroke patients that completed at least a one-month GDS assessment there were 48 recurrent strokes during 1624 person-years of follow up. Though limited by small numbers, a recurrent stroke or any recurrent acute vascular event (up to 5-years) was not associated with depression at one-month or at 12-months after a TIA or minor stroke (table 4.9).

4.4.3 Mortality

For the 2137 patients, during a follow-up of 12,263 person-years, there were 619 deaths (5 per 100 person-years). After adjusting for age and sex, an increased risk of death was associated with symptoms of anxiety and/or depression at one-month for both the TIA (HR 1.39, 1.06-1.82, p=0.018) and minor stroke patients (HR 1.29, 1.03-1.61, p=0.028). On subgroup analysis the association was present for males (HR 1.67, 1.31-2.13, p<0.001) but not females (HR 1.11, 0.87-1.41, p=0.400). The increased risk was seen in patients aged 65 years and older but not in those <65 years (age<65: 1.04, 0.55-1.96, p=0.911, age 65-74:1.56, 1.05-2.32, age≥75: 1.34, 1.10-1.64, p=0.004) (table 4.10, figures 4.7).

Twelve-month symptoms of anxiety and/or depression were also associated with an increased risk of death, but only in the TIA patients (1.64, 1.22-2.21, p<0.001) and not the minor stroke patients (1.23, 0.93-1.62, p=0.150). On subgroup analysis the association was seen again in males but now predominantly in the younger age cohorts (age<65: 2.17, 1.08-4.36, p<0.001, age 65-74: 2.24, 1.43-3.51, p<0.001, age≥75: 1.23, 0.96-1.57, p=0.102) (table 4.10, figure 4.8).

Restricting the analysis to the 555 TIA and minor stroke patients that completed at least a one-month GDS assessment and were followed up to 5 years, the association between

depression and increased mortality remained (one-month symptoms: HR 1.99, 1.05-3.76, p=0.035, 12-month symptoms: 3.61, 1.58-8.28, p=0.002) (table 4.11).

A premorbid history of anxiety and/or depression was not associated with subsequent mortality (aOR 1.06, 0.88-1.28, p=0.558) after a TIA / minor stroke but reporting feeling often low at baseline was (aOR 1.22, 1.01-1.47, p=0.037). When this was included in an adjusted model anxiety and/or depression symptoms at one-month and 12-months still remained associated with subsequent mortality (1-month symptoms: aOR 1.32, 1.10-1.59, p=0.003, 12-months symptoms: 1.46, 1.17-1.81, p=0.001).

4.5 Discussion

Imaging Predictors

In this preliminary study I found that simple brain imaging markers at the time of a TIA or minor stroke may have limited predictive ability for subsequent anxiety and/or depression symptoms within the first year. An acute lesion on brain imaging, whether on CT-imaging or MRI-imaging, was not associated with the development of anxiety and / or depression symptoms at one or 12-months. Similar to a previous study on imaging in TIA patients I found lower, though none significant, rates of anxiety and/or depression in those who were imaging negative.[2] However, in OxVasc, patients with an acute lesion had lower rates of pre-morbid anxiety and depression and after adjusting for this the potential difference was negated suggesting no predictive value. This provides continuing evidence for the use of a time-based definition of a TIA for predicting subsequent post-event psychological disorders rather than tissue-based (imaging-negative). A limitation of this study was that the location of the lesion was not taken into consideration. In stroke patients, frontal and basal ganglia lesions have been demonstrated to be associated with an increased risk of depression whereas posterior circulation lesions have not.[3,5] To elucidate whether this is the case for TIA patients, further exploration of the lesion location in this study should be undertaken.

In addition, I demonstrated that white matter disease was associated with subsequent development of depression in the TIA patients, particularly in those with MRI-imaging. The relationship was not seen consistently in the minor stroke patients although this may have been a consequence of under-powering due to the smaller number of patients who had Geriatric Depression Scale assessments performed.

Seeming somewhat contradictory to this, the association between white matter disease and one and 12-month symptoms of anxiety and/or depression after a TIA or minor stroke was not demonstrated. Numerous studies have shown that white matter disease relates to post-stroke depression and to a lesser degree anxiety, but with the strengths of the associations depending on severity of disease, timing of assessment and cohort characteristics.[1,3,6,23,24] After a stroke, in the acute time period (< 8 weeks) severity of white matter disease correlates poorly with depression but at later time periods (>3 months) there is a stronger association.[6,7,25] Immediately after an event, the risk of anxiety and depression may be less to do with the brain dysfunction itself and more to do with acute stress reactions and the individuals' psychosocial and pre-morbid factors. The association with subsequent depression is particularly demonstrated when studies assess for severe white matter disease rather than mild to moderate.[7] Additionally, in a study on a younger cohort (<55 years) white matter disease was not associated with subsequent post TIA / stroke depression, though this was likely in part is due to a low prevalence of severe white matter disease found in that age group.[1] Similar to as the location of the acute brain lesion may a key determinant, the location of the white matter disease, and the consequent pathways it interrupts, may be more relevant than simply its general presence. Diffusion Tensor Imaging (DTI) has shown that disruptions to the white matter pathway between the amygdala and prefrontal cortex is associated with anxiety and microstructural abnormalities in the white matter in the internal capsule and frontal lobes are associated with post-stroke depression.[3,24] Therefore, the lack of association between white matter disease and anxiety and/or depression symptoms demonstrated in this study may be a consequence of the early

initial assessment (one month), the less strong association of anxiety with white matter disease and combining moderate white matter disease with severe for the analysis. Other markers of small vessel disease such as microbleeds, global atrophy and intracranial stenosis are all potentially associated with post-stroke depression but were not assessed in the current study.[4,26,27]

Recurrent Events

The relationship between post-stroke depression and subsequent risk of recurrent stroke is complex and study results inconsistent.[8.,9,28] Three-month depression in patients on the South London Stroke Registry was not associated with risk of recurrent stroke in the subsequent five years.[28] Furthermore, over 24 years of follow-up in the Whitehall cohort the increased risk of stroke in patients with depression was felt to be explained by shared underlying vascular pathology rather than due to an independent risk conveyed by the depression itself.[29] More recently though, a meta-analysis of 4648 patients did report an increased risk of recurrence, particularly for ischaemic stroke patients.[30] Whilst there are no studies on the risk of recurrent stroke associated with post-stroke anxiety, in the general population anxiety is associated with an increased risk of cardiovascular events.[31]

In this current study I did not find an association between symptoms of anxiety and/or depression after a TIA / minor stroke and the subsequent risk of recurrent stroke or any acute vascular event. Potentially, in OxVasc, the impact of anxiety and depression upon the risk of recurrence may have been negated by the intensive follow-up and management which the study patients were subjected to. Additionally, the risk may have been mitigated in part by the inclusion of anxiety symptoms in the assessment which can have a diverging impact on lifestyle behaviours compared with depression. Whilst anxiety disorders can be associated with poorer lifestyle factors (smoking, hypertension, alcohol) they can also be associated with more protective health effects (greater treatment compliance due to fear of recurrence, earlier attention for medical conditions). Patients with anxiety may have higher rates of hypertension but they also have been found to have faster rates of hypertension

control and in type 2 diabetes an coexistent anxiety disorder is associated with better glycaemic control.[14,15] Both of these outcomes may be in part driven by the increased health-care utilisation associated with anxiety disorders.[15]

Despite the potential roles that anxiety and depression disorders may have in vascular outcomes the underlying mechanisms are not fully understood. It is likely an interplay of the associated unhealthy lifestyle behaviours (smoking, poor diet and physical inactivity), treatment non-compliance, and physiological associations (increased inflammation, change in sympathetic drive, platelet dysfunction and dysregulation of the hypothalamic-pituitary axis). Less clear though is how to intervene to change the association. Studies on antidepressants have failed to demonstrate their ability to reduce recurrent cerebrovascular events, and some antidepressants themselves may potentially be associated with increased risk of intracranial haemorrhage.[33-34]

Mortality

In this population-based study I demonstrated an association between anxiety and/or depression symptoms after a TIA and minor stroke and increased mortality. The association was stronger for depression, though the analysis limited by smaller patient numbers. These results are consistent with previous meta-analyses of both depression and post-stroke depression.[35-38] However, a meta-analysis of anxiety disorders alone did not find that they were associated with increased mortality.[16] There is also conflicting evidence for the relationship between mortality and acute, episodic depression compared with chronic depression. In the general population it is perhaps dysthymia that is more relevant than episodic depression.[40] Similarly, in this study a premorbid history of anxiety and depression was not associated but reporting often feeling low was.

Furthermore, the timing of the assessment of depression in regards to the stroke may lead to variability in the risk conveyed.[34] Likewise, anxiety symptoms at the time of an myocardial infarction are not associated with subsequent mortality risk, but when symptoms are

assessed more than one-month after the event an association is more consistently found.[41] In this current study anxiety and/or depression symptoms and depression disorders alone 12-months after a TIA both conveyed a stronger association of mortality compared with one-month symptoms.

The relationship between anxiety and/or depression symptoms after a TIA or minor stroke and subsequent mortality was found to be strongest in men, similar to that found in a recent meta-analysis.[35] Overall, in population-based studies women have higher rates of anxiety and depression but this has not consistently translated to a higher mortality.[38] This sex differences in the impact of anxiety and depression on risk of death are not fully understood. There are likely to be differences in the response and resilience to acute stressors between the sexes and potentially a greater reluctance in men to seek help for mental health matters due to fear of perceived stigma.[42,43] Additionally the presence of higher proportions of comorbid anxiety symptoms in women may convey greater health–seeking behaviours.

In this study there was a temporal difference in the association between anxiety and/or depression symptoms based on age. Early onset (one-month) anxiety and/or depression symptoms were associated with an increased risk of mortality for older adults (>65 years) but the presence of these symptoms at a later stage (one-year) was associated with increased mortality risk for younger adults (<65 years). Increasing age is strongly associated with increasing mortality but with increasing age there is often increasing comorbidities and physiological frailty. As such the confounding and cumulative pathology may, over time, lessen the strength of the relationship of anxiety and/or depression on the risk of death. Furthermore, depressive and anxiety disorders at older and younger ages may have differing underlying pathophysiology conveying differing risks.[37]

Limitations of this study included that cohabitation status was not adjusted for, particularly as studies have shown that living alone conveys a greater risk of mortality for men than women.[44] The cause of death was not known which may have advanced the understanding of the divergent impact of age and sex on mortality associated with anxiety and/or

depression symptoms. Particularly as the increased mortality does not appear to be due to an increased risk of vascular deaths, as suggested by the lack of association between anxiety / depression symptoms and recurrent events. A further limitation was that cognitive function wasn't adjusted for in this study. Both anxiety and depression symptoms can be seen in the prodromal stages of vascular and Alzheimer's dementias.[45] Given the increased mortality associated with dementia, it may be that the increased mortality in this study could partly be accounted for by different rates of dementia diagnoses. Finally, a more detailed assessment for anxiety disorders and depression disorders separately was not completed for most cases.

4.6 Conclusion

In this current study an acute brain lesion on baseline imaging was not found to be predictive of subsequent anxiety and / or depression symptoms up to one-year after a TIA or minor stroke. However, in a subset of patients with MRI-based imaging the presence of moderate-to-severe white matter disease was associated with subsequent depression. Overall, anxiety and depression symptoms after a TIA and minor stroke were not predictive of future vascular events but were associated with increased mortality. Further analysis in order to illuminate this association in greater detail is required.

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	Acute lesion on imaging	No acute lesion on imaging	p value
Overall, n (%)	597 (28.5)	1501 (71.5)	
TIA alone	158 (14.0)	971 (86.0)	n/a
Minor stroke alone	439 (45.3)	530 (54.7)	
Age at event, mean (s.d)	70.4 (12.9)	71.4 (13.3)	0.114
TIA alone	69.4 (13.6)	71.5 (12.8)	0.051
Minor stroke alone	70.7 (12.7)	71.2 (14.0)	0.645
Female sex, n (%)	253 (42.4)	759 (50.6)	**<0.001**
TIA alone	67 (42.4)	503 (51.8)	**0.028**
Minor stroke alone	186 (42.4)	256 (48.3)	0.067
Pre-morbid anx/dep, n (%)*	126 (21.3)	423 (28.3)	**0.001**
TIA alone	33 (20.9)	266 (27.6)	0.078
Minor stroke alone	93 (21.4)	157 (29.7)	**0.004**
Baseline feeling sad, n (%)*	126 (21.8)	342 (23.3)	0.467
TIA alone	28 (18.2)	211 (22.1)	0.275
Minor stroke alone	98 (23.1)	131 (25.6)	0.376
SED, mean IMD (s.d)	10.9 (6.9)	10.8 (7.3)	0.672
TIA alone	10.8 (5.8)	10.6 (7.1)	0.807
Minor stroke alone	11.0 (7.3)	11.0 (7.8)	0.893
Hypertension, n (%)	341 (57.1)	864 (57.6)	0.835
TIA alone	82 (51.9)	541 (55.7)	0.373
Minor stroke alone	259 (59.0)	323 (60.9)	0.548
Hyperlipidaemia, n (%)	187 (31.3)	509 (33.9)	0.254
TIA alone	52 (32.9)	326 (33.6)	0.863
Minor stroke alone	137 (31.2)	183 (34.5)	0.277
Atrial fibrillation, n (%)	99 (16.6)	204 (13.6)	0.078
TIA alone	25 (15.8)	127 (13.1)	0.357
Minor stroke alone	74 (16.9)	77 (14.5)	0.306
Previous TIA / stroke, n (%)	59 (9.9)	195 (13.0)	0.050
TIA alone	16 (10.1)	117 (12.0)	0.492
Minor stroke alone	43 (9.8)	78 (14.7)	**0.036**
Diabetes mellitus, n (%)	93 (15.6)	202 (13.5)	0.213
TIA alone	17 (10.8)	127 (13.1)	0.422
Minor stroke alone	76 (17.3)	75 (14.2)	0.186
Peripheral vascular disease, n (%)	38 (6.4)	73 (4.9)	0.168
TIA alone	10 (6.3)	39 (4.0)	0.188
Minor stroke alone	28 (6.4)	34 (6.4)	1.000
IHD/ angina, n (%)	100 (16.8)	258 (17.2)	0.826
TIA alone	28 (17.7)	148 (15.2)	0.422
Minor stroke alone	72 (16.4)	110 (20.8)	0.081
Current / prior smoking, n (%)	379 (63.5)	799 (53.2)	0.826
TIA alone	79 (50.0)	527 (54.3)	0.315
Minor stroke alone	300 (56.6)	272 (62.0)	0.077
Education <12 years, n (%)*	356 (60.5)	927 (62.6)	0.375
TIA alone	85 (54.8)	571 (59.5)	0.270
Minor stroke alone	271 (62.6)	356 (68.3)	0.065
TIA (ABCD2 score≥4), n (%)	108 (68.8)	533 (55.1)	**0.001**
Minor stroke (NIHSS) mean, s.d	1.7 (1.3)	1.3 (1.2)	**<0.001**

Table 4.1 Baseline characteristics of TIA/minor stroke patients with and without an acute lesion on the baseline brain imaging. *Missing data=13 pre-morbid anxiety / depression histories, 53 baseline feeling sad, 4 ABCD2 scores, 30 education histories.

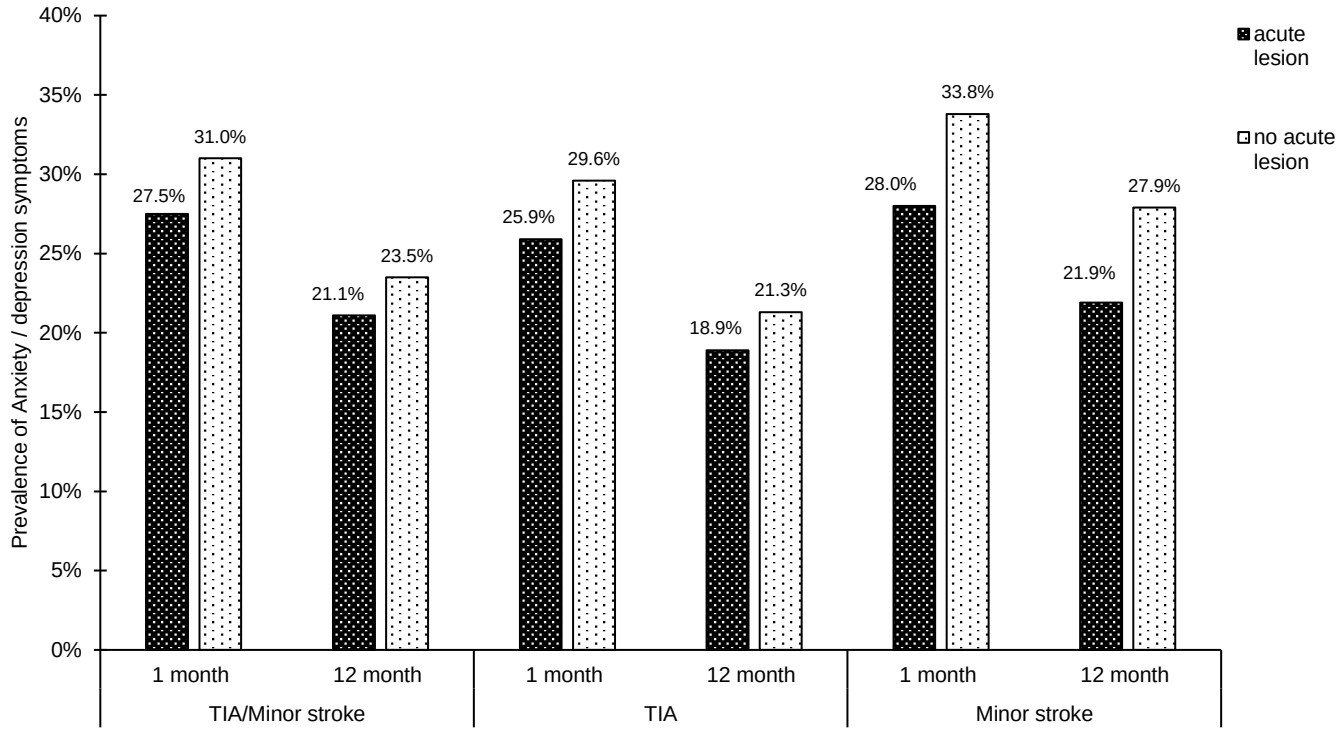

Figure 4.1 Prevalence of anxiety and/or depression symptoms at 1-month and 12-months stratified by event type and the presence and absence of an acute lesion on baseline imaging (CT and MRI). No significant difference between prevalence of symptoms for the acute lesion vs no acute lesions for each subgroup (all p≥0.05).

	Acute lesion n (%)	No acute lesion n (%)	Crude OR (95% CI)	p value	Age / sex adjusted OR (95% CI)	p value	Multivariate OR (95% CI)	p value
(a) All imaging								
Anxiety / depression at 1-month								
TIA / minor stroke	164 (24.5)	466 (31.0)	0.84 (0.68-1.04)	0.107	0.87 (0.70-1.07)	0.191	0.83 (0.71-1.12)	0.332
TIA alone	41 (25.9)	287 (29.6)	0.84 (0.57-1.22)	0.355	0.85 (0.58-1.25)	0.409	0.87 (0.57-1.31)	0.496
Minor stroke alone	123 (28.0)	179 (33.8)	0.76 (0.58-1.01)	0.054	0.78 (0.59-1.03)	0.081	0.85 (0.63-1.14)	0.275
Anxiety / depression at 12-months								
TIA / minor stroke	107 (21.1)	304 (23.5)	0.87 (0.68-1.11)	0.267	0.89 (0.69-1.14)	0.349	0.94 (0.72-1.23)	0.673
TIA alone	25 (12.0)	107 (13.7)	0.86 (0.54-1.37)	0.531	0.91 (0.57-1.45)	0.685	0.99 (0.60-1.62)	0.956
Minor stroke alone	82 (40.4)	293 (48.4)	0.72 (0.82-1.00)	**0.047**	0.74 (0.53-1.02)	0.065	0.72 (0.51-1.03)	0.074
(b) MRI only								
Anxiety / depression at 1-month								
TIA / minor stroke	93 (25.2)	273 (31.9)	0.72 (0.55-0.95)	**0.019**	0.74 (0.56-0.98)	**0.036**	0.77 (0.57-1.03)	0.078
TIA alone	25 (21.7)	182 (30.6)	0.63 (0.39-1.01)	0.056	0.65 (0.40-1.05)	0.078	0.65 (0.39-1.09)	0.105
Minor stroke alone	68 (26.8)	91 (34.9)	0.68 (0.47-1.00)	**0.047**	0.68 (0.47-1.00)	0.051	0.77 (0.51-1.17)	0.221
Anxiety / depression at 12-months								
TIA / minor stroke	62 (19.3)	174 (22.7)	0.81 (0.59-1.13)	0.211	0.84 (0.60-1.16)	0.289	0.96 (0.98-1.37)	0.831
TIA alone	14 (14.1)	114 (21.2)	0.61 (0.34-1.12)	0.111	0.67 (0.37-1.23)	0.197	0.79 (0.41-1.51)	0.473
Minor stroke alone	48 (21.6)	60 (26.4)	0.77 (0.50-1.19)	0.234	0.81 (0.52-1.26)	0.345	0.90 (0.54-1.48)	0.896

Table 4.2 Prevalence of moderate-to-extreme symptoms of anxiety and/or depression in patients with, and without, an acute lesion on baseline brain imaging, stratified by event type (all, TIA only, minor stroke only). (A) all imaging includes both CT and MRI. (b): MRI imaging only. Odds ratio (95% confidence interval), age / sex adjusted odds ratio and multivariate odds ratio included. Variables for inclusion in the multivariate analysis were informed by the previous analysis in Chapter 3. (For the multivariate analysis at 1-month included variables: age, sex, premorbid history of anxiety / depression, reporting often feeling sad at baseline and past history of TIA/stroke. For the multivariate analysis at 12-months: age, sex, premorbid history of anxiety / depression, reporting often feeling sad at baseline, NIHSS (for minor strokes), ischaemic heart disease (for TIA).

	Acute lesion n (%)	No acute lesion n (%)	OR (95% CI)	p value	Age / sex adjusted OR (95% CI)	p value	Multivariate OR (95% CI)	p value
(a) All imaging								
Depression at 1-month								
TIA / minor stroke	26 (20.5)	82 (19.8)	1.05 (0.64-1.71)	0.860	1.05 (0.64-1.73)	0.835	1.09 (0.63-1.88)	0.764
TIA alone	7 (14.9)	56 (18.7)	0.76 (0.32-1.78)	0.528	0.75 (0.32-1.78)	0.517	0.80 (0.31-2.06)	0.640
Minor stroke alone	19 (23.8)	26 (22.4)	1.08 (0.55-2.12)	0.827	1.09 (0.55-2.14)	0.812	1.09 (0.50-2.36)	0.833
Depression at 12-months								
TIA / minor stroke	19 (18.1)	50 (14.7)	1.29 (0.72-2.30)	0.396	1.29 (0.72-2.30)	0.397	1.36 (0.73-2.52)	0.330
TIA alone	5 (12.8)	35 (14.0)	0.90 (0.33-2.47)	0.843	0.91 (0.33-2.48)	0.848	0.93 (0.30-2.91)	0.900
Minor stroke alone	14 (21.2)	15 (16.5)	1.36 (0.61-3.06)	0.452	1.37 (0.61-3.10)	0.444	1.54 (0.66-3.61)	0.324
(b) MRI only								
Depression at 1-month								
TIA / minor stroke	19 (18.1)	51 (16.9)	1.09 (0.61-1.94)	0.778	1.12 (0.62-2.01)	0.709	1.18 (0.62-2.25)	0.613
TIA alone	6 (13.6)	39 (17.3)	0.76 (0.30-1.91)	0.557	0.76 (0.30-1.93)	0.562	0.76 (0.27-2.18)	0.613
Minor stroke alone	13 (21.3)	12 (15.8)	1.44 (0.61-3.45)	0.407	1.60 (0.66-3.91)	0.302	2.43 (0.83-7.13)	0.107
Depression at 12-months								
TIA / minor stroke	16 (18.2)	36 (14.2)	1.34 (0.70-2.56)	0.375	1.37 (0.71-2.62)	0.346	1.45 (0.72-2.93)	0.304
TIA alone	5 (13.9)	26 (13.6)	1.02 (0.37-2.87)	0.965	1.06 (0.38-3.00)	0.908	1.15 (0.35-3.72)	0.820
Minor stroke alone	11 (21.2)	10 (16.1)	1.40 (0.54-3.60)	0.492	1.50 (0.57-3.97)	0.415	1.93 (0.65-5.76)	0.237

Table 4.3 Prevalence of depression (GDS data only) in patients with, and without, an acute lesion on baseline brain imaging, stratified by event type (all, TIA only, minor stroke only). (a) all imaging includes both CT and MRI. (b): MRI imaging only. Odds ratio (95% confidence interval), age / sex adjusted odds ratio and multivariate odds ratio included. Baseline variables for inclusion in the multivariate analysis were informed by the previous analysis in Chapter 3: age, sex, premorbid history of anxiety / depression, reporting often feeling sad at baseline and socio-economic deprivation.

	Moderate-to-severe WMD	None-to-mild WMD	p value
Overall, n (%)	597 (28.5)	1501 (71.5)	
TIA alone	309 (26.4)	820 (72.6)	n/a
Minor stroke alone	288 (29.7)	681 (70.3)	
Age at event, mean (s.d)	77.9 (9.4)	68.4 (13.5)	**<0.001**
TIA alone	78.4 (9.3)	68.5 (13.1)	**<0.001**
Minor stroke alone	77.5 (9.6)	68.2 (13.9)	**<0.001**
Female sex, n (%)	318 (53.3)	694 (46.2)	**0.003**
TIA alone	177 (57.3)	393 (47.9)	**0.005**
Minor stroke alone	141 (49.0)	301 (44.2)	0.171
Pre-morbid anx/dep, n (%)*	158 (26.6)	391 (26.2)	0.852
TIA alone	86 (27.9)	213 (26.2)	0.566
Minor stroke alone	72 (25.2)	178 (26.3)	0.722
Baseline feeling sad, n (%)*	144 (25.0)	324 (22.0)	0.146
TIA alone	71 (23.6)	168 (20.8)	0.314
Minor stroke alone	73 (26.6)	156 (23.5)	0.315
Deprivation, mean IMD (s.d)	11.0 (7.4)	10.8 (7.2)	0.567
TIA alone	10.5 (7.0)	10.7 (6.9)	0.767
Minor stroke alone	11.4 (7.8)	10.8 (7.4)	0.298
Hypertension, n (%)	416 (69.7)	789 (52.6)	**<0.001**
TIA alone	207 (67.0)	416 (50.7)	**<0.001**
Minor stroke alone	209 (72.6)	373 (54.8)	**<0.001**
Hyperlipidaemia, n (%)	213 (35.7)	485 (32.3)	0.136
TIA alone	107 (34.6)	271 (33.0)	0.612
Minor stroke alone	106 (36.8)	214 (31.4)	0.103
Atrial fibrillation, n (%)	88 (14.7)	215 (14.3)	0.814
TIA alone	40 (12.9)	112 (13.7)	0.726
Minor stroke alone	48 (16.7)	103 (15.1)	0.530
Previous TIA / stroke, n (%)	97 (16.2)	157 (10.5)	**<0.001**
TIA alone	55 (17.8)	78 (9.5)	**<0.001**
Minor stroke alone	42 (14.6)	79 (11.6)	**0.197**
Diabetes mellitus, n (%)	83 (13.9)	212 (14.1)	0.905
TIA alone	39 (12.6)	105 (12.8)	0.928
Minor stroke alone	44 (15.3)	107 (15.7)	0.875
Peripheral vascular disease, n (%)	40 (6.7)	71 (4.7)	0.064
TIA alone	20 (6.5)	29 (3.5)	**0.027**
Minor stroke alone	20 (6.9)	42 (6.2)	0.684
IHD/ angina, n (%)	119 (19.9)	239 (15.9)	**0.028**
TIA alone	59 (19.1)	117 (14.3)	**0.048**
Minor stroke alone	60 (20.8)	122 (17.9)	0.291
Current / prior smoking, n (%)	337 (56.4)	841 (56.0)	0.868
TIA alone	163 (52.8)	443 (54.0)	0.719
Minor stroke alone	174 (60.4)	398 (58.4)	0.563
Education <12 years, n (%)*	384 (65.5)	899 (60.7)	**0.043**
TIA alone	186 (61.4)	470 (57.9)	0.291
Minor stroke alone	198 (70.0)	429 (63.9)	0.070
TIA (ABCD2 score≥4), n (%)	224 (73.4)	417 (51.1)	**<0.001**
Minor stroke (NIHSS) mean, s.d	1.5 (1.3)	1.4 (1.3)	0.130

Table 4.4 Baseline characteristics of TIA/minor stroke patients with and without moderate-to-severe white matter disease (WMD) on the baseline brain imaging (CT and MRI). *Missing data=13 pre-morbid anxiety / depression histories, 53 baseline feeling sad, 4 ABCD2 scores, 30 education histories.

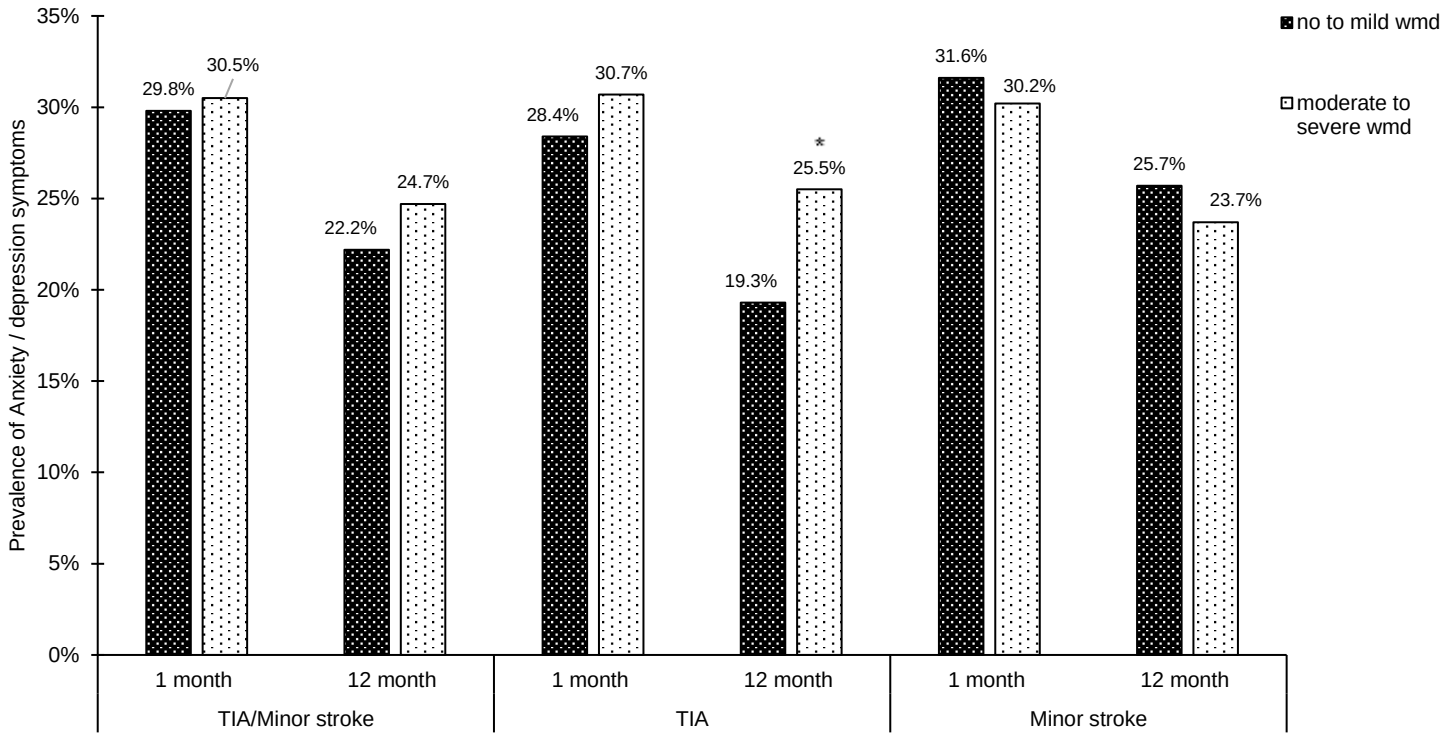

Figure 4.2 Prevalence of moderate-to-extreme symptoms of anxiety and/or depression 1-month and 12-months after the event, stratified by event type and the presence and absence of a moderate-to-severe white matter disease on baseline imaging (CT and MRI). *=p<0.05

	Moderate to severe WMD n (%)	None to Mild WMD n (%)	OR (95% CI)	p value	Age / sex adjusted OR (95% CI)	p value	Multivariate OR (95% CI)	p value
(a) All imaging								
Anxiety / depression at 1-month								
TIA / minor stroke	182 (30.5)	448 (29.8)	1.03 (0.84-1.27)	0.773	1.11 (0.89-1.39)	0.355	1.00 (0.79-1.27)	0.985
TIA alone	95 (30.7)	233 (28.4)	1.12 (0.84-1.49)	0.442	1.27 (0.93-1.74)	0.126	1.11 (0.80-1.55)	0.541
Minor stroke alone	87 (30.2)	215 (31.6)	0.94 (0.70-1.27)	0.676	0.96 (0.70-1.31)	0.781	0.89 (0.93-1.25)	0.490
Anxiety / depression at 12-months								
TIA / minor stroke	125 (24.7)	286 (22.2)	1.15 (0.90-1.46)	0.256	1.23 (0.95-1.59)	0.116	1.18 (0.90-1.55)	0.242
TIA alone	69 (25.5)	139 (19.3)	1.43 (1.03-1.98)	**0.035**	1.36 (0.96-1.94)	0.087	1.29 (0.89-1.87)	0.180
Minor stroke alone	56 (23.7)	147 (25.7)	0.90 (0.63-1.28)	0.557	1.06 (0.73-1.55)	0.748	1.00 (0.67-1.50)	0.995
(b) MRI only								
Anxiety / depression at 1-month								
TIA / minor stroke	105 (29.5)	261 (30.1)	0.97 (0.41-1.28)	0.842	1.08 (0.80-1.46)	0.605	0.98 (0.71-1.34)	0.882
TIA alone	63 (31.0)	144 (28.5)	1.13 (0.79-1.61)	0.495	1.38 (0.93-2.05)	0.109	1.20 (0.78-1.82)	0.408
Minor stroke alone	42 (27.5)	117 (32.3)	0.79 (0.52-1.20)	0.275	0.79 (0.50-1.24)	0.298	0.75 (0.46-1.24)	0.261
Anxiety / depression at 12-months								
TIA / minor stroke	69 (21.8)	167 (21.7)	1.01 (0.74-1.39)	0.957	1.11 (0.78-1.57)	0.568	1.05 (0.72-1.52)	0.808
TIA alone	46 (25.0)	82 (18.1)	1.51 (1.00-2.27)	0.050	1.46 (0.93-2.30)	0.103	1.34 (0.82-2.19)	0.250
Minor stroke alone	23 (17.4)	85 (26.8)	0.58 (0.35-0.96)	**0.035**	0.71 (0.41-1.23)	0.224	0.65 (0.35-1.18)	0.153

Table 4.5 Prevalence of moderate-to-extreme symptoms of anxiety and/or depression in patients with, and without, moderate-to-severe white matter disease on baseline brain imaging, stratified by event type (all, TIA only, minor stroke only). (a) all imaging includes both CT and MRI. (b): MRI imaging only. Odds ratio (95% confidence interval), age / sex adjusted odds ratio and multivariate odds ratio for subsequent anxiety / depression included. Variables for inclusion in the multivariate analysis were informed by the previous analysis in Chapter 3. (For the multivariate analysis at 1-month included variables: age, sex, premorbid history of anxiety / depression, reporting often feeling sad at baseline and past history of TIA/stroke. For the multivariate analysis at 12-months: age, sex, premorbid history of anxiety / depression, reporting often feeling sad at baseline, NIHSS (for minor strokes), ischaemic heart disease (for TIA).

	Moderate to severe WMD n (%)	None to Mild WMD n (%)	OR (95% CI)	p value	Age / sex adjusted OR (95% CI)	p value	Multivariate OR (95% CI)	p value
(a) All imaging								
Depression at 1-month								
TIA / minor stroke	38 (24.7)	70 (18.0)	1.49 (0.95-2.33)	0.082	1.71 (1.04-2.79)	**0.033**	1.47 (0.86-2.52)	0.159
TIA alone	23 (23.2)	40 (16.2)	1.57 (0.88-2.79)	0.127	1.88 (0.99-3.57)	0.053	1.78 (0.88-3.58)	0.107
Minor stroke alone	15 (27.3)	30 (21.3)	1.39 (0.68-2.84)	0.371	1.50 (0.69-3.26)	0.307	1.29 (0.52-3.20)	0.576
Depression at 12-months								
TIA / minor stroke	26 (20.3)	43 (13.5)	1.63 (0.95-2.79)	0.075	1.91 (1.06-3.44)	**0.031**	1.75 (0.94-3.26)	0.079
TIA alone	16 (18.8)	24 (11.8)	1.74 (0.87-3.47)	0.116	2.05 (0.96-4.38)	0.065	2.33 (1.01-5.37)	**0.047**
Minor stroke alone	10 (23.3)	19 (16.7)	1.52 (0.64-3.59)	0.345	1.73 (0.67-4.42)	0.255	1.50 (0.55-4.11)	0.435
(b) MRI only								
Depression at 1-month								
TIA / minor stroke	30 (24.6)	40 (14.0)	2.00 (1.18-3.40)	**0.011**	3.10 (1.65-5.83)	**<0.001**	2.96 (1.47-5.96)	**0.002**
TIA alone	20 (24.4)	25 (13.3)	2.10 (1.09-4.06)	**0.026**	3.24 (1.48-7.08)	**0.003**	3.32 (1.39-7.95)	**0.007**
Minor stroke alone	10 (25.0)	15 (15.5)	1.82 (0.74-4.50)	0.193	2.87 (0.98-8.37)	0.054	3.98 (1.03-15.32)	**0.045**
Depression at 12-months								
TIA / minor stroke	19 (18.8)	33 (13.8)	1.45 (0.78-2.70)	0.237	1.93 (0.96-3.90)	0.067	1.80 (0.84-3.94)	0.132
TIA alone	13 (18.6)	18 (11.5)	1.76 (0.81-3.83)	0.153	2.15 (0.89-5.20)	0.091	2.71 (1.01-7.31)	**0.049**
Minor stroke alone	6 (19.4)	15 (18.1)	1.09 (0.38-3.12)	0.875	1.50 (0.46-4.87)	0.500	1.12 (0.29-4.36)	0.866

Table 4.6 Prevalence of depression (GDS data) in patients with, and without, moderate-to-severe white matter disease on baseline brain imaging, stratified by event type (all, TIA only, minor stroke only). (a) all imaging includes both CT and MRI. (b): MRI imaging only. Odds ratio (95% confidence interval), age / sex adjusted odds ratio and multivariate odds ratio for subsequent anxiety / depression included. Baseline variables for inclusion in the multivariate analysis were informed by the previous analysis in Chapter 3: age, sex, premorbid history of anxiety / depression, reporting often feeling sad at baseline and socio-economic deprivation.

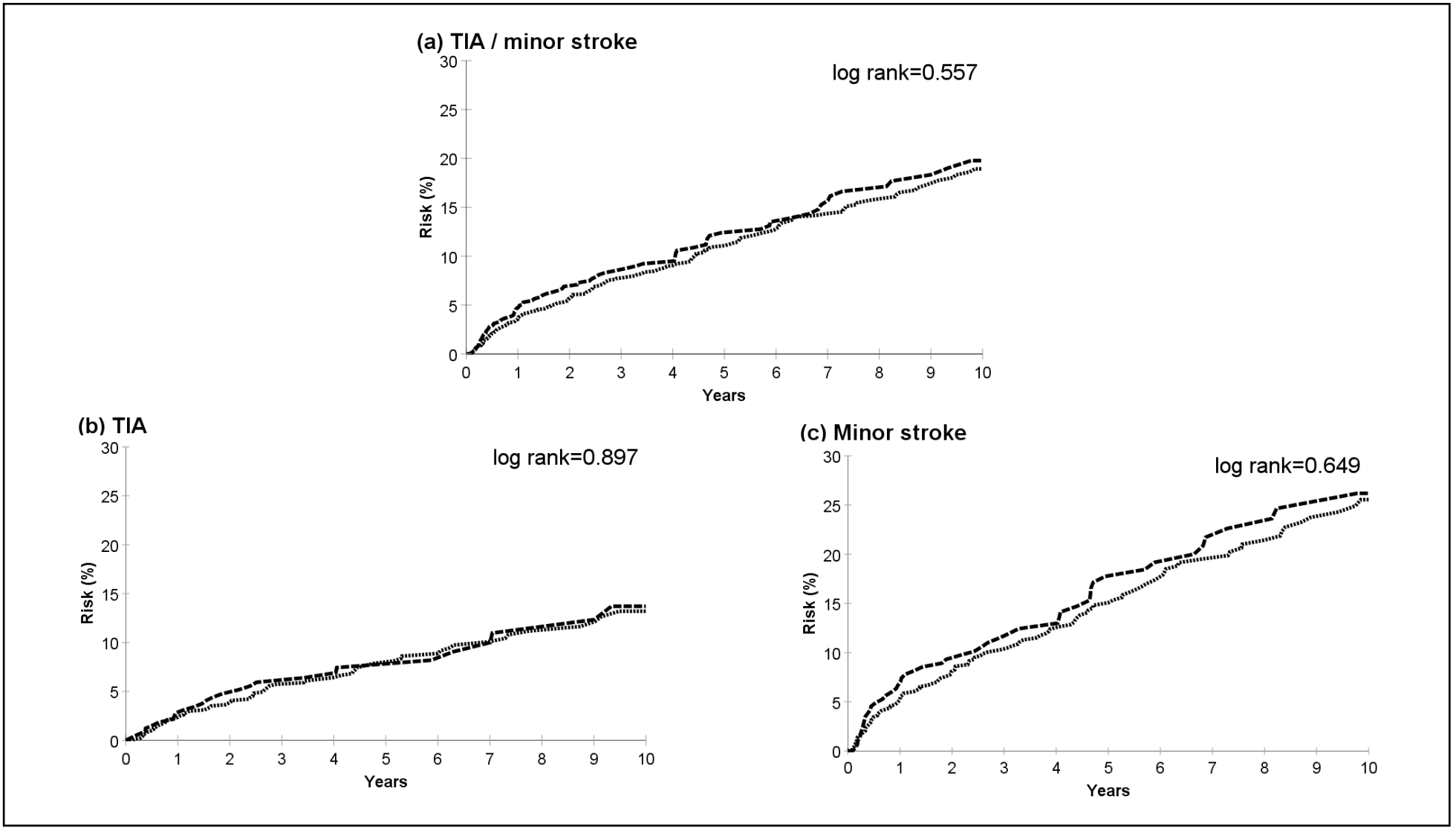

Figure 4.3 Kaplan Meier survival curves of risk of recurrent stroke (up to 10 years) after a TIA / minor stroke stratified by the presence (dashed line) or absence (dotted line) of symptoms of anxiety and/or depression at 1-month. Recurrent stoke includes: any stroke (ischaemic stroke, intracranial haemorrhage, and subarachnoid haemorrhage. Results are presented for (a) TIA / minor stroke, (b) TIA alone, and (c) minor stroke alone. Patients with recurrent stroke events between the initial event and the one-month assessment have been excluded from the analysis.

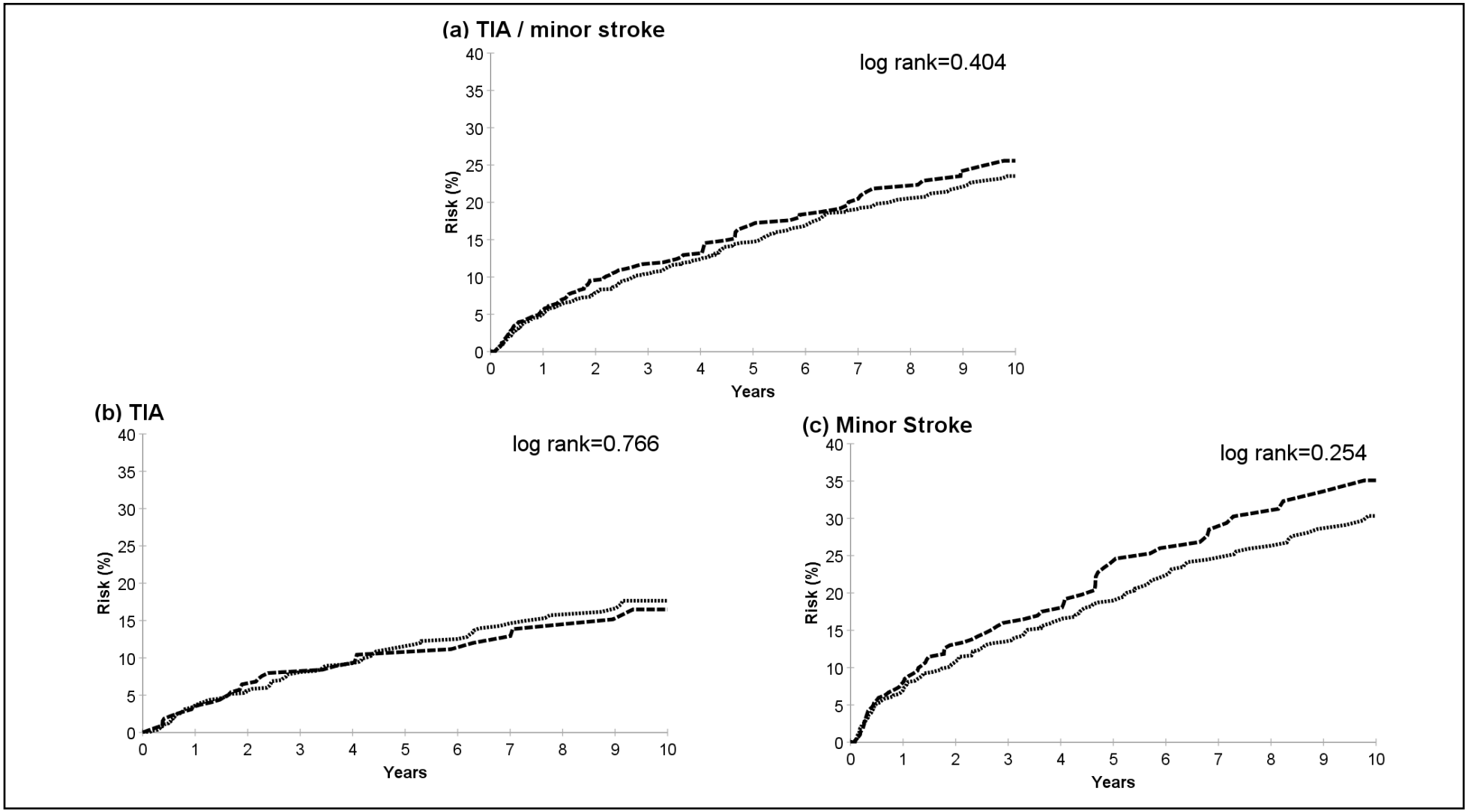

Figure 4.4 Kaplan Meier survival curves of risk of any acute vascular events (up to 10 years) after a TIA / minor stroke stratified by the presence (dashed line) or absence (dotted line) of symptoms of anxiety and/or depression at 1-month. Recurrent events include: any stroke (ischaemic stroke, intracranial haemorrhage, and subarachnoid haemorrhage, myocardial infarction (MI), any vascular event (stroke / MI / acute peripheral vascular disease (PVD)). Results are presented for (a) TIA / minor stroke, (b) TIA alone, and (c) minor stroke alone. Patients with recurrent acute vascular events between the initial event and the one-month assessment have been excluded from the analysis.

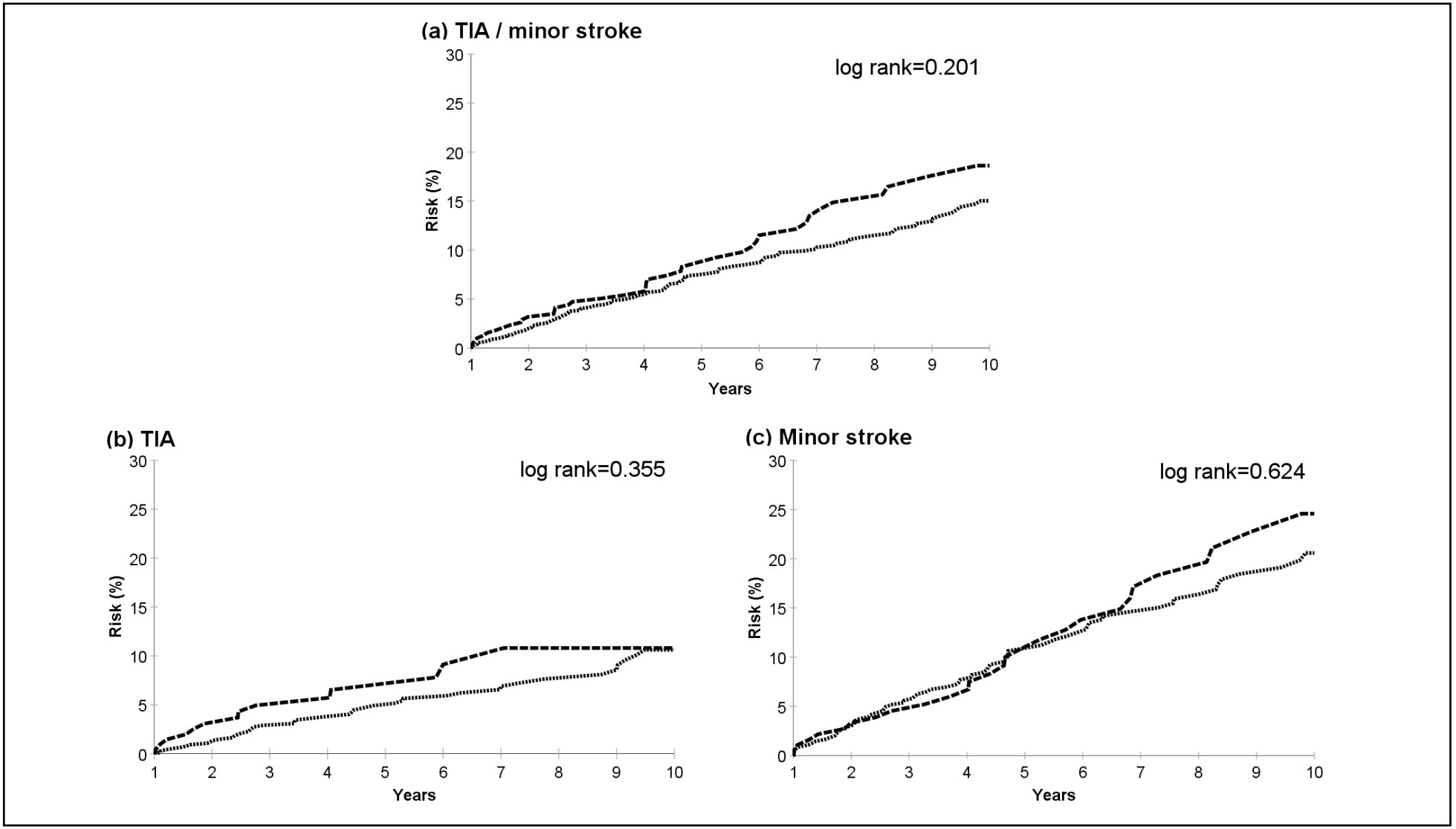

Figure 4.5 Kaplan Meier survival curves of risk of recurrent stroke (up to 10 years) after a TIA / minor stroke stratified by the presence (dashed line) or absence (dotted line) of symptoms of anxiety and/or depression at 12-months. Recurrent stokes include: any stroke (ischaemic stroke, intracranial haemorrhage, and subarachnoid haemorrhage. Results are presented for (a) TIA / minor stroke, (b) TIA alone, and (c) minor stroke alone. Patients with recurrent acute stroke events been the initial event and the 12-month assessment have been excluded from the analysis.

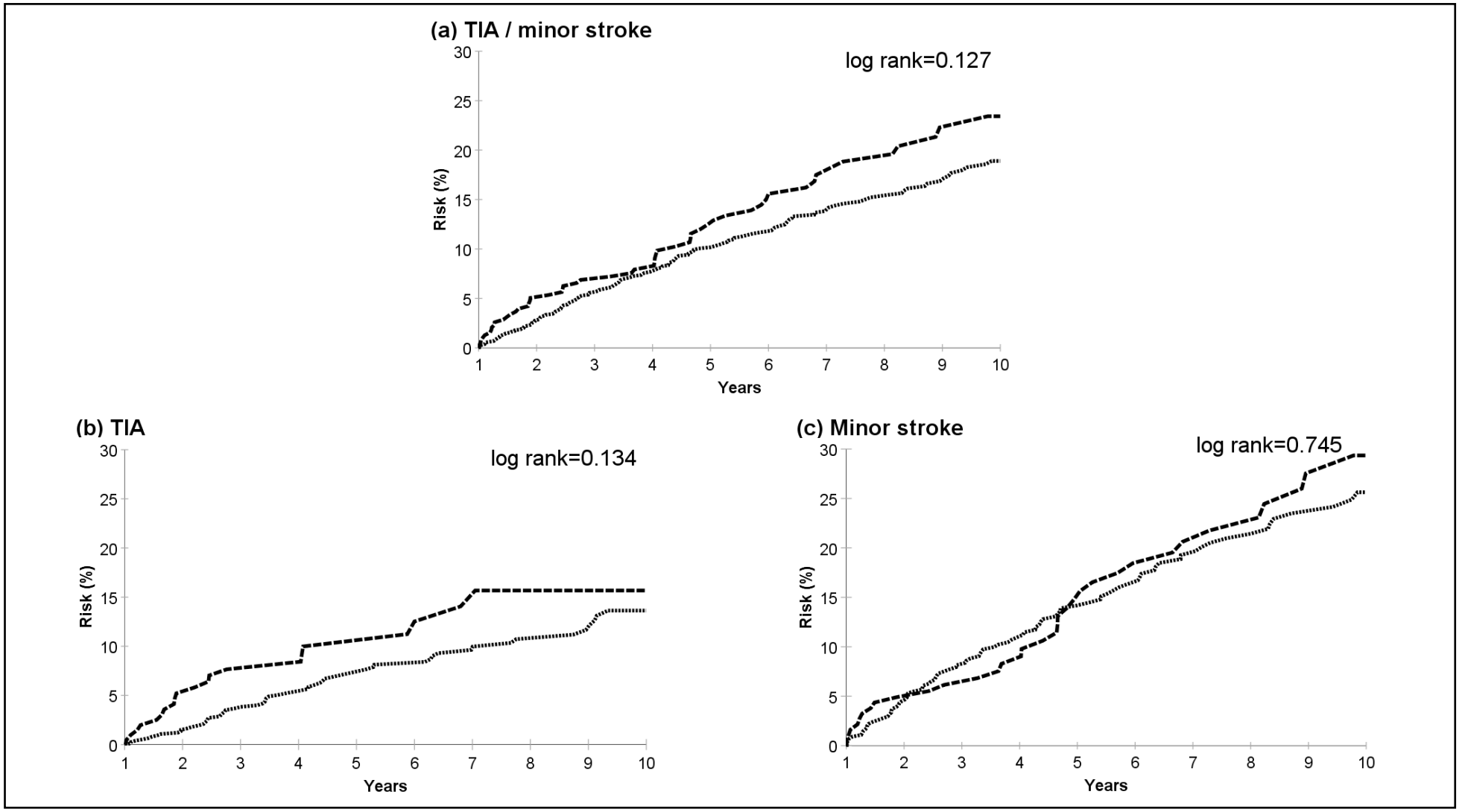

Figure 4.6 Kaplan Meier survival curves of risk of any acute vascular events (up to 10 years) after a TIA / minor stroke stratified by the presence (dashed line) or absence (dotted line) of symptoms of anxiety and/or depression at 12-months. Recurrent events include: any stroke (ischaemic stroke, intracranial haemorrhage, and subarachnoid haemorrhage, myocardial infarction (MI), any vascular event (stroke / MI / acute peripheral vascular disease (PVD)). Results are presented for (a) TIA / minor stroke, (b) TIA alone, and (c) minor stroke alone. Patients with recurrent acute vascular events between the initial event and the 12-month assessment have been excluded from the analysis.

	Recurrent stroke					Any recurrent vascular event				
	Event / total	**Crude HR (95% CI)**	**p value**	**Age / sex adjusted HR (95% CI)**	**p value**	**Event / total**	**Crude HR (95% CI)**	**p value**	**Age / sex adjusted HR (95% CI)**	**p value**
All TIA / minor stroke										
Anxiety / depression symptoms	77/614	1.07 (0.82-1.40)	0.627	1.14 (0.87-1.49)	0.356	104/614	1.10 (0.88-1.39)	0.405	1.20 (0.95-1.51)	0.135
No symptoms	180/1451	ref	ref	ref	ref	236/1451	ref	ref	ref	ref
TIA alone										
Anxiety / depression symptoms	26/324	0.99 (0.63-1.56)	0.970	1.17 (0.74-1.85)	0.501	35/324	0.94 (0.64-1.39)	0.764	1.12 (0.76-1.66)	0.564
No symptoms	69/811	ref	ref	ref	ref	97/811	ref	ref	ref	ref
Minor stroke alone										
Anxiety / depression symptoms	51/290	1.08 (0.78-1.51)	0.650	1.08 (0.77-1.51)	0.654	69/290	1.18 (0.89-1.58)	0.257	1.21 (0.90-1.62)	0.207
No symptoms	111/640	ref	ref	ref	ref	139/640	ref	ref	ref	ref

Table 4.7 Risk of recurrent stroke and risk of any vascular event (stroke / MI / acute PVD) stratified by the presence or absence of moderate-to-extreme symptoms of anxiety and/or depression 1-month after a TIA / minor stroke (up to 10 years). Crude hazard ratio and age / sex adjusted hazard ratios for recurrent event (with 95% confidence intervals) are also presented. Data presented for all TIA / minor stroke patients and TIA and minor stroke patients separately. Patients (n=72) with a recurrent vascular event prior to the 1-month assessment were excluded from the analysis.

	Recurrent stroke					Any recurrent vascular event				
	Event / total	**Crude HR (95% CI)**	**p value**	**Age / sex adjusted HR (95% CI)**	**p value**	**Event / total**	**Crude HR (95% CI)**	**p value**	**Age / sex adjusted HR (95% CI)**	**p value**
All TIA / minor stroke										
Anxiety / depression symptoms	41/390	1.30 (0.91-1.85)	0.154	1.26 (0.88-1.81)	0.206	56/390	1.29 (0.95-1.76)	0.100	1.28 (0.94-1.74)	0.119
No symptoms	113/1308	ref	ref	ref	ref	124/1308	ref	ref	ref	ref
TIA alone										
Anxiety / depression symptoms	15/205	1.48 (0.82-2.67)	0.189	1.29 (0.71-2.32)	0.403	22/205	1.52 (0.94-2.48)	0.091	1.34 (0.82-2.18)	0.244
No symptoms	43/758	ref	ref	ref	ref	61/758	ref	ref	ref	ref
Minor stroke alone										
Anxiety / depression symptoms	26/185	1.09 (0.70-1.71)	0.701	1.10 (0.70-1.73)	0.687	34/185	1.07 (0.72-1.58)	0.746	1.11 (0.74-1.65)	0.625
No symptoms	70/550	ref	ref	ref	ref	63/550	ref	ref	ref	ref

Table 4.8 Risk of recurrent stroke and risk of any vascular event (stroke / MI / acute PVD) stratified by the presence or absence of moderate-to-extreme symptoms of anxiety and/or depression 12-months after a TIA / minor stroke (up to 10 years). Crude hazard ratio and age / sex adjusted hazard ratios (with 95% confidence intervals) are also presented. Data presented for all TIA / minor stroke patients and TIA and minor stroke patients separately. Patients with a recurrent vascular event (n=124) prior to the 12-month assessment were excluded from the analysis.

	Recurrent stroke					Any recurrent vascular event				
	Event / total	Crude HR (95% CI)	p value	Age / sex adjusted HR (95% CI)	p value	Event / total	Crude HR (95% CI)	p value	Age / sex adjusted HR (95% CI)	p value
1-month symptoms										
All TIA / minor stroke										
Depression	7/114	0.94 (0.41-2.15)	0.883	0.90 (0.39-2.07)	0.807	8/114	0.97 (0.45-2.10)	0.934	0.96 (0.44-2.08)	0.907
No depression	29/429	ref	ref	ref	ref	33/429	ref	ref	ref	ref
TIA alone										
Depression	3/69	0.92 (0.26-3.19)	0.891	0.85 (0.24-2.98)	0.793	4/69	1.09 (0.67-3.28)	0.873	1.10 (0.36-3.34)	0.873
No depression	14/281	ref	ref	ref	ref	16/281	ref	ref	ref	ref
Minor stroke alone										
Depression	4/45	0.89 (0.29-2.67)	0.831	0.88 (0.29-2.65)	0.817	4/45	0.80 (0.27-2.38)	0.689	0.78 (0.26-2.33)	0.780
No depression	15/148	ref	ref	ref	ref	17/148	ref	ref	ref	ref
12-month symptoms										
All TIA / minor stroke										
Depression	3/68	1.50 (0.42-5.37)	0.536	1.50 (0.42-5.41)	0.534	4/48	1.65 (0.54-5.07)	0.381	1.65 (0.53-5.11)	0.383
No depression	11/366	ref	ref	ref	ref	13/366	ref	ref	ref	ref
TIA alone										
Depression	1/40	1.40 (0.16-12.51)	0.765	1.47 (0.16-13.23)	0.734	2/40	2.63 (0.48-14.43)	0.266	2.80 (0.50-15.56)	0.239
No depression	4/246	ref	ref	ref	ref	4/246	ref	ref	ref	ref
Minor stroke alone										
Depression	2/28	1.40 (0.29-6.73)	0.677	1.27 (0.26-6.21)	0.282	2/28	1.07 (0.23-4.96)	0.930	0.97 (0.45-5.67)	0.475
No depression	7/120	ref	ref	ref	ref	9/120	ref	ref	ref	ref

Table 4.9 Risk of recurrent stroke and risk of any vascular event (stroke / MI / acute PVD) stratified by the presence / absence of depression (GDS data) 1-month and 12-months after a TIA / minor stroke (up to 5 years) . Crude hazard ratio and age / sex adjusted hazard ratios for recurrent event (with 95% confidence intervals) are also presented. Data presented for all TIA / minor stroke patients and TIA and minor stroke patients separately. Patients with a recurrent vascular event (n=12) prior to the 1-month assessment were excluded from the 1-month analysis and patients with a recurrent vascular event (n=22) prior to the 12-month assessment were excluded from the 12-month analysis.

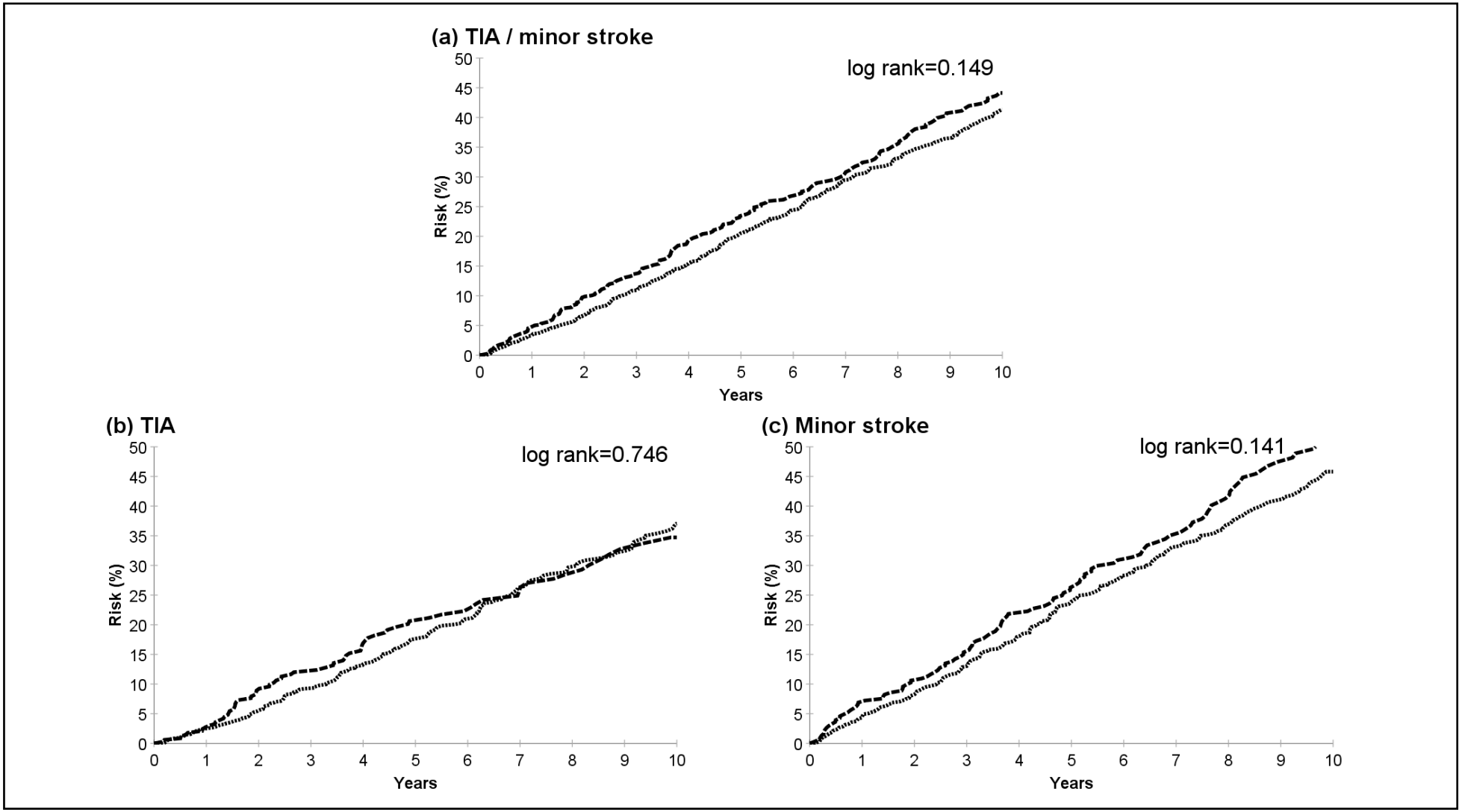

Figure 4.7 Kaplan Meier survival curves of risk of (any) death (up to 10 years) after a TIA / minor stroke stratified by the presence (dashed line) or absence (dotted line) of symptoms of anxiety and/or depression at 1-month. (a) TIA / minor stroke (b) TIA, and (c) minor stroke.

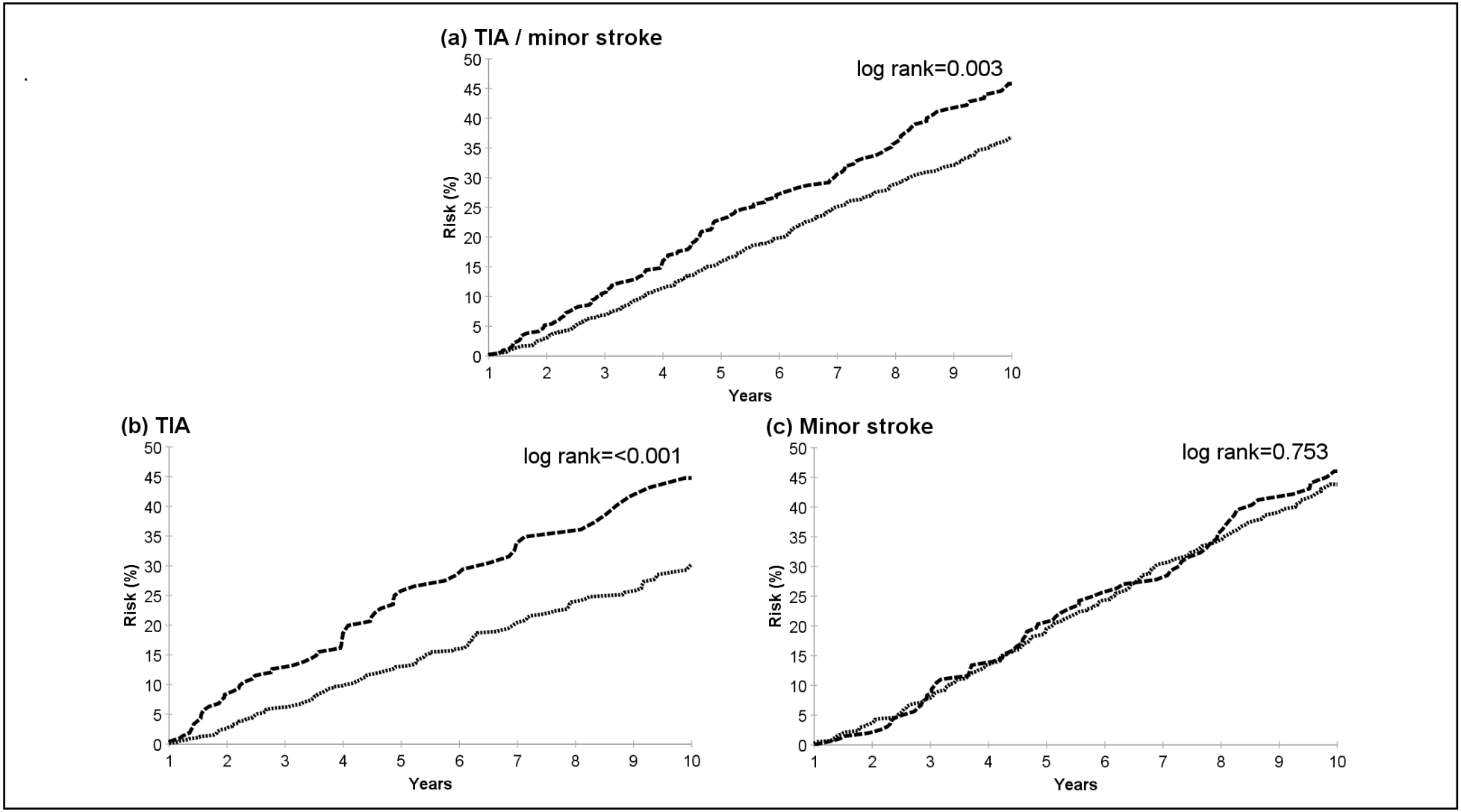

Figure 4.8 Kaplan Meier survival curves of risk of (any) death (up to 10 years) after a TIA / minor stroke stratified by the presence (dashed line) or absence (dotted line) of symptoms of anxiety / depression at 12-months. (a) TIA / minor stroke (b) TIA, and (c) minor stroke

	1-month symptoms of anxiety / depression					12-month symptoms of anxiety / depression				
	Event / total	**Crude HR (95% CI)**	**p value**	**Age / sex adj HR (95% CI)**	**p value**	**Event / total**	**Crude HR (95% CI)**	**p value**	**Age / sex adj HR (95% CI)**	**p value**
All TIA / minor stroke										
Anxiety / depression symptoms	193/639	1.13 (0.96-1.34)	0.150	1.35 (1.13-1.60)	**0.001**	130/418	1.36 (1.11-1.67)	**0.003**	1.44 (1.17-1.76)	**0.001**
No symptoms	426/1498	ref	ref	ref	ref	336/1404	ref	ref	ref	ref
Event Type										
TIA alone										
Anxiety / depression symptoms	77/334	1.05 (0.80-1.36)	0.746	1.39 (1.06-1.82)	**0.018**	61/211	1.80 (1.33-2.42)	**<0.001**	1.64 (1.22-2.21)	**0.001**
No symptoms	196/828	ref	ref	ref	ref	147/799	ref	ref	ref	ref
Minor stroke alone										
Anxiety / depression symptoms	116/305	1.18 (0.95-1.48)	0.142	1.29 (1.03-1.61)	**0.028**	69/207	1.05 (0.79-1.38)	0.754	1.23 (0.93-1.62)	0.150
No symptoms	230/670	ref	ref	ref	ref	189/605	ref	ref	ref	ref
Sex										
Female										
Anxiety / depression symptoms	100/365	0.90 (0.71-1.45)	0.395	1.11 (0.87-1.41)	0.400	67/227	1.14 (0.86-1.52)	0.360	1.21 (0.91-1.61)	0.193
No symptoms	202/666	ref	ref	ref	ref	158/645	ref	ref	ref	ref
Male										
Anxiety / depression symptoms	93/274	1.44 (1.13-1.83)	**0.003**	1.67 (1.31-2.13)	**<0.001**	63/191	1.65 (1.24-2.20)	**0.001**	1.74 (1.30-2.32)	**<0.001**
No symptoms	224/832	ref	ref	ref	ref	178/759	ref	ref	ref	ref
Age cohorts										
Age < 65 years										
Anxiety / depression symptoms	14/190	0.98 (0.52-1.84)	0.940	1.04 (0.55-1.96)	0.911	13/130	2.08 (1.03-4.18)	**0.040**	2.17 (1.08-4.36)	**0.030**
No symptoms	30/388	ref	ref	ref	ref	20/384	ref	ref	ref	ref
Age 65-74 years										
Anxiety / depression symptoms	39/165	1.50 (1.02-2.21)	**0.042**	1.56 (1.05-2.32)	**0.029**	30/95	2.09 (1.36-3.22)	**0.001**	2.24 (1.43-3.51)	**<0.001**
No symptoms	72/418	ref	ref	ref	ref	65/423	ref	ref	ref	ref
Age ≥ 75 years										
Anxiety / depression symptoms	140/284	1.17 (0.96-1.43)	0.123	1.34 (1.10-1.64)	**0.004**	87/193	1.11 (0.87-1.41)	0.413	1.23 (0.96-1.57))	0.102
No symptoms	324/692	ref	ref	ref	ref	251/597	ref	ref	ref	ref

Table 4.10 Risk of (any) death (up to 10 years) stratified by the presence / absence of moderate to extreme symptoms of anxiety and/or depression 1-month and 12-months after a TIA / minor stroke. Crude hazard ratio and age / sex adjusted hazard ratios (with 95% confidence intervals) are also presented. Data presented for all TIA / minor stroke patients, for TIA and minor stroke patients separately, by sex and age cohorts. Patients that died prior to the 1-month assessment and prior to the 12-month assessments were excluded from the relevant analyses.

	1-month assessment					12-month assessment				
	Event / total	**Crude HR (95% CI)**	**p value**	**Age / sex adjusted HR (95% CI)**	**p value**	**Event / total**	**Crude HR (95% CI)**	**p value**	**Age / sex adjusted HR (95% CI)**	**p value**
All TIA / minor stroke										
Depression	13/116	2.09 (1.11-3.91)	**0.022**	1.99 (1.05-3.76)	**0.035**	10/71	3.85 (1.71-8.68)	**0.001**	3.61 (1.58-8.28)	**0.002**
No depression	28/439	ref	ref	ref	ref	14/385	ref	ref	ref	ref
TIA alone										
Depression	9/69	2.77 (1.20-6.40)	**0.017**	2.48 (1.06-5.83)	**0.037**	7/42	5.59 (1.95-15.9)	**0.001**	4.94 (1.70-14.34)	**0.003**
No depression	14/285	ref	ref	ref	ref	7/253	ref	ref	ref	ref
Minor stroke alone										
Depression	6/47	1.41 (0.54-3.69)	0.478	1.37 (0.52-3.63)	0.522	3/29	2.16 (0.56-8.35)	0.265	2.00 (0.49-8.19)	0.335
No depression	14/154	ref	ref	ref	ref	7/132	ref	ref	ref	ref

Table 4.11 Risk of (any) death (up to 5 years) stratified by the presence / absence of depression (GDS) 1-month and 12-months after a TIA / minor stroke. Crude hazard ratio and age / sex adjusted hazard ratios (with 95% confidence intervals) are also presented. Data presented for all TIA / minor stroke patients and TIA and minor stroke patients separately. Patients that died prior to the 1-month assessment and prior to the 12-month assessments were excluded from the relevant analyses.

CHAPTER 5

PREVALENCE, INCIDENCE AND FACTORS ASSOCIATED WITH PRE-STROKE DEMENTIA: POPULATION-BASED STUDY, SYSTEMATIC REVIEW AND META-ANALYSIS

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5.1 Abstract

Introduction: According to a previous review 1-in-10 patients who have a stroke also have pre-stroke dementia. However, due to the small number of studies included the review was limited in its ability to assess the impact of methodological factors and did not include patients who had presented with a transient ischaemic attack (TIA) rather than a stroke. Furthermore, it was unable to draw conclusions on independent associations of pre-stroke dementia.

Methods: I updated the systematic review and meta-analysis of studies on pre-stroke dementia that have been published since the prior review was completed in 2009. Studies were included if they were on patients with symptomatic stroke either through recruitment of consecutive eligible patients or volunteers in prospective cohorts. The results were collated with those of the previous review along with the data from a recent longitudinal population-based study. Pooled rates of pre-stroke dementia were calculated in conjunction with an assessment of the impact of methodological factors (such as hospital-based versus population-based) upon the rates. Pooled odds ratios were also produced for associated factors and data on independent associations extracted where available.

Results: Overall, 46 studies on pre-stroke dementia were included (38 hospital-based, 8 population-based). The pooled prevalence of pre-stroke dementia in studies using an informant-based structured interview (13.6%, 95% CI 11.6-15.5%) or a non-structured interview (12.1%, 9.0-15.3%) was higher than in studies using medical records / coding only (6.1%, 5.2-6.9%). The setting of the patient cohort had only a limited impact on the prevalence rates once other methodological factors had been controlled for (hospital-based: 12.3%, 10.3-14.3%, population-based: 12.5%, 11.3-13.6%). Timing of assessment remained critical with studies done in survivors at a subsequent follow-up time producing lower rates (8.6%, 7.1-10.1%). Pre-stroke dementia prevalence rates were unchanged over the past two decades. Independent associations were reported in 10 studies with pre-stroke dementia included factors associated with Alzheimer's disease such as increasing age,

female sex, cortical atrophy and medial temporal lobe atrophy but additionally factors associated with vascular dementias such as prior stroke, silent strokes, diabetes and increasing severity of stroke.

Conclusions: This study reaffirms that approximately 1-in-10 patients presenting to hospital will have pre-stroke dementia with no demonstrable time-trend over the past two decades. However, methodological factors such as method and timing of diagnosis impact significantly upon the measured prevalence rates. Independent associations with pre-stroke dementia reflect likely contributions from both neurodegenerative and vascular pathology and further work to delineate the aetiologies of pre-stroke dementias should be undertaken.

5.2 Introduction

Stroke patients with pre-morbid dementia are at increased risk of poorer functional outcomes, increased mortality and are significantly less likely to be discharged home.[1,2,3] Therefore, in order to inform discussions with patients and their relatives and to facilitate planning of clinical and social services having a better understanding of the prevalence rates of pre-stroke dementia is vital. A previous meta-analysis in 2009 found that one-in-ten patients who has a stroke has pre-stroke dementia.[4] However, that review only included data from 11 studies regarding pre-stroke dementia and was not able to draw conclusions about its independent associations. Additionally, methodological factors such as baseline selection bias, timing and method of diagnosis are known to have a significant impact in determining the rates of dementia in stroke cohorts.[5-7] Due to the limited number of studies these factors could not be fully examined in the previous review. Furthermore, recently transient ischaemic attacks (TIAs) have been found to be associated with an increased risk of subsequent dementia but there remains limited data on the pre-TIA dementia prevalence.[8]

It is oft stated that, in general, the factors associated with pre-stroke dementia are those that are associated with Alzheimer's and the factors associated with post-stroke dementia those that are associated with vascular disease in general.[4] However, there is increasing recognition of the presence of mixed and synergistic neurodegenerative pathologies in dementia patients.[9] Therefore, it is feasible that factors associated with pre-stroke dementia may reflect both neurodegenerative disease and vascular processes but the prior systematic review was limited in its analysis by inclusion of only 11 studies. Finally, there is evidence that the incidence rate of dementia, particularly Alzheimer's disease is decreasing over the decades, at least in high-income countries, but this has not yet been demonstrated in a stroke population.[10-13]

Therefore, through updating the systematic review and including the results of a recent longitudinal population-based study I aim to answer the following questions. Firstly, what is

the prevalence and time-trend of pre-stroke dementia and how do methodological factors impact upon the rate? Secondly, what are the independent associations of pre-stroke dementia? Finally, what proportion of patients who present with a TIA have pre-existing dementia?

5.3 Methods

5.3.1 Systematic Review

To identify studies on pre-stroke dementia I searched (up until 18 Feb 2020) Ovid Medline, EMBASE and PsychInfo using a comprehensive search strategy (Appendix XIX). As this was an update to a previous review, the search was limited to studies published since April 2009. Relevant review articles were also hand-searched, as were the title pages of the four journals that contained the largest number of relevant papers in the electronic search. The review was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14]

A risk of bias assessment was completed but due to the strict selection criteria as defined in the previous systematic review it was found to have limited utility. [4] Criteria for inclusion of papers in the systematic review were:

i. Series of consecutive eligible patients with a symptomatic stroke, or volunteers in a prospective cohort study
ii. Inclusion of all transient ischaemic attacks, all strokes, all ischaemic strokes or all primary intracerebral haemorrhagic strokes (i.e. not on sub-sets e.g. lacunar strokes or minor strokes)
iii. Published in English, or English translation available
iv. Minimum of 50 patients included

Two types of population-based study were eligible: those in which all stroke patients within a defined population were ascertained, and those in which cohorts of normal volunteers

were recruited and followed prospectively, with data reported on those who had a stroke during follow-up. Any method of diagnosis of pre-stroke dementia was permitted for inclusion in the review. I reviewed all abstracts of the papers identified on the initial search with subsequently the full text of eligible articles reviewed by both myself and STP. Where multiple studies used a subset or the whole of the same data set, the duplicate studies were only included if additional risk factor data were provided, otherwise, the article with the largest complete patient series was included. Data were extracted on study setting, method of diagnosis, number of cases of pre-stroke dementia, any associated factors and independent factors, mean severity of stroke and country of study. Mean severity was determined by the stroke or functional scale as reported by the individual study (Appendix XX) In cases of disagreement between STP and myself regarding eligibility of studies or data extraction, consensus was reached through joint re-assessment.

5.3.2 Population-Based Study

Study methods for the population-based study are detailed in Chapter One and have previously been published in detail.[8] In brief, the Oxford Vascular Study (OxVasc) is a longitudinal, prospective population-based study of the incidence and outcomes of all acute vascular events occurring within a defined population of 92,728 in Oxfordshire, UK. Consecutive patients with a transient ischaemic attack (TIA) or stroke were prospectively recruited from April 1, 2002 to March 31, 2012. Case ascertainment was achieved through both 'hot' and 'cold' methods which have been demonstrated to achieve near complete ascertainment of all TIA and strokes. All patients with a TIA, ischaemic or haemorrhagic stroke were reviewed by a study physician as soon as possible after their initial presentation either on a hospital ward or in an outpatient neurovascular clinic. A TIA was defined, according to the World Health Organisation (WHO) criteria, as focal neurological symptoms lasting less than 24 hours with a stroke defined as symptoms lasting more than 24 hours and the probability of the event being defined according to National Institute of Neurological and Communicative Disorders and Stroke (NINDS) criteria.[15] For this analysis, all patients

with a probable or definite TIA or stroke were included in the analysis. Subject data, including vascular risk factors, were collected by interview with a standardised form and supplemented by primary care records. Multiple methods were used to identify the presence of pre-event dementia: baseline clinical assessment by study clinician, discussion with an informant (including the IQCODE), hospital and outpatient clinic records and the primary care record. The diagnosis of pre-event dementia was done by a senior study physician with an expertise in dementia (STP) using Diagnosis and Statistical Manual of Mental Disorders – IV (DSM-IV) criteria. An additional sub-analysis on patients recruited only from the hospital-wards was performed to permit additional inclusion in the meta-analysis.

5.3.3 Analysis

Data from the previous review, the population-based study and the current search results were combined for the analysis. Pooled estimates of the prevalence of pre-stroke dementia were calculated with the 95% confidence intervals to allow for extra-binomial variation. This was done because standard methods of calculating confidence intervals produce artificially narrow intervals if there is heterogeneity of risk between different studies.[16] Studies were stratified by study setting (hospital versus population-based), method and timing (at the time of the stroke or at a subsequent follow-up point) of diagnosis of dementia, mid-study year (mid-year of the patient recruitment period) and whether it was the first or any (first or recurrent) stroke. Analyses of heterogeneity of prevalence across studies were done with X^2 tests. The proportion of the overall heterogeneity of prevalence of pre-stroke dementia across all studies that could be accounted for by the above sub-categorisations was determined by an inverse-variance weighted regression of log(risk) against study type.

To determine the factors associated with pre-stroke dementia, pooled odds ratios were calculated for patients with dementia versus those without dementia. A fixed effects analysis was used unless there was evidence of significant heterogeneity ($p \leq 0.1$) in which case a random-effects analysis was used. Hospital-based and population-based studies

were combined for calculation of the pooled odds ratios. Additionally, pooled odds ratios of pre-event dementia were calculated for studies that reported on both a TIA cohort and stroke cohort separately. All analyses were done in SPSS version 26.

5.4 Results

The literature search produced 24,419 references (including 7604 duplicates) of which, after full text review, 43 articles were eligible for inclusion. Hand searching reference lists and relevant journals identified 5 further articles. After exclusion of duplicate datasets a total of 32 articles (encompassing 32 different studies), published since the previous review in 2009, were found to be eligible (figure 5.1). Reasons for exclusion included a failure to include consecutive patient series, reporting data for cognitive impairment not dementia, less than 50 patients, asymptomatic stroke data and a lack of availability of an English translation. Studies that excluded patients with a history of seizure disorder were not included in the meta-analysis due to the increased risk of a seizure disorder in patients with dementia. The 32 studies were combined with the relevant 13 studies from the 2009 review and the OxVasc study to yield 46 eligible studies on pre-stroke dementia.[1-,3,8,17-67] Only studies that utilised a structured or non-structured interview to diagnose pre-stroke dementia were used for calculation of relative odds for pre-stroke dementia due to the lower prevalence rates captured by record or coding review. One study stated that it excluded patients with a known history of dementia and reported rates of pre-stroke dementia on the remaining cohort. Due to this confusion, it was not included in the pooled prevalence rate calculation.[50]

The eligible hospital- and population-based studies are shown in table 5.1 and table 5.2 respectively together with demographic details, study design, and pre-stroke dementia diagnosis method. Four of the hospital-based studies identified stroke patients retrospectively through records review,[31,33,36,54] with the remainder prospectively identifying cases. For the population-based studies, six collected data on all patients with incident

strokes during a particular period (five prospectively,[8,62-67] one retrospectively[59]) and two collected data prospectively on volunteer cohorts who were stroke-free at enrolment.[60,61]

5.4.1 Study characteristics

38 hospital-based studies (34,2088 patients, mean study age range 61-80 years) and 8 population-based studies (7039 patients, mean age range 72-79 years) reported data on pre-stroke dementia. One of the hospital-based studies reported data on pre-TIA dementia only so was not included further in the meta-analysis on pre-stroke dementia.[31]

Similar to in the previous review, the majority of population-based studies focused on first strokes (five of the eight) compared with only three of the 38 hospital-based studies with the remainder reporting on any-stroke.[31,51,53,59-66] In order to identify cases of pre-stroke dementia in the hospital-based studies 14 of the 38 studies used an informant interview with the IQCODE though with differing cut-offs ranging from 3.3 to 4.0.[2,19-25,27-29,37,40,42,43,50,51,57,58] Three of the studies used other structured questionnaires (Astrand questionnaire, Independent Activities of Daily Living, Blessed Dementia Rating),[32,45,46] six used an informant interview,[3,17,18,26,30,34,35] ten relied on a medical records review,[31,33,38,39,44,48,49,52,56,59] four on coding[36,41,47,53] and one on a combination of coding and medical records.[54] In the population-based studies two used IQCODE,[8,66] three used a standardised questionnaire or informant interview[62-65] and one relied on medical records.[59] Two of the studies were longitudinal prospective cohorts using DSM criteria for pre-event dementia diagnoses.[60,67] There were also differences in the stroke sub-set studied with 12/38 hospital-based and 1/8 population-based studies including only ischaemic stroke and 3/38 hospital-based and 1/8 population-based studies including only intracerebral haemorrhages.

More than half of the hospital-based studies (20/38) originated in Europe, but since 2009 there have been cohorts from wider areas including Egypt, Malaysia and India. Similarly, more than half of the population-based studies (5/8) originated from Europe with the remainder from America (2/8) or Australasia (1/8).

5.4.2 Pre-stroke dementia prevalence

Data on pre-stroke dementia prevalence were available from 35 of the 38 hospital-based studies (one reporting on pre-TIA dementia prevalence, two reporting on subsets of patients only) and all eight of the population-based studies. Nine of the 35 hospital-based studies reported the prevalence at a subsequent time period after the stroke (ranging from at the point of discharge from hospital to one year after the event),[17,18,27,30,40,42,46,55,57] with the remainder of the hospital-based studies and all of the population-based studies reporting the prevalence at the time of (or prior to) the stroke. Similarly to as in 2009, the prevalence rates of pre-stroke dementia were highly heterogeneous ($p<0.001$). Overall, the cohort setting (population-based versus hospital-based), method of diagnosis, first versus any stroke, mean severity and mean age of the cohort accounted for 78% of the variance between studies. Mean age of the cohort overall accounted for the greatest degree of heterogeneity (59%) but, significantly, the method of diagnosis accounted for a greater degree of heterogeneity (18%) than the cohort setting (3%). Including the mid-year of the cohort recruitment into the model did not further explain any heterogeneity. No change in the prevalence of pre-stroke dementia over the past two decades could be demonstrated (figure 5.2). A summary of the rates of pre-stroke dementia are presented in figure 5.3, according to method in figure 5.4 and according to cohort in figure 5.5.

For any stroke, the pooled prevalence of pre-stroke dementia measured at the time of admission using an IQCODE or other structured questionnaire was 13.6% (95% CI 11.6-15.5%, p het=0.044) and 12.6% (9.0-15.3%, p het<0.001) with a non-structured interview. However, the rate was lower if records or coding were used (6.1%, 5.2-6.9%, p het<0.001). For first strokes, rates were overall lower and showed a similar trend to differing rates of detection based on diagnosis method (IQCODE / questionnaire: 10.0%, 8.0-12.0%, p het<0.001, non-structured interview: 7.3%, 6.0-8.6%, p het=0.004, records / coding: 1.9%,-2.0-5.9, p het<0.001). Even after exclusion of studies that relied on coding or records, in hospital-based studies, the rates of pre-stroke dementia were lower when ascertained at a

subsequent follow-up point (8.6%, 7.1-10.1%, p het=0.015) rather than at the time of the event (12.3%, 10.3-14.3%, p het<0.001).

5.4.3 Associations of pre-stroke dementia

In addition to the data from the OxVasc study, data on clinical associations of pre-stroke dementia were available from 12 hospital-based studies[2,3,18,19,29,33,34,37,39,50,57,58] and two further population-based studies.[63-65,67] Pooled analysis showed that patients with pre-stroke dementia were older (weighted mean difference in age 10.6 years, 10-2-10.9, p<0.001) than those without pre-stroke dementia. Rates of pre-stroke dementia were higher in women (OR 1.74, p<0.001), in patients with lower levels of education (OR 1.92, p<0.001), and patients with a family history of dementia (OR 3.84, p<0.001). Numerous vascular risk factors were also associated with pre-stroke dementia: atrial fibrillation (OR 1.80, p<0.001), ischaemic heart disease (OR 1.35, p<0.001), a previous TIA (OR 1.72, p<0.001), a previous stroke (OR 2.39, p<0.001) and hypertension (OR 1.12, p=0.032). In terms of aetiology of the index stroke, only cardioembolic strokes were associated with a higher rate of pre-stroke dementia (OR 1.84, p<0.001) not large artery, lacunar nor cryptogenic aetiologies. Imaging markers such as leuokoaraiosis (OR 2.39, p<0.001) medial temporal lobe atrophy (OR 7.67, p<0.001) and overall cerebral atrophy (OR not available) were all associated with pre-stroke dementia but a prior silent stroke was not (OR 0.98, p=0.931) (tables 6.3-6.6).

Multivariate analyses were performed in 10 studies (including OxVasc) to determine independent variables associated with pre-stroke dementia with the results from the individual studies reported in table 5.7. Independent factors included increasing age (6 studies), prior stroke or TIA (5 studies), female sex (4 studies), low education (3 studies), silent strokes (3 studies), cortical atrophy (3 studies), medial temporal lobe atrophy (2 studies), atrial fibrillation (2 studies), diabetes (1 study), a family history of dementia (1 study) and increasing severity of stroke (1 study).

5.4.4 Pre-TIA dementia

In addition to the OxVasc study, four other studies (all hospital-based) reported on the prevalence of pre-event dementia in a TIA cohort.[31,35,51,58] One study was in patients with atrial fibrillation and had only 17 patients with a TIA so was excluded from the prevalence analysis.[58] Pooled prevalence rate of pre-TIA dementia at the time of a first TIA (without prior stroke) was 4.2% (1.4 -8.3%, p het=0.002) and at the time of any TIA (including patients with a prior stroke) was 6.2% (3.3-11.2%, p het<0.001) (figure 5.6a). Comparing the prevalence of pre-TIA dementia with pre-(ischaemic) stroke dementia within cohorts that reported on both also found lower pooled odds of pre-event dementia for the TIA patients (first event: OR 0.30 95% CI 0.19-0.47, p<0.001, any event: OR 0.84, 0.77-0.90, p<0.001) (figure 5.6b).

5.5 Discussion

This systematic review and meta-analysis has expanded upon the previous review in 2009 by significantly increasing the number of included studies (13 to 46), patients (4491 to 349,127) and in addition included data from the Oxford Vascular Study.[4] Furthermore, studies were from a wider area, though with still a noticeable dominance from European countries. Despite the increase in numbers, similarities to the previous review were found: hospitalised patients with any stroke had a pre-stroke dementia prevalence rate of 13.6% in this study similar to 14.4% found previously. However, important differences were found. The significantly increased patient numbers allowed a more detailed examination of the importance of the method of diagnosis with rates varying from 1.9% to 13.6% depending on method. There is neither a gold standard tool nor a consensus on how to retrospectively diagnosis dementia in stroke patients. A patient interview is likely to be confounded by the current stroke related limitations and instead a structured informant interview (for example, with the IQCODE) is accepted as the best solution.[68] However, there was a lack of agreement as to the optimal cut-off value for the IQCODE with values ranging from 2.7 to 4.0. Despite this a structured interview detected the highest rates of pre-stroke dementia

(13.6%) with studies that relying on coding or medical records review finding the lowest rates (1.9%).

The cohort setting (population-based versus hospital-based) had less of an impact in this analysis than in the previous review. However, in the original review all the population-based studies reported rates of pre-stroke dementia in those with a first stroke only rather than any (first or recurrent). In the current study, inclusion of population-based studies of any stroke found similar rates to those of any stroke in hospital-based studies: 12.5% and 12.3% respectively. It was also postulated in the previous study that patients with dementia were more likely to have severe strokes and lower capacity to cope at home and therefore that would increase the proportion seen in a hospital-based setting. However, with the introduction of the FAST campaign, more urgent assessment in neurovascular clinics and the introduction of more invasive treatment options, it is feasible that hospital attendance for all patients after a stroke of any severity may have increased.[69]

Similar to in the previous review, studies that reported the prevalence of pre-stroke dementia at a follow-up point, rather than at the time of the stroke, found lower rates of dementia (8.8%). This is likely due to biased attrition bias resulting from increased early mortality of stroke patients with pre-morbid dementia and caution should be taken against using results from these studies in order to plan acute clinical services.

Even in studies of first stroke the prevalence rate of pre-stroke dementia (10.0%) is double that found in age-standardized prevalence of dementia in all patients aged over 60 years.[70] A recent study reported that compared to age- and sex-matched controls pre-event dementia prevalence was not increased in patients with a TIA or minor stroke but was in patients who had a major stroke (standardised prevalence ratio 1.9 (1.5-2.5) for NIHSS>10).[8] A shared underlying vascular process likely accounts for part of the difference, along with conflicting treatment aims in patients with dementia (for example more relaxed HbA1c and blood pressure targets to reduce falls which may increase risk of subsequent stroke). Additionally Alzheimer's disease is associated with an increased risk of stroke,

particularly intracerebral haemorrhage for example in those with underlying cerebral amyloid angiopathy.[71] This synergistic relationship may also explain why a decreasing time-trend over the decades was not demonstrated in this systematic review in contrast to numerous incidence studies of the rates of dementia in the general population. The increased risk of stroke associated with dementia may confound the ability to detect the decrease in the incidence rate in the general population.

In this review the prevalence rate of pre-TIA dementia was found to be low. However, caution should be applied in interpreting this result as it is likely confounded by the dementia itself. The person themselves may not remember the transient episode so seeking medical attention may only occur if the episode was witnessed, for example by a carer. Furthermore, there may be a degree of nihilism applied particularly if there is a concern that a perceived unnecessary visit to a hospital may cause distress to a person with dementia.

Similar to in the previous review, the strongest associations with pre-stroke dementia were those associated with neurodegenerative processes such as family history of dementia and medial temporal lobe atrophy suggesting a role for Alzheimer's disease. However, additionally leukoariaosis, prior stroke, multiple strokes and vascular comorbidities were also associated with pre-stroke dementia. Many of these factors were found to be independent associations in studies that reported multivariate analyses. It is likely, unsurprisingly, that pre-stroke dementia represents a mix of pathologies in particular vascular dementia and Alzheimer's disease each with differing associations. Only one study in this review attempted to delineate the underlying subtype of the dementia and further work should be undertaken on this as, in addition to differing associations, the outcomes may vary between the groups.[37]

In this review, out of all stroke aetiologies cardio-embolic strokes were found to be associated with pre-stroke dementia. Rates of anticoagulation in patients with known atrial fibrillation are generally still poor, and disproportionately so in patients with known

dementia.[72] Furthermore, the presence of dementia potentially increases the risk of missed doses and therefore 'treatment-failure' related strokes.

Smoking was found to be reduced in those with pre-stroke dementia but care should be taken in interpreting this as smoking is a major cause of early mortality and patients may die prior to the age at which neurodegenerative processes occur.[73] Perhaps more complex is the association of hypercholesterolaemia with a lower risk of pre-stroke dementia. High cholesterol in mid-life is associated with subsequent worse cognitive outcomes but a reverse association of later-life cholesterol has been found with Alzheimer's disease.[74] Total cholesterol tends to decline at older ages and it may be that a lower cholesterol at an older ages represents an increasingly fragile physiology and potentially a decreasing cognitive reserve.[75]

This study has numerous limitations. Due to the small numbers of studies, intracerebral haemorrhages were not analysed separately from ischaemic strokes and no attempt was made to delineate them further. A recent review found that pre-intracerebral haemorrhage dementia was likely attributable to two different mechanisms.[76] In lobar haemorrhages dementia was associated with increasing age, low education and increasing cortical atrophy suggesting an association with Alzheimer's dementia and cerebral amyloid angiopathy. Conversely, pre-stroke dementia in deep haemorrhages was associated with white matter disease and old infarcts suggesting an underlying vascular pathology. A further limitation of this current study was that the calculation of pooled odds ratios for a given association only included data from studies where they provided it which may mean they are subject to a publication bias. As mentioned earlier the specific mechanism of the underlying dementia was not examined and there are concerns about the validity of the TIA prevalence rates. Overall, the studies are still heavily biased towards European countries and therefore likely mostly Caucasian populations so may not be representative of the global population. Finally, whilst studies were classified by the method of diagnosis there is likely a degree of

variance even within the same method as, for example, “interview” can have multiple interpretations.

5.6 Conclusion

One-in-ten patients admitted to hospital with their first stroke have pre-stroke dementia with the method of capture of the diagnosis having a significant impact on prevalence rates. Associations with pre-stroke dementia include factors linked to Alzheimer’s disease (medial temporal lobe atrophy, family history of dementia, global atrophy) and those associated with vascular dementia (leukoaraoiosis, prior strokes, silent strokes). Further work to delineate the differing aetiologies of pre-stroke dementia is required.

5.7 References

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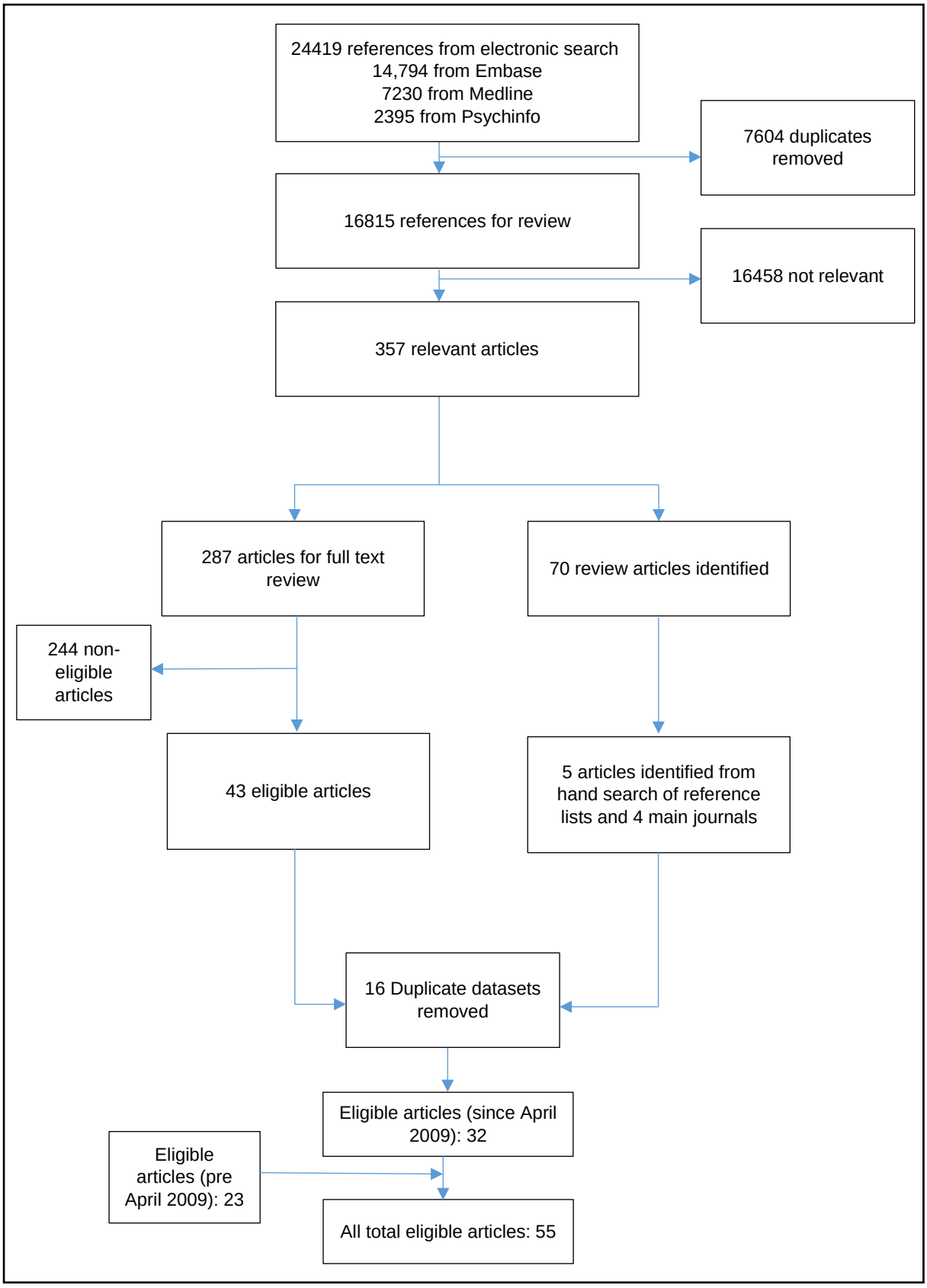

Figure 5.1: Literature searches and results for studies on pre-stroke dementia prevalence.
For full search strategy see Appendix XIX.

Study centre	Date of cohort collection	Study type	Mean age (yrs)	Female	Stroke type	First ever stroke	Exclusion criteria	Pre-stroke dementia diagnosis
Florence, Italy[12]	1993-94	X	71	48%	IS, H, SAH	N	N/S	IQCODE
Helsinki SAM Study, Finland[13]	1993-95	X, L	71	48%	IS	N	ICH, SAH, age <55 or >85, not living in Helsinki, not speaking Finnish language, severe aphasia, severe hearing impairment	DSM III and others
Madrid, Spain[14,15]	1994-95	X, L	69	47%	IS, H	N	primary brain lesion, aphasia, comorbidity	IQCODE
Lille Stroke/ Dementia Study, France[2,16-19]	1995-96	L	72	46%	IS, H	N	Non-white, no informant, age <40 years, not fluent in French, not from Lille, history of severe head trauma	IQCODE
Sydney Stroke Study, Australia[20]	1997-2000	X, L	72	39%	IS, TIA	N	Concomitant neurological disorder, severe aphasia, too unwell to participate	IQCODE
Ege Stroke Registry, Turkey[21]	1998-2009	L	66	43%	IS, H	N	Lack of consent	Records, informant interview
Chongqing Stroke Study, China†,[22]	1999-2000	X	68	47%	IS	N	Concomitant neurological disorder, <55 years, severe medical co-morbidity or sensory impairment, reduced GCS, severe aphasia	IQCODE
Cracow, Poland[23,24]	2000-01	X	66	55%	IS, H	N	Age <40 years, no reliable informant, other brain lesion	IQCODE
Rotterdam-Rijnmond, Netherlands[25]	2000-02	X	70	38%	IS, H, TIA	N	Aphasia, sensory impairment, non-fluent in Dutch, reduced conscious level	Interview
Olmsted County, USA[26]	2000-17	X	73	49%	TIA	Y	Residual deficit > 24 hours, acute infarction on imaging, prior stroke/TIA, hypertensive encephalopathy, reversible cerebral vasoconstriction syndrome, on dialysis/ transplant list/ organ transplant recipients / left ventricular assist device	Medical records review
Gothenburg, Sweden†, [27]	2002-N/S	X	78	47%	IS, H	N	Age< 65 years, low consciousness, severe medical conditions, severe aphasia, severe dementia, difficulties in understanding the Swedish language or inability to perform an assessment with the MMSE	Astrand questionnaire
Badojoz, Spain[28]	2002-09	X	74	48%	IS	N	TIA, intracerebral haemorrhage, subarachnoid haemorrhage	Medical record review
Ontario Stroke Registry, Canada[29,30]	2003-12	X,L	72	48%	IS, H, TIA	N	Pre-existing hemiparesis for the TIA cohort, SAH	Medical record review
Tyneside, UK[31]	2003-15	X, L	N/S	53%	IS, H	N	Subsequent recurrent stroke, missing data, SAH, age <18 years	Coding
PITCH, Lille, France[32]	2004-09	X, L	66	46%	H	N	intraventricular haemorrhage, ICH from intracranial vascular malformation, intracranial venous thrombosis, head trauma, tumour, haemorrhagic transformation within an infarct, referral from other hospitals, pre-existing dementia (IQCODE => 64)	IQCODE
NASIS, Israel[33]	2004-13	X	71	45%	IS, H	N	Age < 18 years	Medical record review
Cork, Ireland[34]	2005	X	73	49%	IS, H	N	TIA	Medical record review
Chongqing Stroke Study, China†, [35]	2005-08	L	67	50%	IS	N	Haemorrhage, SAH, aged <55	IQCODE
California, USA[36]	2005-2011	X	74	53%	IS	N	Age < 50 years, hospice admissions	Coding
South Korea[37]	2007-08	L	64	39%	IS	N	Severe / deteriorated medical or neurological conditions, severe aphasia, death within 2 weeks, use of cognitive enhancers at follow up	K-IQCODE and K-ADLs

Zagazig, Egypt[38]	2007-08	X, L	63*	47%	IS, H	N	TIA, stroke due to cerebral venous thrombosis, SAH, <40 years, without reliable informant, patients with history of severe head trauma or cerebral surgery	IQCODE
CNSR, China[39]	2007-08	X,L	66	38%	IS	N	N/S	Medical record review
CICAS, China[39]	2007-09	X,L	64	34%	IS	N	TIA, pre-event Rankin > 3, inability to undergo MRI for vascular imaging	Medical record review
Fukuoka, Japan[3]	2007-15	X	N/S	N/S	IS	N	Non-ischaemic stroke	Records/ informant interview
Amiens / Soissons, France[40]	2008-09	X	68	37%	IS, H	N	Severe medical conditions, illiteracy, mental retardation, non-fluent in French, psychosis, prior traumatic brain injury	IADLs
Brno, Czech Republic[41]	2009-10	X	71	44%	IS, H	N	TIA, history of severe head trauma or neurosurgery, SAH, venous infarction, brain tumour, psychosis, non-fluent in Czech, comatose / stuporous on admission and did not improve during the first week	BDR
Cáceres, Spain[42]	2009-11	X	71	35%	IS, H	N	Lack of signed consent from patient	Medical record review
ERICH, USA[43]	2010-15	X,L	62	41%	H	N	Resident for less than 6 months within 75 miles of the recruiting centre, race other than non-Hispanic white, non-Hispanic black or Hispanic, non-spontaneous causes of ICH, inability to provide consent (either patient or legal representative)	Medical record review
Chicago, USA[44]	2010-17	X	65	50%	H	N	ICH due to trauma, haemorrhagic conversion of ischaemic stroke, structural lesions or vascular malformations	Medical record review
Brescia, Italy[45]	2011	X,L	71	44%	IS, H	N	Previous diagnosis of dementia, pre-morbid cognitive impairment, TIA, <18 years, lack of caregiver	IQCODE
Heidelberg, Germany[46]	2011-12	X	67	39%	IS, H, TIA	Y	Previous strokes on CT/MRI	IQCODE
Bologna, Spain[47]	2011-12	X	78	46%	IS	N	TIA, SAH, deceased in hospital, nursing home or Rankin=5 prior to index event, thrombolytic therapy	Medical record review
Riksstroke (Swedish Stroke Registry)[48]	2011, 2013	X, L	N/S	N/S	IS	Y	Functionally dependent pre-stroke, previous stroke, incomplete information	Coding
Melbourne, Australia[49]	2013-15	X	80	47%	IS, H	N	Age < 65 years	Coding / medical record review
Ibadan, Nigeria[50]	2014–16	L	61	47%	IS, H	N	Unable to communicate reliably (aphasia), severe co-morbidities (CKD, metastatic cancer, open tuberculosis)	IQCODE ≥4.0
Kuala Lumpur, Malaysia[51]	2015-16	X	64	66%	IS	N	Age <18, haemorrhagic stroke, GCS <8, requiring mechanical ventilation, duration of stroke > 7 days on admission	Medical record review
Hong Kong, China[52]	N/S	X	71	55%	IS, H	N	Non-Chinese, Non Cantonese- speaking, age <50	IQCODE
SAFE II Dementia sub-study, France/Italy[53]	N/S	N/A	79	59%	IS, H, TIA	N	N/S	IQCODE

Table 5.1 Hospital-based studies of pre-stroke dementia. X=cross-sectional. L=longitudinal. N=no. Y=Yes. IS=ischaemic stroke. H=Haemorrhagic stroke. TIA=Transient Ischaemic Attack. SAH=subarachnoid haemorrhage. GCS=Glasgow coma scale. DSM=diagnostic and statistical manual of mental disorders. FU=follow-up. IQCODE=informant questionnaire on cognitive decline in the elderly. SAM=Stroke, Ageing and Memory study. SAFE=stroke in Atrial Fibrillation Ensemble II. PITCH=Prognosis of Intracerebral Haemorrhage. CNSR=China National Stroke Registry. CICAS=Chinese Intracranial Atherosclerosis Study. N/A=not applicable. N/S= not stated. MMSE= mini mental state examination.*median values †Data from (non-overlapping) cohorts from same study group included.

Study centre	Date of cohort collection	Study type	Mean age (years)	Female	Stroke type	First ever stroke	Exclusion criteria	Pre-stroke dementia diagnosis
Rochester, Minnesota[54]	1960-1984	L, RPS	N/S	50%	IS	Y	Previous stroke or dementia	Medical record review
Prospective Population Study of Women in Gothenburg[55]	1974–2011	L,V	78	100%	IS, H	Y	Prior stroke or TIA, dementia before 1968,	DSM III-R
Framingham[56]	1982-2001	L, V	79	61%	IS/H	Y	Previous stroke or dementia	DSM-III, MMSE, DSM-IV
Melbourne, Australia (NEMESIS)[57]	1996-1999	X, L, PPS	74	56%	IS, H, TIA, SAH	Y	Recurrent stroke, aphasia, non-English-speaking, inadequate vision or hearing	Questionnaire, DSM-IV
Orebro, Sweden[58-60]	1999-2000	X, L, PPS	74	50%	IS, H	Y	Aphasia	Interview
OxVasc, UK[8]	2002-12	L, PPS	74	51%	IS, H, TIA	N	None	IQCODE / DSM-IV
LATCH, Scotland[†,61]	2010-11	L, PPS	76-79**	57%	H	Y[†]	Age ≤16 years, extra-axial intracranial haemorrhage, traumatic ICH or haemorrhagic transformation of an ischaemic stroke	IQCODE
Dijon Stroke Registry[62]	2013-15	L, PPS	75	53%	IS, H	N	None	N/A

Table 5.2 Population-based studies of pre-stroke dementia *mean of total volunteer sample. **Median values. L=longitudinal study. X=Cross-sectional. V=volunteer cohort. RPS=retrospective patient study. PPS=prospective patient study. H=intracerebral haemorrhage. IS=ischaemic stroke. TIA=Transient Ischaemic Attack. SAH=subarachnoid haemorrhage Y=yes. N=no. DSM=diagnostic and statistical manual of mental disorders. MMSE=Mini-mental state examination. NEMESIS=North East Melbourne Stroke Incidence Study. LATCH= Lothian Audit of the Treatment of Cerebral Haemorrhage, †LATCH is a study of first intracerebral haemorrhage. OxVasc=Oxford Vascular Study.

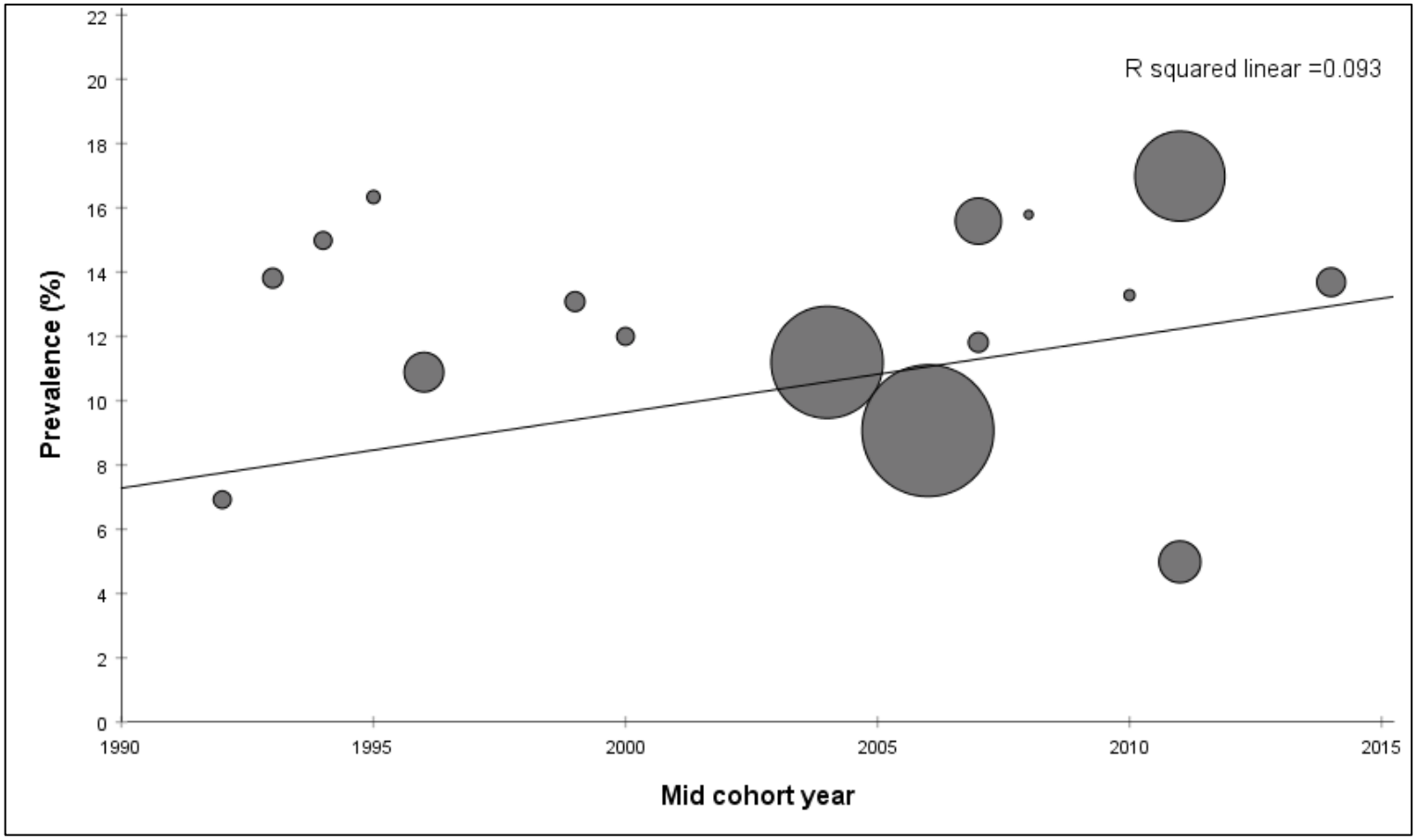

Figure 5.2 Time-trend in the pre-stroke prevalence rate in studies included in the systematic review. Symbol size is proportional to the inverse variance for each study and the line is linear regression weighted by inverse variance. Studies where the diagnosis was based on records or coding alone were excluded.

	Number of studies	Dementia / total		Pooled prev (%)	95% CI	p het*
A) By Method						
Any stroke – IQCODE / questionnaire	8	413 /	3043	**13.6**	11.6-15.5	0.044
Any stroke – non structured interview	5	3595 /	29599	**12.1**	9.0-15.3	<0.001
Any stroke – records / coding	12	17742 /	292987	**6.1**	5.2-6.9	<0.001
First stroke – IQCODE / questionnaire	7	417 /	4161	**10.0**	8.0-12.0	<0.001
First stroke – non structured interview	3	829 /	11367	**7.3**	6.0-8.6	0.004
First stroke – records / coding	2	249 /	12913	**1.9**	-2.0-5.9	<0.001
B) By Cohort						
Any stroke – hospital-based	11	3770 /	30659	**12.3**	10.3-14.3	<0.001
Any stroke – population-based	3	334 /	2677	**12.5**	11.3-13.6	0.432
Any stroke – hospital-based, late follow-up	12	320 /	3769	**8.6**	7.1-10.1	0.015
First stroke – hospital-based	5	915 /	12368	**7.4**	6.5-8.3	0.001
First stroke – population-based	6	409 /	3781	**10.8**	6.9-12.1	0.168

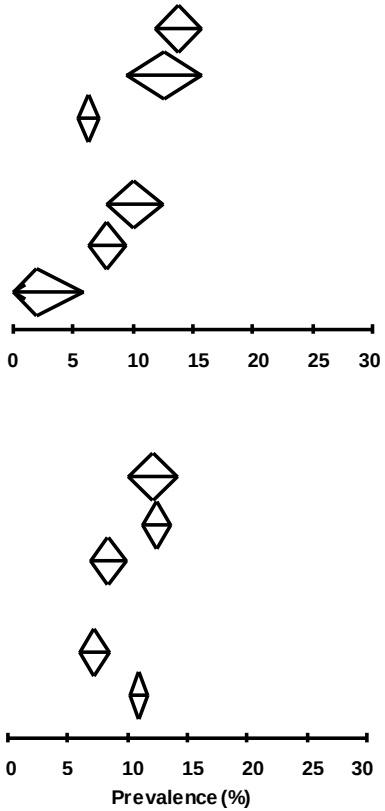

Figure 5.3: Summary of pooled prevalence rates of pre-stroke dementia stratified by A) method and B) cohort. For each any (first or recurrent) compared with first stroke. *p het = p value for heterogeneity. Prev=prevalence. IQCODE=informant questionnaire on cognitive decline in the elderly. A) Method stratified by method of diagnosis of pre-stroke dementia. B) By cohort stratified by stroke recurrence (any compared with first stroke), and population-based versus hospital-based recruitment. Hospital-based, late follow-up includes studies where diagnosis of pre-stroke dementia was only made in those that survived to a follow-up time-point. Stratification by cohort excludes studies where pre-stroke dementia prevalence is based on coding or records alone. For further details of the meta-analysis see figure 5.3 (method) and figure 5.4 (cohort) for more details.

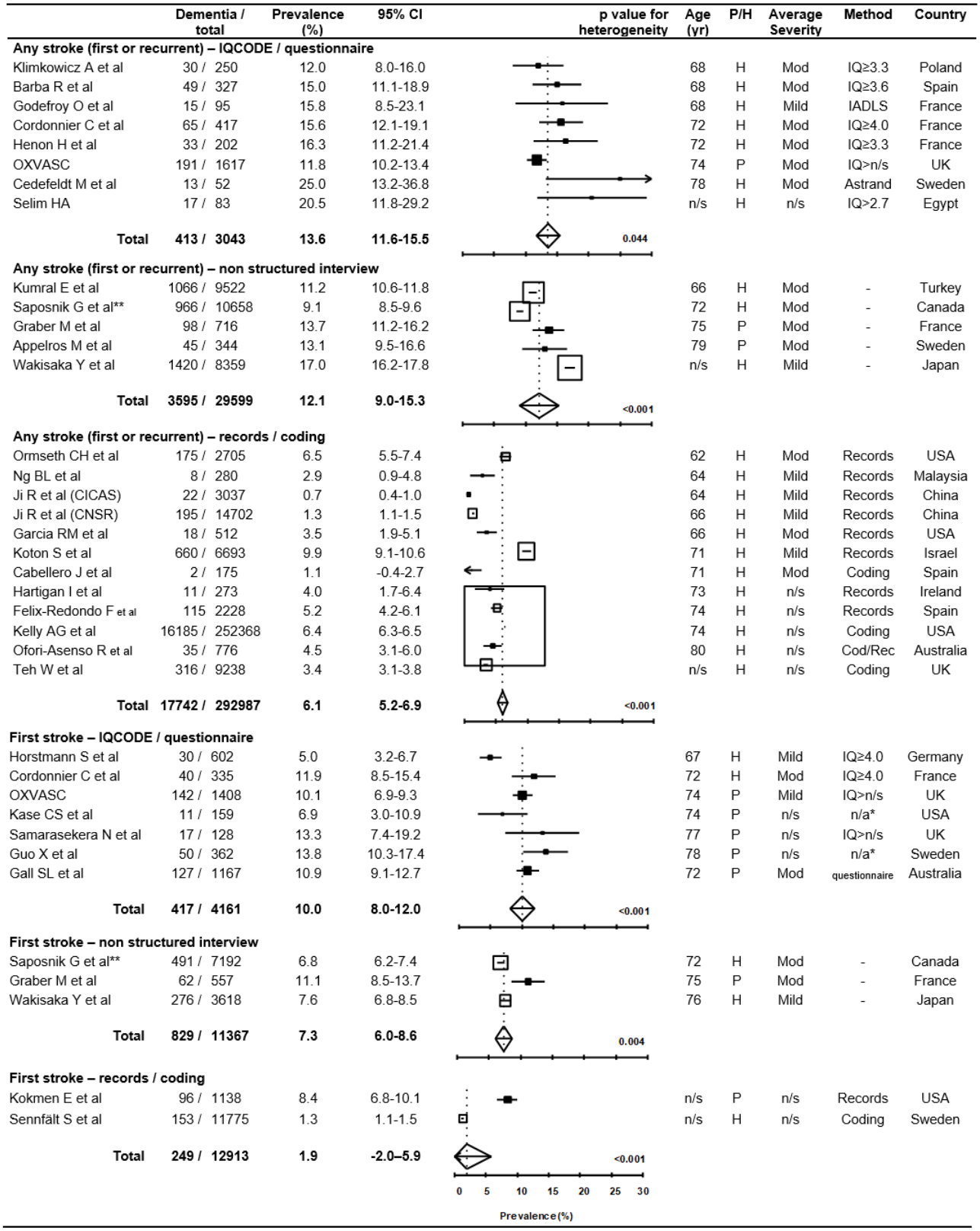

Figure 5.4: Prevalence of pre-stroke dementia stratified by method of diagnosis and stroke recurrence (first versus any). The mean age of the patients in each study, the average severity of the strokes in each study, the method of dementia diagnosis and country of study. Bars indicate 95% confidence intervals (CI). IQ=IQCODE=informant questionnaire on cognitive decline in the elderly. Rec=records. n/s=not stated. Mod=moderate. P=population-based study. H=hospital-based study. *diagnosis of pre-stroke dementia made pre-event in prospective longitudinal population-based study based on diagnostic and statistical manual of mental disorders criteria. **Also included record review.

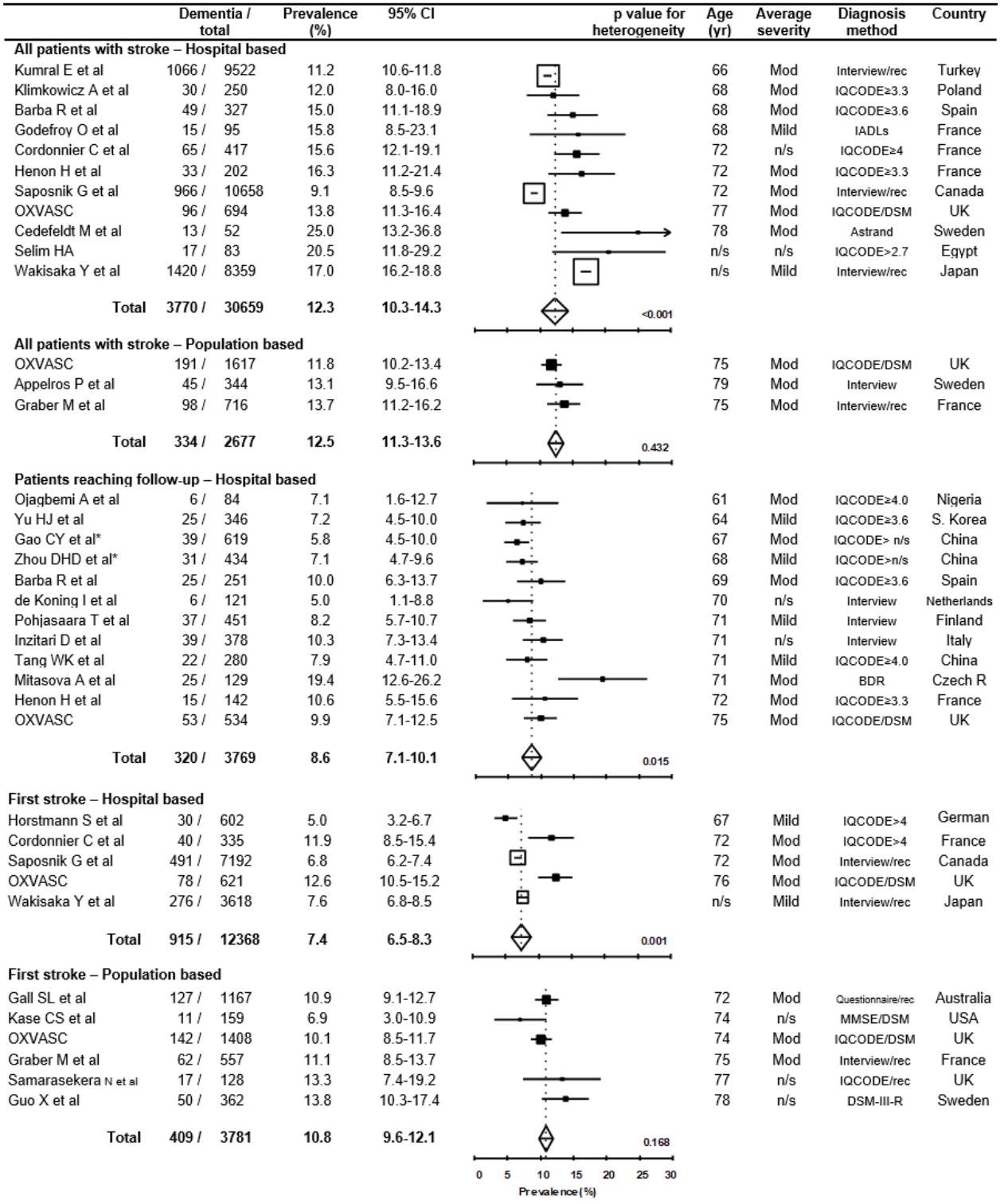

Figure 5.5: Prevalence of pre-stroke dementia according to cohort. Pooled prevalence of pre-stroke dementia stratified by study setting (hospital-based vs population-based) and time of assessment (at the time of the stroke or at follow-up) are shown, together with the mean age of the patients in each study, the average severity of the strokes in each study, the method of dementia diagnosis and country of study. Studies where diagnosis was based on records or coding alone were excluded. Bars indicate 95% CI. *Gao CY et al and Zhou DHD are both from the Chongqing Stroke Study but different (non-overlapping) cohorts. IQCODE=informant questionnaire on cognitive decline in the elderly. Rec=record review in addition to interview or questionnaire. Interview=interview of informant without IQCODE questionnaire. DSM=diagnostic and statistical manual of mental disorders. MMSE=Mini-Mental State Examination. n/s=not stated. Mod=moderate.

	Mean (s.d) (number)		WMD	95% CI
	Dementia	No dementia		
Pohjasvaara et al	72.9 (9.9) (31)	69.9 (7.4) (306)	3.0	-0.6-6.6
Lefebvre et al	86.0 (2.9) (39)	78.0 (3.2) (165)	8.0	7.0-9.0
Klimkowicz-M. et al	73.2 (12.8) (30)	66.5 (11.0) (220)	6.7	1.9-11.5
Tang et al	78.8 (5.9) (22)	68.5 (11.1) (267)	10.3	7.5-13.1
Henon et al	84.0 (3.2) (33)	73.0 (4.6) (169)	11.0	9.7-12.3
Barba et al	80.0 (7.0) (49)	69.3 (13.5) (275)	10.7	8.2-13.2
Appelros et al	84.0 (11.0) (45)	79.0 (11.0) (282)	5.0	1.5-8.5
Wakisaka Y et al	81.5 (7.4) (347)	70.0 (12.2) (3890)	11.5	10.6-12.4
Saposnik G et al	82.4 (8.5) (966)	71.2 (14.2) (9692)	11.2	10.6-11.8
Graber M et al	85.2 (9.3) (98)	73.3 (16.2) (618)	11.9	9.7-14.1
Caratozzolo S et al	77.4 (10.5) (37)	68.4 (14.3) (121)	9.0	4.8-13.2
OxVasc	83.5 (7.7) (191)	73.9 (13.1) (1426)	9.6	8.3-10.9
Total			**10.6***	10.2-10.9

Table 5.3: Difference in mean age of patients with and without pre-stroke dementia. s.d=standard deviation, n=number of patients, WMD=weighted mean difference (years), *p<0.0001

	Measurement method	Severe stroke/total or Mean (SD) score		Significance
		Dementia	No dementia	
Klimkowicz A et al	SSS	36.9 (18.0)	45.5 (15.5)	0.003
Barba R et al	CNS	5.2 (2.6)	6.7 (2.6)	<0.001
Henon H et al	Orgogozo*	35 (5-100)	70 (0-100)	0.0028
Tang WK et al	3 month NIHSS*	6 (1-20)	5 (0-31)	0.270
Appelros P et al	NIHSS≥6	OR 1.97 (1.1-3.7, p=0.04)		
Pohjasvaara T et al	3 month SSS	53.4 (6.7)	55.7 (5.5)	0.0335
Graber M et al	NIHSS	12.0 (10.2)	7.6 (8.7)	<0.001
Saposnik G et al	CNS	6.28 (3.12)	7.87 (3.04)	0.52
Wakisaka Y et al	NIHSS	7.94 (6.86)	5.78 (6.25)	<0.01
Cordonnier C et al	NIHSS*	17 (9-26)	13 (6-22)†,16 (4-23)‡	0.060
OxVasc	NIHSS	8.3 (7.6)	5.1 (6.7)	<0.001

Table 5.4: Stroke severity in patients with and without pre-stroke dementia SSS=Scandinavian stroke scale, CNS=Canadian neurological scale, NIHSS=National institute of health stroke scale, OR=odds ratio, n/s=not stated. *median values (interquartile range), †no cognitive decline, ‡cognitive impairment with no dementia. Significance values are taken from individual papers.

	Atrophy measurement method	Measured atrophy		Significance
		Dementia	No dementia	
Henon et al	Median (range) cerebral atrophy score 0-3	1 (0-3)	2 (1-3)	<0.001
Pohjasvaara et al	% with moderate or severe atrophy	63.5	32.2	<0.001
Klimkowicz et al	Degree of atrophy (mean (SD) on scale of 0-3)	1.7 (1.0)	1.09 (0.9)	0.001
Tang et al	Mean (SD) cerebral atrophy index	11.9 (4.1)	7.8 (3.4)	<0.001
Cordonnier C et al*	Median (range) cerebral atrophy score 0-3	2 (2-3)	1 (1-2)†, 2 (2-3)‡	<0.0001

Table 5.5: Global cerebral atrophy in patients with and without pre-stroke dementia. SD=standard deviation, See individual papers for details of atrophy scoring methods. Significance values are taken from individual papers. *Intracerebral haemorrhage study, †no pre-stroke cognitive decline, ‡cognitive impairment with no dementia.

	Number of studies	Patients with factor/total		OR (95% CI)	p value for OR	p value for heterogeneity
		With dementia	Without dementia			
Demographic factors						
Female sex	15	1230/2079	9048/20060	1.74 (0.58-1.91)	<0.001	0.322
Low education	8	331/444	1859/3096	1.92 (1.52-2.43)	<0.001	0.458
Family history of dementia	3	29/116	51/632	3.84 (2.22 – 6.66)	<0.001	0.052
Vascular risk factors						
Diabetes	12	501/1908	4297/17501	1.29 (1.02-1.63)	0.033	0.005
Atrial fibrillation	12	597/1965	3500/18010	1.80 (1.61-2.01)	<0.001	0.805
Ischaemic heart disease	9	421/1808	3150/16810	1.35 (1.20-1.52)	<0.001	0.710
Previous TIA	6	65/421	320/3112	1.72 (1.28-2.30)	<0.001	0.211
Hypertension	12	1355/1908	12129/17501	1.12 (1.01-1.25)	0.032	0.832
Smoking – current / prior	8	86/512	706/3332	0.77 (0.59-0.99)	0.043	0.369
Moderate alcohol	4	25/233	176/1260	0.73 (0.46 – 1.17)	0.197	0.356
Hypercholesterolaemia	9	513/1807	6334/16739	0.71 (0.56-0.90)	0.005	0.010
Peripheral vascular disease	2	5/79	73/495	0.42 (0.16-1.07)	0.415	0.714
Stroke factors						
Haemorrhagic	4	45/392	295/2679	1.02 (0.56-1.87)	0.939	0.048
Brainstem / posterior	4	92/283	470/1837	0.91 (0.51-1.63)	0.759	0.053
TOAST: LAA	3	22/220	162/1461	0.86 (0.52-1.41)	0.542	0.111
TOAST: CE	3	193/567	1396/5351	1.84 (1.53-2.22)	<0.001	0.376
TOAST: Lacunar	3	12/220	230/1461	0.54 (0.29-1.01)	0.056	0.930
TOAST: cryptogenic/und	3	100/220	582/1461	1.25 (0.92-1.68)	0.153	0.967
Previous stroke	8	219/805	1053/7123	2.39 (1.78-3.21)	<0.001	0.030
Multiple strokes	5	133/377	307/1149	2.62 (1.37-5.02)	0.004	<0.001
Silent strokes	2	21/72	98/334	0.98 (0.56-1.70)	0.931	0.129
Brain imaging factors						
Leukoaraiosis	6	913/1363	4971/10589	2.39 (2.12-2.70)	<0.001	0.295
MTLA	3	60/77	183/594	7.67 (4.26-13.81)	<0.001	0.712

Table 5.6: Pooled odds ratios for factors associated with pre-stroke dementia. OR=odds ratio. FHx= family history. TIA=Transient Ischaemic Attack. TOAST= trial of ORG 10172 in acute stroke treatment classification system. LAA = large artery atherosclerosis. CE=cardioembolic. Crypto/und= cryptogenic / undetermined. MTLA=medial temporal lobe atrophy.

	Increasing age (per year)	Female sex	Low education	Prior strokes (on imaging)	Leucoaraiosis	Atrophy	Prior TIA/ strokes (clinical)	Vascular risk factors	Other
Cordonnier C*	1.05 (1.01 - 1.10)		5.25 (1.90 - 14.52)	3.35 (1.40 - 9.02)	Increasing score: 1.91 (1.19 - 3.08)	Global cortical atrophy: 1.90 (1.04 - 3.47)			Lobar (vs deep) location of ICH: 3.39 (1.52 - 7.57)
Caratozzolo S et al	1.05 (1.0-1.1, p=0.05)	2.3 (0.9-5.5, p=0.05)				MTL atrophy: 1.1 (0.9 - 1.3)			
Horstmann S et al	1.05 (1.02-1.08, p=0.001)							AF: 1.87 (1.07-3.27)	
Barba R et al		3.7 (1.2-12)	2.1 (1.1-4.2)			Global cortical atrophy: 3.8 (1.7-8.3)	Stroke: 3.6, 1.2-11)		
Henon H et al		p=0.0002			p=0.0002	Global cortical atrophy: p=0.0102			Family history of dementia: p=0.0016
Tang WK et al	p =0.033						TIA: 10.03 (2.00 - 50.37)	AF 5.44 (1.22-24.34)	
Lefebvre C et al**	1.10 (1.04-1.17)								
Pohjasvaara T et al						MTL atrophy: 7.5 (3.2-18.2)	Stroke: 4.4 (1.8-10.6)		
Klimkowicz A et al		3.47 (1.25-9.64)		1.58 (1.08-2.33)			Stroke: 3.46 (1.26-9.51)		
OxVasc	1.09 (1.07-1.11, p<0.001)			1.83 (1.21 - 2.76 p=0.001)	Moderate-severe: 1.61 (1.14-2.29, p=0.01)		Stroke: 2.70 (1.84 - 3.94 p<0.0001)	Diabetes: 1.90, 1.25-2.88, p=0.003	Increasing stroke severity, per point in NIHSS: 1.05, 1.03-1.08, p<0.001

Table 5.7. Independent factors associated with pre-stroke dementia. Factors shown to be independent associations in multivariate analyses in each individual study. For details of the analysis refer to individual studies. Odds ratio (OR) presented with 95% confidence intervals and p values (where available from individual studies). MTL=medial temporal lobe. AF=atrial fibrillation. TIA=Transient Ischaemic Attack *Intracerebral haemorrhage (ICH) study. ** All patients had atrial fibrillation.

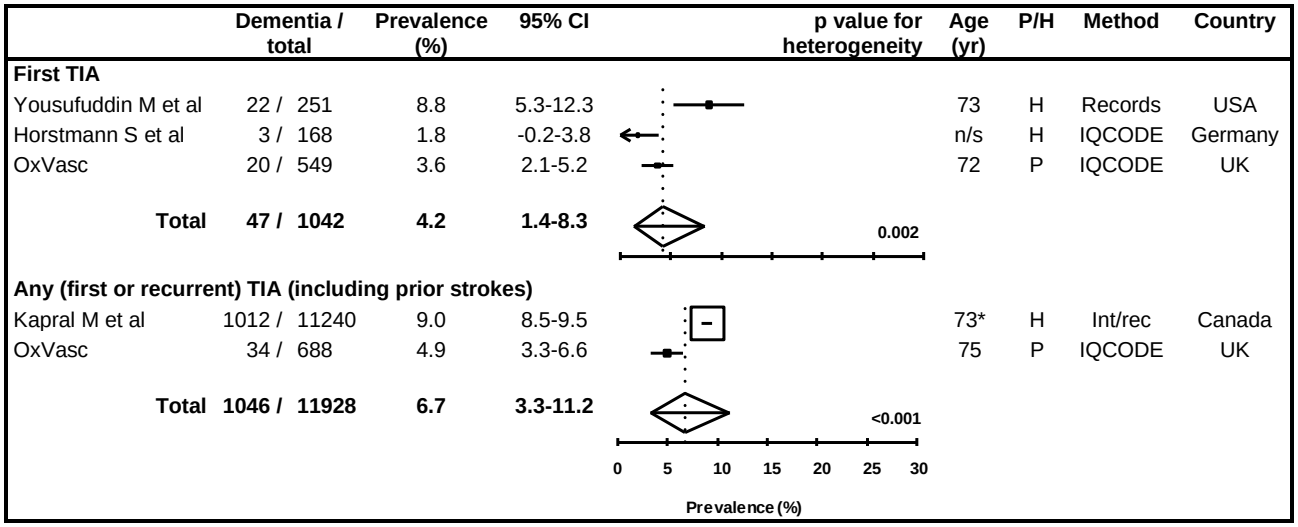

Figure 5.6 (a): Prevalence of pre-TIA dementia stratified by first or any (first or recurrent) event. The mean age of the patients in each study, the method of dementia diagnosis and country of study are also presented. Bars indicate 95% CI. IQ=IQCODE=informant questionnaire on cognitive decline in the elderly. Int/rec=information from interview or medical record review. n/s=not stated. P=population-based study. H=hospital-based study. *median.

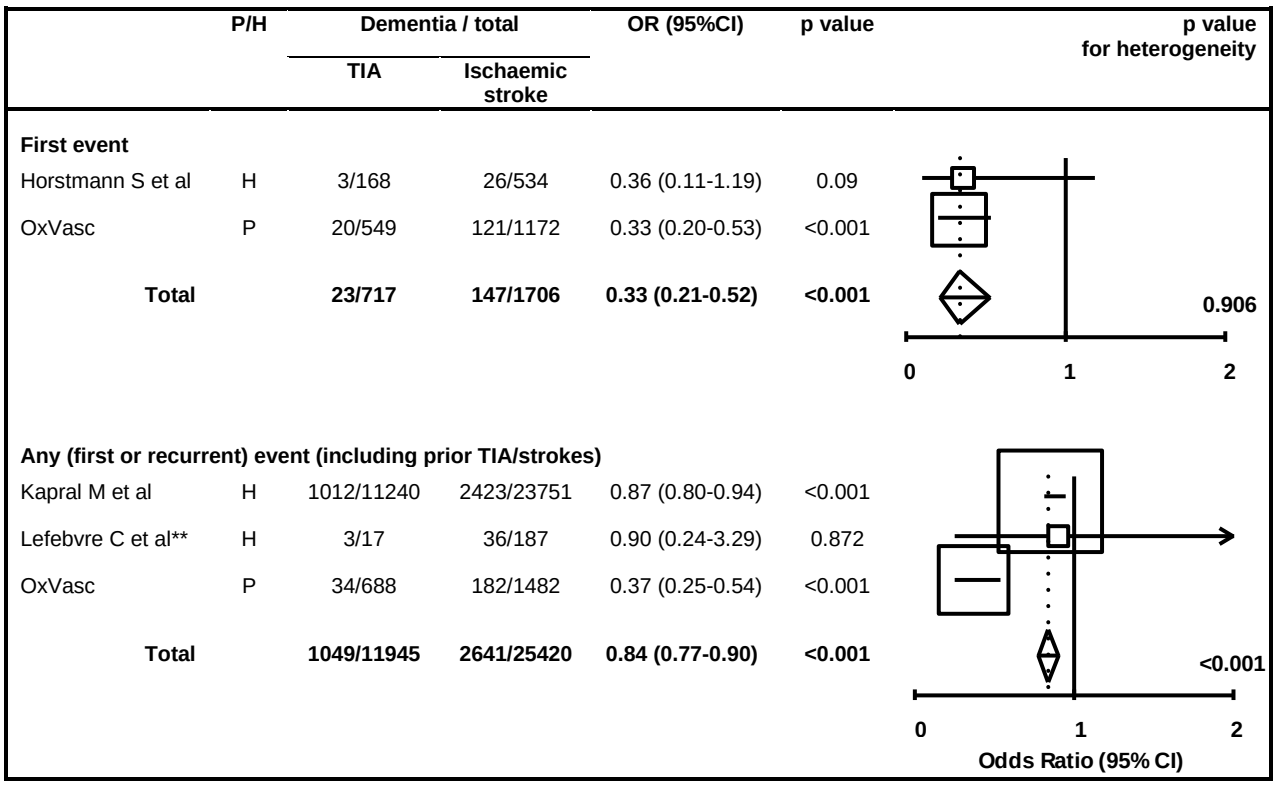

Figure 5.6 (b): Odds ratio of pre-event dementia for Transient Ischaemic Attack (TIA) patients compared with ischaemic stroke patients. OR=odds ratio (with 95% confidence interval). H=hospital-based study, P=population=based study. **All patients have atrial fibrillation.

CHAPTER 6

PREVALENCE, TIME-TRENDS AND FACTORS ASSOCIATED WITH POST-STROKE DEMENTIA: POPULATION-BASED STUDY, SYSTEMATIC REVIEW AND META-ANALYSIS

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6.1 Abstract

Introduction: According to a previous review one-in-ten patients develop dementia after their first stroke with prevalence rates being significantly impacted by case mix. However, numerous large new studies have since been published and stroke care has improved mandating a need to update the review.

Methods: I updated a previous systematic review and meta-analysis on studies of post-stroke dementia by the addition of studies published since the prior review was completed in 2009. Studies were included if they were on patients with symptomatic stroke or transient ischaemic attack (TIA) either through recruitment of consecutive eligible patients or volunteers in prospective cohorts. The results were collated with those of the previous review along with data from a recent longitudinal population-based study. Pooled prevalence rates of post-stroke dementia (up to the first year) were calculated in conjunction with weighted linear regression modelling of the time-trend of the rates. Pooled odds ratios were also produced for associated factors and data on independent associations extracted where available.

Results: Including those identified in the prior review, 64 studies on post-stroke dementia were included (49 hospital-based, 15 population-based). The pooled prevalence of post-stroke dementia was lowest in population-based studies of first stroke excluding pre-stroke dementia (10.3%, 95% CI 6.5-14.1%) and highest in hospital-based studies of recurrent stroke including pre-stroke dementia (40.5%, 26.4-54.7%). Heterogeneity was significant between studies ($p<0.001$) but 82% of the variance was explained by the average stroke severity, the inclusion of pre-stroke dementia, the stroke event (first, any, recurrent stroke) and the mid-study year in which the study recruited their cohort. Post-stroke dementia prevalence rates in published studies have halved over the past two decades with new onset dementia in the first year after any stroke decreasing from 20.6% in 1989 to 8.3% in 2015. Independent associations with post-stroke dementia reflect those associated with the

stroke itself (severity, recurrence) and with those associated with cognitive susceptibility (age, low education, prior cognitive impairment).

Conclusion: Rates of post-stroke dementia (within the first year) remain high but the prevalence is declining. This maybe attributable in part to the improved acute stroke care and secondary prevention leading to a reduction in stroke severity and stroke recurrence with both factors independent predictors of subsequent post-stroke dementia.

6.2 Introduction

Post-stroke dementia is defined as dementia that occurs subsequent to a clinical stroke with one-in-ten patients having dementia shortly after their first-stroke and more than a third after a recurrent stroke, and is an independent predictor of mortality.[1-3] Post-stroke dementia is an all-encompassing phrase which does not delineate the subtype of dementia syndrome nor the underlying pathology. Whilst the previous review was not able to classify the dementia subtype since then numerous small studies have done so with increasing evidence that neurodegenerative processes and stroke-related factors are synergistic in dementia development after a stroke.[4,5,6] This could be supported by the finding that factors independently associated with post-stroke dementia either relate to the stroke itself (such as severity or recurrence) or cognitive susceptibility (such as older age, lower educational level).[1]

Yet even describing just the prevalence rate of post-stroke dementia is problematical. Different study methods such as whether a study is hospital-based or population-based, has included or excluded pre-stroke dementia or first stroke versus any (first or recurrent) stroke have a significant impact on the prevalence rate reported.[1,7-9] The previous review identified these issues but was limited by the inclusion of only a few population-based studies which, when there is robust ascertainment of patients, are intrinsically less biased than hospital-based studies which tend to overlook more minor strokes.[1] Since then a longitudinal population-based study (OxVasc) has also published 10-years of data on pre- and post-stroke dementia.[10]

Furthermore, whilst there is an increasingly ageing population which would suggest an expected increase in the absolute numbers of patients with stroke and dementia there is a suggestion that, at least in high-income countries, both the incidence of stroke and dementia overall are decreasing.[11,12] There have been significant changes in acute and post-stroke care over the decades: improved primary and secondary prevention, the concept of a stroke ward as an intervention, thrombolysis and most recently thrombectomy,

all of which may decrease stroke mortality, stroke severity and stroke recurrence. As a consequence the age-specific prevalence of post-stroke dementia may be expected to be on the decline. However, contrary to this there is also the risk that decreased mortality comes at a cost of surviving with greater disability which may off-set any decline in post-stroke dementia prevalence rate.

Finally, a recent study suggested that patients who have a Transient Ischaemic Attack (TIA) are also at increased risk of developing dementia,[10] but there have been no previous systematic reviews assessing this risk in comparison with ischaemic stroke.

Therefore, through updating the systematic review and including the results of OxVasc, I aim to answer the following questions. Firstly, what is the prevalence and the time-trend of post-stroke dementia? Secondly, how do the independent associations of post-stroke dementia inform our understanding of the underlying aetiologies? Finally, what is the risk of developing dementia after a TIA in comparison to after an ischaemic stroke?

6.3 Methods

6.3.1 Systematic Review

To identify studies on post-stroke dementia I searched (up until 18 Feb 2020) Ovid Medline, EMBASE and PsychInfo using a comprehensive search strategy (Appendix XIX). As this was an update to a previous review, the search was limited to studies published since April 2009. Relevant review articles were also hand-searched, as were the title pages of the four journals that contained the largest number of relevant papers in the electronic search. The review was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

Criteria for inclusion of papers in the systematic review were:

i. Series of consecutive eligible patients with a symptomatic stroke, or volunteers in a prospective cohort study who had a stroke during follow-up;

ii. Inclusion of all transient ischaemic attacks (TIA), all strokes, all ischaemic strokes or all primary intracerebral haemorrhagic strokes (i.e. not on sub-sets e.g. lacunar strokes or minor strokes). Both time-based and tissue-based definitions of stroke and TIA were eligible for inclusion;
iii. Published in English, or English translation available;
iv. Minimum of 50 patients included
v. Dementia diagnosed by standard criteria such as Diagnostic and Statistical Manual of Mental Disorders IV or mini-mental state examination (MMSE) < 24;
vi. Follow-up time of at least 3-months after stroke onset to avoid potential overlap with delirium in the acute phase after the stroke.

Studies that identified cases of dementia only by medical records review or by coding data were excluded.

Two types of population-based study were eligible: those in which all stroke patients within a defined population were ascertained, and those in which cohorts of normal volunteers were recruited and followed prospectively, with data reported on those who had a stroke during follow-up. Where there was uncertainty about the methodology used for patient recruitment for a given cohort, the authors were contacted and asked for clarification.

I reviewed all abstracts of the papers identified on the initial search with subsequently the full text of eligible articles reviewed by both myself and STP. Where multiple studies used a subset or the whole of the same data set, the duplicate studies were only included if additional risk factor data were provided, otherwise, the article with the largest complete patient series was included. Data were extracted on study setting, method of diagnosis, number of cases of post-stroke dementia, any associated and independent factors, mean severity of stroke and country of study. Mean severity was determined by the stroke or functional scale as reported by the individual study (Appendix XX) In cases of disagreement between STP and myself regarding eligibility of studies or data extraction, consensus was reached through joint re-assessment

6.3.2 Population-Based Study

Study methods for the population-based study are detailed in Chapter One and have previously been published in detail.[10] In brief, the Oxford Vascular Study (OxVasc) is a longitudinal, prospective population-based study of the incidence and outcomes of all acute vascular events occurring within a defined population of 92,728 in Oxfordshire, UK. Consecutive patients with a transient ischaemic attack (TIA) or stroke were prospectively recruited from April 1, 2002 to March 31, 2012. Case ascertainment was achieved through both 'hot' and 'cold' methods which have been demonstrated to achieve near complete ascertainment of all TIA and strokes.[14] All patients with a TIA, ischaemic or haemorrhagic stroke were reviewed by a study physician as soon as possible after their initial presentation either on a hospital ward or in an outpatient neurovascular clinic. A TIA was defined, according to the World Health Organisation (WHO) criteria, as focal neurological symptoms lasting less than 24 hours with a stroke defined as symptoms lasting more than 24 hours and the probability of the event being defined according to National Institute of Neurological and Communicative Disorders and Stroke (NINDS) criteria.[15] For this analysis, all patients with a probable or definite TIA or stroke were included in the analysis. Subject data, including vascular risk factors, were collected by interview with a standardised form and supplemented by primary care records. Follow-up interviews were done by trained nurses or study physicians at 1-month, 6-months, 1-year and 5-years including depression screening and cognitive assessments with the mini-mental-state examination (MMSE) and Montreal Cognitive Assessment (MoCA).[16,17] Telephone versions of the assessments were completed for patients who were unable to be seen in clinic or at home.[18]

Multiple methods were used to identify the presence of pre-event dementia: baseline clinical assessment by study physician, discussion with an informant (including the IQCODE), hospital and outpatient clinic records and the primary care record. Post-event dementia was identified through baseline and follow-up clinical and cognitive assessment data, supplemented by primary care records up to death or 5-years' follow up. Dementia was

defined as consistently scoring less than 24 on the MMSE on consecutive follow-up assessments, or if testing was unavailable through review of study, hospital, death and primary care records.[19] The diagnosis of pre- or post-event dementia was done by a senior study physician with an expertise in dementia (STP) using Diagnosis and Statistical Manual of Mental Disorders – IV (DSM-IV) criteria. An additional sub-analysis on patients recruited only from the hospital-wards was performed to permit additional inclusion in the meta-analysis.

6.3.3 Analysis

Data from the previous review, the population-based study and the current search results were combined for the analysis. Studies that provided prevalence rates of dementia beyond the first year, included less than 50% of eligible survivors, restricted to specific aetiologies, or excluded severe strokes were excluded from the pooled prevalence rate calculations. Pooled estimates of the prevalence of post-stroke dementia (between 3 and 12-months after the event) were calculated with the 95% confidence intervals of the pooled risk estimates calculated to allow for extra-binomial variation because standard methods of calculating confidence intervals produce artificially narrow intervals if there is heterogeneity of risk between different studies.[20] Analyses of heterogeneity of prevalence across studies were done with X^2 tests. Only studies that used a standard diagnostic criteria (e.g. DSM-IV) rather than a brief cognitive test cut-off score were included in the pooled prevalence rates. Analyses were stratified by study setting (hospital versus population-based), the inclusion or exclusion or pre-stroke dementia, whether it was the first, any (first or recurrent) or a recurrent stroke and by the mid-year of recruitment of the cohort. The proportion of the overall heterogeneity of prevalence of post-stroke dementia across all studies that could be accounted for by the above sub-categorisations was determined by an inverse-variance weighted regression of log (risk) against study type. Time trend in prevalence of post-stroke dementia was assessed through weighted linear regression modelling against the mid-study year of the patient cohort recruitment. The cumulative incidence of dementia after

stroke, excluding pre-stroke dementia, was calculated with data extracted from longitudinal studies that had reported at multiple time-points, using logistic regression.

Studies that used only a brief cognitive test (e.g. MMSE) to diagnose dementia or used a brief cognitive test with a cut-off value associated with dementia were analysed separately from those studies which had used a standard criteria. Pooled odds ratios of the rates of post-stroke dementia in studies that used a brief screening tool were compared with those that used a standard dementia criteria.

One-year prevalence rates and pooled odds ratios of post-event dementia for TIA versus stroke were calculated for studies that reported on both a TIA cohort and stroke cohort separately.

To determine the factors associated with post-stroke dementia, pooled odds ratios were calculated for patients with dementia versus those without dementia. A fixed effects analysis was used unless there was evidence of significant heterogeneity ($p \leq 0.1$) in which case a random-effects analysis was used. Hospital-based and population-based studies, studies up to 5 years follow-up, studies on a restricted sub-set of patients and those where the diagnosis was based on brief cognitive testing only were all combined for the calculation of the pooled odds ratios. All analyses were done in SPSS version 26.

6.4 Results

The literature search produced 24,419 references (including 7604 duplicates) of which, after full text review, 48 articles were eligible for inclusion. Hand searching reference lists and relevant journals identified 8 further articles. After exclusion of duplicate datasets a total of 45 articles published since the previous review in 2009 were found to be eligible (encompassing 34 new studies[3-6,69-88,91,107,108,111-121] and 7 updates to previous studies[44,60,95,96,104-106]). Reasons for exclusion included a failure to include consecutive patient series, reporting data for cognitive impairment not dementia, providing cross-sectional data at variable time periods after the stroke, less than 50 patients, asymptomatic

stroke data and a lack of availability of an English translation. The 45 articles were combined with the relevant 62 articles[2,21-43,45-59,61-68,89-90,92-94,97-103,109,110,122] from the 2009 review and with the OxVasc study[10] (figure 6.3) to yield 108 eligible papers (from 64 studies) on post-stroke dementia (figure 6.1).[2-6,10,21-122]

The eligible hospital- and population-based studies where the diagnosis of dementia was made according to a standard criteria are shown in table 6.1 and table 6.2 respectively together with demographic details, study design and post-stroke dementia diagnosis method. All hospital-based studies[2-6,21-89] (n=42) prospectively ascertained patients whereas for the population-based studies (n=7) three collected data on all patients with incident strokes during a particular period (one retrospectively[90], two prospectively[10,98-100]) and four collected data prospectively on volunteer cohorts who were stroke-free at enrolment.[91-97] All 15 of the studies (8 population-based, 7 hospital-based) where a cognitive test alone was used to ascertain a dementia diagnosis prospectively recruited patients with the details shown in table 6.3.[101-122]

6.4.1 Study Characteristics

42 hospital-based stroke patient cohorts (19,176 patients, mean study age range 53 - 80 years) and seven population-based cohorts (4543 patients, mean study age range 72-79 years) reported data on post-stroke dementia.

Apart from OxVasc, all other population-based studies included only first ever strokes, compared with nine of the 42 hospital-based studies.[5,22-24,37,66-67,71,74,78,80,84,88,89] There were also differences in the stroke sub-set studies with 1/7 population-based[90] and 12/42 hospital-based studies[3,21-35,37,40-44,56,61-62,66,67,73,75,76,80] only including ischaemic stroke and 2/42 hospital-based studies[69-70] only including intracerebral haemorrhages.

The diagnosis of dementia was most often made in accordance with DSM-IV criteria (19/42 hospital-based,[3,4,54,61-69,71,75,76,78-85,88,89] 3/7 population-based[10,92,93,98-100]) followed by DSM-III-R (5/42 hospital-based,[2,22-35,39,45-53] 3/7 population-based[91,94-97]) and ICD-10 (4/42

hospital-based[5,55,56,74,77]). The majority of studies (28/42 hospital-based, 7/7 population-based) screened for depression as part of their dementia assessment to exclude pseudo-dementia. More than half of the hospital-based studies originated in Europe (22/42) but there was a greater proportion of studies from non-Caucasian continents (11/42 Asia,[3,22-24,56,61,62,73,75,76,78,81,82,86,89] 4/42 Africa[77,83,87,88]) than in the previous review. However, population-based studies were from traditionally Caucasian areas (three USA/Canada,[90,92,93,97] three Europe[10,91,94-96] and one Australia[98-100]) similar to the previous review.

The 15 studies on post-stroke cognitive assessments with cut-off scores in keeping with dementia included five on ischaemic stroke[115-120] and one on intracerebral haemorrhage only.[113] Four of the seven hospital-based studies used MMSE with two using (different) education adjusted cut-offs and two using cut-offs values of 21 and 24.[115,120-122] Six of the eight population-based studies used MMSE with cut-offs ranging from 19 to 24.[101-110,112] Other assessment tools included the Abbreviated Mental Test,[102-106] Hodkinson Mental Test (HMT),[114] Modified Mental State (3MSE),[116] Telephone Interview for Cognitive Status (TICS, TICS-modified)[111,113] and Addenbrooke's Cognitive Examination (ACE-R).[116]

6.4.2 Post-stroke Dementia Prevalence

6.4.2.1 Post-stroke Dementia Prevalence (Up to One-Year)

30/42 hospital-based studies provided prevalence rates for dementia within the first year after a stroke.[2,3,5,6,21-38,40-53,61-65,68,70-72,74-76,79,81-89] Of the remaining 12 studies not included in the pooled rate calculation, eight reported prevalence rates beyond the first year,[4,39,55,69,73,77,78,80] three included less than 50% of eligible patients[54,56-60] and one excluded patients with a MMSE score of less than 15 at the initial follow-up.[66-67] Only two of the population-based studies could not be included in the pooled rate calculation as they only provided prevalence rates beyond the first year.[94-97]

Even within the first year the prevalence rates of post-stroke dementia were highly heterogeneous ($p<0.001$). Overall, the severity of the stroke, the inclusion or exclusion of

pre-stroke dementia, the stroke number (first, any, recurrent) and the year of cohort recruitment accounted for 82% of the variance between studies. Inclusion of mean age of patients, time to assessment, cohort country, and whether the study was hospital-based or population-based to the model together accounted for only a further 3% of variance between studies.

In keeping with the previous review, the prevalence rate of dementia was highest in hospital-based studies of recurrent stroke including pre-stroke dementia (40.5%, 26.4-54.7%) and lowest in population-based studies of first-stroke excluding pre-stroke dementia (10.3%, 6.5-14.1%). The pooled prevalence rate of post-stroke dementia in hospital-based studies of any stroke were 25.4% including pre-stroke dementia and 16.3% excluding pre-stroke dementia. Population-based studies found lower rates of post-stroke dementia even when stratified by stroke recurrence and the inclusion and exclusion of pre-stroke dementia likely due to inclusion of milder events (figures 6.3-6.4).

Studies that used a single brief cognitive assessment (such as MMSE <24) rather than a standard diagnostic criteria to report rates of dementia in general reported higher prevalence rates with an overall pooled odds ratios of 1.80 (1.27-2.54, p=0.001) (table 6.4). For the studies reliant upon MMSE different cut-off values were used with some using education adjusted cut-off values and others using values ranging from 19 to 24. However, there were insufficient studies identified to assess agreement for the different cut-off values with standard dementia criteria.

In the included studies the prevalence of post-stroke dementia (up to the first year) decreased over time from the initial cohort mid-study recruitment in 1987 to last cohort mid-study recruitment in 2016 (figure 6.5). Through weighted linear regression modelling the prevalence of post-stroke dementia has halved over the past two decades (any stroke including pre-stroke dementia: 1993: 27.4%, 2015: 13.5%. Any stroke excluding pre-stroke dementia: 1989: 20.6%, 2013: 8.3%). The trend was seen in studies of first stroke, any stroke, including and excluding pre-stroke dementia. As no change in the pre-stroke

dementia prevalence rates over time had been identified in Chapter 5 (figure 5.2) the declining prevalence of post-stroke dementia cannot be accounted for by this.

Two studies reported on the rates of post-stroke dementia on cohorts recruited using the same study methods but over different years. The Chongqing Stroke Study found a non-significant decrease in the 3-month post-stroke prevalence rate of new onset dementia after any stroke (1999-2000: 21.6%, 95% CI 17.6% - 25.6%. 2005-2008: 18.4%, 15.3%-21.6%, p=0.251).[3,61] Similarly, a hospital-based study of any stroke based in Rotterdam-Rijnmond reported a non-significant decrease in the 3-month post-stroke prevalence rate of dementia (1993-1996: 28.9%, 20.8-37.0%, 2000-2002: 23.7%, 18.9-28.5%, p=0.267).[45,46,68] Within the population-based OxVasc study there has also been a non-significant decrease in the 1-year post-stroke prevalence of new onset dementia (2002-2007:13.5%, 10.9-16.7% vs 2007-2012: 10.5%, 8.2-13.3%, p=0.127). In contrast one study, using a brief cognitive assessment only, reported no change over the years (1995-2000) in the prevalence rates of those with either a MMSE<24 or AMT<8 in patients assessed 3 months after their first stroke (including pre-stroke dementia).[105]

6.4.2.2 Post-stroke Dementia Prevalence (Beyond One-Year)

There were insufficient studies to report pooled prevalence rates of post-stroke dementia beyond the first year. However, one hospital-based study of any stroke (including pre-stroke dementia) found a prevalence rate of 18.9% in 5-year survivors and a hospital-based study of first stroke (excluding pre-stroke dementia) reported a prevalence of 22.0% in 7-year survivors.[4,74] In OxVasc there was a 5-year prevalence rate of 24.7% in survivors of any stroke (excluding pre-stroke dementia).

Nine studies, and OxVasc, reported the proportion of patients with post-stroke dementia at multiple time points in their follow-up.[2,5,10,25-35,47-53,55,70,74,90,91] In addition to the heterogeneity issues mentioned previously, longitudinal studies also differed in their methods of reporting at serial time points with 4 reporting point prevalences[5,50-53,70,85,74] and 5 reporting cumulative incidences.[2,10,25-35,47-49,55,90,91] However, despite this even for studies on point

prevalence an overall increasing trend was seen (figure 6.6). Two of the ten studies (from 3 to 6-months, from 2 to 3-years) showed a decline in the prevalence rate when assessed in survivors only though the difference was not significant.[2,47-49,50-53]

6.4.3 Post-stroke Dementia Incidence

Population-based studies (n=5) of the cumulative incidence of post-stroke dementia up to ten-years demonstrate a yearly incidence rate after a first stroke of 1.6% per year (1.3-2.0%) with an initial post stroke incidence of 7.0% (6.7-7.3%) over the first 12 months (figure 6.7). [2,10,25-35,47-49,55,90,91]

In comparison to patients who did not have a stroke, a large recent meta-analysis (of 1.3 million patients) reported that a stroke conveyed a hazard ratio of 2.18 (1.90-2.50) for new onset dementia.[123] In OxVasc, compared with an age- and sex-matched stroke-free population, the 1-year standardised morbidity ratio for the incidence of dementia was 3·5 (95% CI 2·5–4·8) after a TIA, 5·8 (4·4–7·5) after a minor stroke, and 47·3 (35·9–61·2) after a severe stroke.[10]

6.4.4 Post-stroke Dementia Subtype

Seven studies, in which pre-stroke dementia had been excluded, reported on the sub-type of dementia diagnosed after a stroke.[5,6,50,55,56,71,93] The majority were hospital-based studies (6/7) of any stroke (4/7). Most studies applied the NINDS-AIREN criteria to diagnose probable vascular dementia and the NINCDS-ADRDA for possible Alzheimer's dementia with one study using the newer VASCOG criteria and one using a consensus diagnosis.[5,6] No study reported neuropathological confirmation of diagnoses. The proportion of new post-stroke dementia attributed to probable vascular dementia ranged from 39% to 100%.[5,71] Studies with shorter follow-up periods identified higher proportions of probable vascular dementia than studies with longer duration (3-months: 100%,[56,71] 10-years: 51%).[93] Furthermore, studies that included a sub-type of "mixed dementia" also reported lower proportions of probable vascular dementia (range 39% to 79%)[5,6] than studies that did not (range 63% - 100%).[55,56,71] The proportion of post-stroke dementia attributed to mixed

dementia ranged from 21% to 56%,[5,6] of possible Alzheimer's dementia 6% to 37%[5,55] and other forms of dementia (including Parkinson's disease) 12%.[93] One further hospital-based study, excluding pre-stroke dementia, of 78 patients with an intracerebral haemorrhage reported that post-ICH dementia could be sub-divided into 94% vascular dementia and 6% Alzheimer's disease.[69] Due to the small number of studies, heterogeneity in study methods and varying follow-up time period pooling of results was not attempted.

6.4.5 Associations of Post-stroke Dementia

In addition to the data from the OxVasc study, data on univariate clinical associations of post-stroke dementia were available from 30 hospital-based and three further population-based studies.[21,24,26,27,30,37-39,41-43,45-47,50,51,54-59,61,63-65,67-71,76,77,80,85,86,89,93,98,105,114,119] Pooled analysis showed that predictors of post-stroke dementia were similar to those identified in the previous review (table 6.5). Demographic factors included female sex (OR 1.36, 1.18-1.60, p<0.001), older age (weighted mean difference 7.3, 6.6-8.0 years, p<0.001, table 6.6), low educational attainment (OR 2.02, 1.55-2.65, p<0.001, table 6.7, prior cognitive decline (table 6.8) and premorbid disability (table 6.9). Being Caucasian remained protective (OR 0.58, 0.49-0.70, p<0.001). Additionally, not reported in the past review, a low-socioeconomic status was predictive of post-stroke dementia (OR 1.24, 1.05-1.47, p=0.013) but a family history of dementia was not (OR 1.87, 0.79-4.40, p=0.153), although statistical power was low.

With regards to vascular risk factors for post-stroke dementia, similar to previously, both diabetes (1.42, 1.25-1.61, p<0.001) and atrial fibrillation (1.75, 1.33-2.30, p<0.001) were predictive. However, differing from the previous review, in this analysis both hypertension (OR 1.19, 1.07-1.33, p=0.002) and a prior TIA (OR 1.21, 1.02-1.43, p=0.031) were found to be predictive. Haemorrhagic stroke (OR 1.29, 1.06-1.59, p=0.009), left hemisphere stroke (OR 1.48, 1.22-1.79, p<0.001), dysphasia (OR 3.12, 2.19-4.43, p<0.001), stroke severity (table 6.10), previous stroke (OR 1.94, 1.65-2.28, p<0.001), multiple infarcts (OR 2.16, 11.53-3.05, p<0.001) and recurrent stroke (OR 1.85, 1.20-2.84, p=0.005) all remained

associated with post-stroke dementia. A visual field deficit was newly found to be associated with post-stroke dementia (OR 2.57, 2.03-3.24, p<0.001) whereas a brainstem or posterior circulation stroke on its own had lower association with post-stroke dementia (OR 0.64, 0.043-0.95, p=0.029).

Stroke complications remained strongly associated with the risk of post-stroke dementia: incontinence (OR 6.08, 4.03-9.17, p<0.001), hypoxic ischaemic episodes (OR 2.41, 1.38-4.21, p=0.002), acute confusion (OR 4.46, 3.50-5.68, p<0.001), early seizures (OR 5.70, 2.76-11.75, p<0.001), abnormal EEG (OR 2.66, 1.43-4.92). As previously reported, imaging factors that were predictive of post-stroke dementia included white matter disease (OR 2.14, 1.72-2.67, p<0.001), generalised cerebral atrophy (OR 3.99, 1.33-6.72, p<0.001, table 6.11) and medial temporal lobe atrophy (OR 3.62, 2.13-6.05, p<0.001).

Restricting the pooled analyses to the 20 studies that excluded patients with pre-stroke dementia produced similar results (table 6.12).[24,37,38,50,54-59,64,65,69-71,77,80,85,86,93,114,119] However, family history of dementia (OR 1.03, 0.33-3.41, p=0.926), low-socio-economic status (OR 1.18, 0.94-1.148, p=0.158), haemorrhagic stroke (OR 1.11, 0.84-1.46, 0.462) and visual field deficits (OR 1.82, 0.97-3.42, p=0.064) were no longer associated with post-stroke dementia.

In addition to the OxVasc data,[10] multivariate analyses were performed in a further 27 studies to determine the independent variables associated with post-stroke dementia (table 6.13).[21,24,26,37,38,41,47,50,55-57,61,65,67,69,70,72,76,77,81,85,89,90,95,98,102] The most frequently reported independent predictors included increasing age (20 studies), increasing stroke severity (10 studies), low educational attainment (9 studies), pre-stroke cognitive impairment (8 studies), diabetes (7 studies), prior stroke (7 studies), and white matter disease (6 studies).

6.4.6 Post-TIA Dementia

In addition to the OxVasc study, four studies (all hospital-based) reported on the prevalence of post-event dementia in a TIA cohort (769 patients).[5,10,45,68,81] Pooled prevalence rate of

post-TIA dementia (within the first year) at the time of a first TIA, in studies excluding pre-stroke dementia, was 4.1% (2.7-5.7%, p het=0.570). Comparing the prevalence of post-TIA dementia with post-ischaemic stroke dementia within cohorts that reported on both types of events also found lower pooled odds ratio of post-event dementia for the TIA patients (OR 0.28, 0.19-0.41, p<0.001) (figure 6.8).

Apart from the OxVasc study, no other study reported on the risk of post-TIA dementia beyond the first year. In the OxVasc study, at 5 years the cumulative incidence of post-TIA dementia (excluding pre-event dementia) was 16.2% (14.6-17.8%) with the risk increased further if there was a previous or recurrent stroke. The risk still remained significantly lower than if the index event had been an ischaemic stroke even after adjusting for age, sex and education (OR 0.45, 0.34-0.59, p<0.001).

6.5 Discussion

This systematic review has expanded upon the previous review by significantly increasing the number of included studies (from 29 to 64) and including the results from a large longitudinal population-based study (OxVasc). Overall, the prevalence rates of post-stroke dementia remained similar to the previous review, with the rate depending on the cohort characteristics. Highest rates were described in hospital-based studies of recurrent stroke which included pre-stroke dementia (41%) and the lowest rates in population-based studies of first stroke which excluded pre-stroke dementia (10%). Using a single brief cognitive assessment tool rather than a diagnostic criteria for dementia leads to an over-estimation of the risk and should be interpreted with caution. Overall, about 1-in-6 patients who present to hospital with a stroke will subsequently develop new dementia within the first year.

In this review, the increased number of studies with cohorts recruited over nearly three decades allowed us to assess for any potential time trend in the post-stroke dementia prevalence rate. Even after adjusting for the heterogeneity introduced by different study methods, there appears to be a significant decrease in the prevalence of post-stroke

dementia with rates halving between 1990 and 2015. Over the decades acute and post-stroke care has improved with more robust secondary prevention, the stroke ward as a holistic intervention, the introduction of thrombolysis and more recently thrombectomy.[124] There has also been an increasing emphasis on better primary prevention with an awareness of the importance of mid-life hypertension control and population-education about stroke.[125,126] This has led to a gradual, but sustained, decrease in the age-specific risk of stroke and specifically severe stroke.[11] As recurrent stroke and stroke severity are significant risk factors for post-stroke dementia it is feasible that these interventions are also contributing to the decreased prevalence rate seen. The reduction in post-stroke dementia rates seen in the PROGRESS trial were attributed to their reduction in the risk of recurrent stroke through improved blood pressure control.[127] This is counter to the increasingly ageing population which would predict an increased prevalence of dementia overall and also the increased survival rate, and therefore greater disability, of those with more severe stroke. In the general population, particularly in high income countries, the incidence of all cause dementia has decreased through the decades.[128,129] However, this was not sufficient to explain the trend seen in this meta-analysis as demonstrated by the lack of temporal trend in pre-stroke dementia prevalence rates (demonstrated in Chapter 5). Ideally, an assessment of the factors associated with the decreasing prevalence rate should be undertaken in longitudinal studies that have reported on dementia prevalence rates at different points over the years. However, no such study of time trends in risk factors was identified in this systematic review.

Post-stroke dementia, as a term, is often used to describe any form of dementia that occurs after a stroke but the underlying aetiology cannot be inferred from the description.[130] It may reflect subclinical Alzheimer's disease or a subcortical vascular dementia process, either of which are then accelerated or decompensated by a stroke. Alternatively, it may reflect a specific subtype of vascular dementia that is caused by the infarct itself. A limited number of studies attempted sub-typing with vascular dementia accounting for the aetiology of

between 51% and 100% of post-stroke dementias.[71,93] Sub-typing of dementia syndromes is notoriously difficult and the clinical diagnosis is often at odds with the subsequent pathological description.[131] Additionally there has been an increasing recognition of the importance of mixed pathology with the complex interplay of stroke and neurodegenerative diseases having been well described.[123,132] Alzheimer's disease is associated with increased risk of stroke, and stroke is associated with acceleration in Alzheimer's pathology.[123,132] APOE-ε4 homozygosity, a known risk factor for sporadic Alzheimer's disease, has also been demonstrated to be associated with post-stroke dementia even after adjustment for baseline cognitive impairment.[133] The mechanism behind this synergistic susceptibility is less well understood with theories including stroke leading to increased autoimmune response and decreased amyloid clearance and amyloid plaques in Alzheimer's affecting vessel wall integrity.[123,134,135] As such mixed pathology is increasingly seen, particularly in older ages, further complicating the ability to sub-type the syndrome.[136] Yet, despite this complexity a clear description of the sub-types of dementias seen after a stroke would better inform the risk factors analysis and as such potentially improve subject selection for clinical trials and patient discussions.

Whilst it is generally agreed that post-stroke dementia should be diagnosed when there is a clear temporal relationship between the stroke and the onset of cognitive impairment, there is no agreed definition about the timing of that relationship with most studies assessing between three and 12-months and a degree of ambiguity in the commonly used diagnostic criteria. The majority of studies included used the DSM-IV (or DSM-III or DSM-III-R) criteria as their diagnostic standard for post-stroke dementia. However, since these publications the DSM-5 criteria has been introduced with noticeable differences in the criteria for dementia with an as yet unknown impact on subsequent assessment of prevalence rates. Previously a hospital-based study found that changing the diagnostic criteria from DSM-III to DSM-IV led to a one third reduction in the number of cases of post-stroke dementia when applied to the same cohort.[40]

In this review the majority of studies used a single point of time to assess for post-stroke dementia but yet improvements in cognitive functioning, and even a 'reversal' of a dementia diagnosis, after a stroke have also been described in longitudinal studies.[2,74] Furthermore, whilst the yearly incidence of dementia after a stroke, in population-based studies, was described as 1.6% per year the risk of post-stroke dementia in an individual is unlikely to be linear. Similar to vascular dementia itself, there is the risk of step-wise changes with an immediate up front impact of the stroke itself and then subsequent deterioration from any underlying neurodegenerative processes, any recurrent (clinical and silent) strokes and even the impact of acute illnesses and hospitalisations.

Predictors of post-stroke dementia identified by the pooled analysis in this systematic review were, in general, similar to those identified in the previous review.[1] Factors associated with the stroke and its severity predominated in their contribution to post-stroke dementia: left hemispheric, dysphasia, acute confusion, early seizures, atrial fibrillation, stroke severity, recurrence, multiple infarcts and prior infarcts. Whilst all were identified as independent predictors by various studies, the majority of these variables are confounded by either the severity of the stroke or a recurrent stroke, and even in multivariate analyses few studies adjusted for this. Non-stroke related risk factors identified included increasing age, low education, diabetes and white matter disease all of which may reflect an association with underlying neurodegenerative pathology. In this review lacunar strokes were found to be associated with a lower risk of post-stroke dementia which is unsurprising given they are often more minor in nature than other aetiologies. However, this may under-estimate their long term risk of dementia given their association with the more diffuse and degenerative white matter disease.[137]

There were limited studies on the assessment of dementia after a TIA with pooled prevalence rates in the first year of 4.1% not dissimilar to the rates seen in the general population.[138] However, caution should be taken in interpreting this as comparison with age-matched controls have not been made and studies on TIA patients are subject to numerous

risks of bias from the characteristics of patients not seeking help and the differing definitions of time versus tissue based.

There are numerous potential limitations of the review. As mentioned earlier the majority of the studies included in the meta-analysis provided only a single assessment within the first 12-months after the stroke which limited the assessment for the longer-term risk. Many studies excluded patients with aphasia and severe sensorimotor impairment. Given that these impairments are likely a consequence of an increased stroke severity, exclusion leads to a risk of under-estimation of post-stroke prevalence rates. Intracerebral haemorrhages were not analysed separately from ischaemic strokes and no attempt made to delineate them further. Despite the inclusion of OxVasc there remain limited population-based studies on post-stroke dementia. There were limited studies reporting the time-trend of the prevalence of post-stroke dementia within the same population using the same methods introducing heterogeneity into the time trend assessment. The meta-analysis of prevalence rates does not account for the time-trend so may over-estimate the current rate particularly in the analyses where older studies predominate. The calculation of the pooled odds ratios for a given association only included data from those studies that had reported a given risk factor meaning that they were potentially subject to a publication bias. Finally, the independent associations reported were dependent upon the variables included in the multivariable analyses which were heterogeneous across studies.

6.6 Conclusion

One-in-six patients admitted to hospital with a stroke with subsequently develop dementia within the first year. However, the prevalence of post-stroke dementia has been decreasing over the recent decades likely attributable, at least in part, to improved acute and post-stroke care and better secondary prevention.

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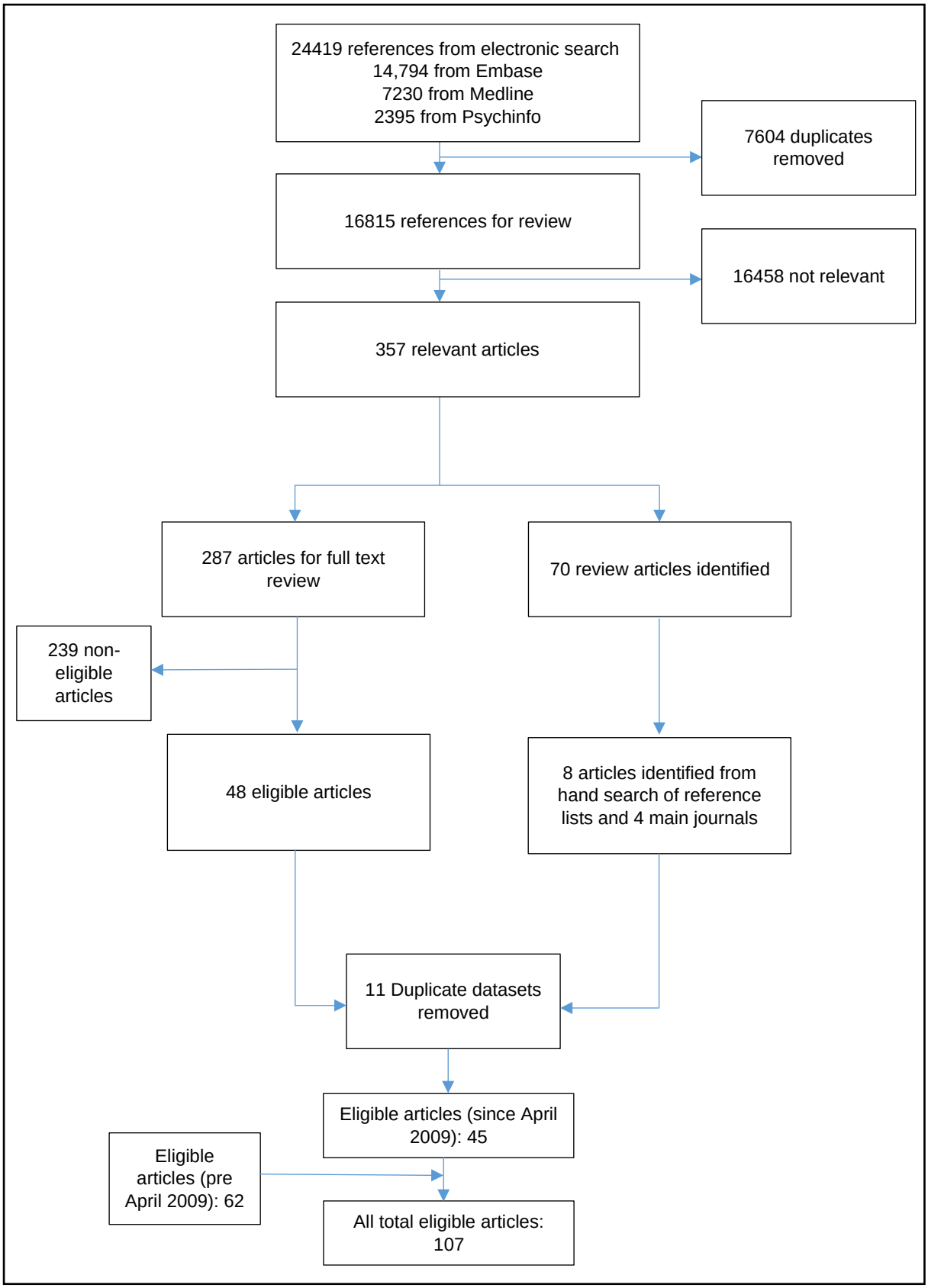


Figure 6.1: Literature searches and results for studies on post-stroke dementia prevalence.
For full search strategy see Appendix XIX.

Study centre	Date of cohort collection	Study type	Mean age (yrs)	Female	Stroke type	First ever stroke	Exclusion criteria	Pre-stroke dementia excluded	Pre-stroke dementia quantified	Follow-up	Post-stroke dementia diagnosis
Chicago, USA[21]	1987-90	X	72	49%	IS	N	Aphasia, Parkinson's disease, possible prior Alzheimer's disease	N**	N	2-3 months	DSM III
Tel Aviv, Israel[22-24]	1988-90	L	73	40%	IS	Y	Aphasia	Y	N	6 monthly to 5 years	DSM-III-R
Columbia Presbyterian Medical Centre, USA[25-35]	1988-90, 1994-97	X, L	70	53%	IS	N	Dysphasia, non-English or Spanish speaking, low GCS, <60 years	N (Y in longitudinal study)	N	3 months to 4 years	DSM III-R
Farsoe and Aalborg Hospitals, Denmark[36]	1991-1992	L	72	49%	IS, H	N	Other neurological disorder, psychiatric, age<60 or >80 years	Y	N	1,6,12 months	Mattis dementia rating scale
Bergamo, Italy[37]	1993-94	X	65	35%	IS	Y	Age <40 or >80 years, other neurological disorder, unusual cause of stroke, comorbidity, depression, sensory impairment	Y	N	3 months	NINDS AIREN
Florence, Italy[†,38]	1993-94	X	71	48%	IS, H, SAH	N	None stated	Y	Y (FU only)	12 months	Informant interview
Gothenburg, Sweden[39]	1993-94	X	80	65%	IS, H	N	Resident in nursing home, other cerebral lesion, coma, age<70	N	N	Mean 20 months	DSM III-R
Helsinki SAM Study, Finland[40-44]	1993-95	X, L	71	48%	IS	N	ICH, SAH, age <55 or >85, not living in Helsinki, not speaking Finnish language, severe aphasia, severe hearing impairment	N	N	3 months	DSM-III
Rotterdam-Rijnmond, Netherlands[†,45,46]	1993-96	X	70	40%	IS, H, TIA	N	Aphasia, sensory impairment, non-fluent in Dutch, reduced conscious level	N	N	3-9 months	DSM III-R
Madrid, Spain[2,47-49]	1994-95	X, L	69	47%	IS, H	N	Primary brain lesion, aphasia, comorbidity	N	Y	3, 6, 24 months	DSM III-R /DSM IV
Lille Stroke/ Dementia Study, France[50-53]	1995-96	L	72	46%	IS, H	N	Non-white, no informant, age <40 years, not fluent in French, not from Lille, history of severe head trauma	N	Y	6 months annually to 3 years	ICD-10, DSM III-R
Lisbon, Portugal[54]	1995-97	X	59	45%	IS, H	N	Previous dependency, dysphasia	Y	N	3 months	DSM IV
Rome, Italy[55]	1995-97	L	71	30%	IS, H	N	Severe aphasia or neglect, <5years education, SAH, age<40, concomitant neurologic disorder, severe co-morbidity	Y	N	annually, to mean 45 months	ICD-10
Taiwan[56]	1995-99	X	64	34%	IS	N	Other brain lesion, severe medical co-morbidity	Y	N	3 months	ICD-10
Sydney Stroke Study, Australia[57-60]	1997-2000	X, L	72	39%	IS, TIA	N	No other neurological disorder, severe aphasia, too unwell to participate	Y	Y	3-6 months, to 3 years	By consensus

Ege Stroke Registry, Turkey[4]	1998-2009	L	66	43%	IS, H	N	Non-consent	N	Y	6 months to 5 years	DSM-IV, NINDS-AIREN
Chongqing Stroke Study, China[†, 61,62]	1999-2000	X	68	47%	IS	N	Concomitant neurological disorder, <55 years, severe medical co-morbidity or sensory impairment, reduced GCS, severe aphasia	N	Y	3 months	DSM IV
Cracow, Poland[63-65]	2000-01	X	66	55%	IS, H	N	Age <40 years, no reliable informant, other brain lesion	N	Y	3 months	DSM IV, IQCODE
Maastricht CODAS, Netherlands[66-67]	2000-01	L	68	45%	IS	Y	Age <40, severe aphasia, other neurological or psychiatric condition, not fluent in Dutch, MMSE>15 at 1 month	Y	N[‡]	1, 6, 12, 24 months	DSM IV
Rotterdam-Rijnmond, Netherlands[†, 68]	2000-02	X	70	38%	IS, H, TIA	N	Aphasia, sensory impairment, non-fluent in Dutch, reduced conscious level	N	Y (FU only)	3-9 months	DSM IV
Amiens, France[69]	2002-06	X	62	36%	H	N	Prior traumatic brain injury, haemorrhagic transformation of an infarct, cerebral venous thrombosis, SAH, haemorrhage related to tumours	Y	N	40 months	DSM-IV and others
PITCH, Lille, France[70]	2004-09	X, L	66	46%	H	N	Non primary ICH, intraventricular haemorrhage, referral from other hospitals, death<6 months, pre-existing dementia (IQCODE => 64)	N	Y	6 months up to 6 years	NIA-AA
Fogarty-Mexico Stroke Cohort, Mexico[71]	2005	L	56	38%	IS, H	Y	Prior stroke, TIAs, pre-existing dementia, neurological or psychiatric diseases, severe aphasia, SAH, iatrogenic or traumatic stroke	Y	N	3 months	DSM-IV
Chile[72]	2005-06	L	72	42%	IS, H	N	Age≤60 years, TIA, SAH, juxtadural haematoma, other CNS disorders (e.g. Parkinson disease, brain tumours), severely impaired stroke (mRS >3), persistent consciousness impairment at discharge	N	N	3, 12 months	IQCODE, PFAQ
Chongqing Stroke Study, China[†, 3]	2005-08	L	67	50%	IS	N	Haemorrhage, SAH, aged <55	N	Y	3 months	DSM IV
Hyderabad, India[73]	2006-13	L	57	21%	IS	N	ICH, modified Rankin score>4, severe comorbidities, pre-existing dementia	N	N	3 – 24 months	NINDS-AIREN
Oslo, Norway[5,74]	2007-08	L	72	49%	IS, H, TIA	Y	SAH, dementia/MCI pre stroke (IQCODE≥ 2.44), prior stroke or TIA, non-fluent in Norwegian, life expectancy <1 year	Y	N	12 months up to 7 years	ICD-10
South Korea[75,76]	2007-08	L	64	39%	IS	N	Severe/deteriorated medical/neurological conditions, severe aphasia, death < 2 weeks, use of cognitive enhancers at subsequent follow up	N	Y	3 months	K-VCIHS-NP, DSM-IV
Zagazig, Egypt[77]	2007-08	X, L	63*	47%	IS, H	N	TIA, pre-stroke dementia, previous seizures/epilepsy, stroke due to cerebral venous thrombosis, SAH, Age<40 years, without reliable informant, patients with history of severe head trauma or cerebral surgery	Y	Y	6, 12, 18 months	ICD-10
TABASCO, Israel[78]	2008-14	L	67	41%	IS, TIA	Y	NIHSS ≥ 17, ICH, cognitive impairment pre event (IQCODE≥3.3), severe aphasia or disability, type 1	Y	N	6, 12, 24 months	DSM-IV

							diabetes, stroke from trauma or invasive brain procedures				
Florence, Italy[†, 79]	2009-10	L	68	44%	IS, H	N	Age<18, non-Italian language, living outside Florence	N	N	6 - 9 months	DSM IV
Skopje, Macedonia[80]	2009-10	L	72	46%	IS	Y	TIA, ICH, death during hospitalisation, severe aphasia, coexisting cerebral or serious medical disorders, previous cerebral insults, cognitive impairment before stroke	Y	N	2 years	DSM IV
STRIDE, Hong Kong[81]	2009-10	L	69	44%	IS, TIA	N	Died prior to assessment, severe visual/language/hearing impairment, recurrent (interval) stroke, severe physical disability, non-cantonese speaking, non-Chinese ethnicity, active psychiatric condition, pre-stroke dementia, incomplete data	Y	N	3-6 months	DSM-IV
Singapore[82]	2009-11	L	60	32%	IS, TIA	N	Major disability (rankin>4), significant aphasia/ dysarthria impeding cognitive assessment, major/ active psychiatric illness, pre-existing dementia, score of >3.38 on IQCODE, acute delirium	Y	N	3-6 months	DSM-IV
CogFAST, Nigeria[83]	2010-12	L	60	43%	IS, H	N	Age<45, SAH, significant physical illness, motor impairment, psychiatric or neurologic illness including pre-stroke dementia, any systemic disease that could impair cognition (e.g. chronic liver / kidney disease)	Y	N	3 months	DSM IV criteria
University Hospital, Dijon[84]	2010-12	L	66	44%	IS, H	Y	SAH, severe aphasia, LOC / severe hemiparesis / hemiplegia / vision or hearing loss that could limit the participation, illiteracy, mental retardation, not fluent French, psychiatric disorders, pre-stroke dementia, severe cognitive impairment pre stroke	Y	N	3 months	DSM-IV criteria
GRECOG-VASC, France[6]	2010-16	L	64	38%	IS, H	N	Conditions (other than stroke) affecting cognition (e.g. chronic alcoholism, dementia, epilepsy, severe traumatic brain injury, Parkinson's disease, multiple sclerosis, a brain tumour) or conditions precluding assessment (illiteracy, severe sensory or motor impairments), life expectancy <2 years, contra-indication to MRI	Y	N	6 months	VASCOG criteria
Brescia, Italy[85]	2011	X,L	71	44%	IS, H	N	Previous diagnosis of dementia, pre-morbid cognitive impairment, TIA, Age <18 years, lack of caregiver	Y	Y	3, 12 months	DSM-IV
Uttar Pradesh, India[86]	2011-13	L	59	27%	IS, H	N	SAH, pre-stroke dementia, aphasia / impaired consciousness, history of psychiatric disorders (e.g. major depression and schizophrenia)	Y	N	3, 6 months	NINDS-AIREN
Ibadan, Nigeria[87]	2014–16	L	61	47%	IS, H	N	Unable to communicate reliably (aphasia), severe co-morbidities (chronic kidney disease, metastatic cancer, open tuberculosis)	N	Y	3 months	NINDS-AIREN
Assiut, Egypt[88]	N/S	L	58	33%	IS, H, TIA	Y	Age <40 or >75, event>7 days prior, prior stroke, persistent disturbed level of consciousness, aphasia, pre-stroke cognitive impairment, psychosis or other neurological diseases, SAH,	Y	N	3 months	DSM-IV

							severe sensory impairment (blindness, deafness), cancer in the past 5 years, severe head trauma or neurosurgical operation at any time				
Hong Kong, China[89]	N/S	X	71	55%	IS, H	N	Non-Chinese, Non Cantonese- speaking, age <50	N	Y	3 months	DSM IV

Table 6.1: Hospital-based studies of post-stroke dementia. X=cross-sectional. L=longitudinal. N=no. Y=Yes. IS=ischaemic stroke. H=Haemorrhagic stroke. TIA=Transient Ischaemic Attack. SAH=subarachnoid haemorrhage. GCS=Glasgow coma scale. DSM=diagnostic and statistical manual of mental disorders. FU=follow-up. IQCODE=informant questionnaire on cognitive decline in the elderly. ICD=International classification of disease. NINDS-AIREN=National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences. SAM=Stroke, Ageing and Memory study. CODAS=Cognitive Disorders After Stroke. SAFE=stroke in Atrial Fibrillation Ensemble II. VASCOG=Vascular Behavioural and Cognitive Disorders. NIHSS=National Institutes of Health Stroke Scale. NIA-AA=National Institute on Aging and Alzheimer's Association. PFAQ=Pfeffer Functional Activities Questionnaire.TICS-m=modified Telephone Interview for Cognitive Status. K-VCIHS-NP=Korean Vascular cognitive impairment harmonisation standards neuropsychological protocol. PITCH=Prognosis of Intracerebral Haemorrhage. CODAS=Cognitive disorders after stroke. STRIDE=Stroke registry investigating cognitive decline. GRECOG-VASC= Groupe de Réflexion pour l'Évaluation Cognitive Vasculaire TABASCO, CogFAST=Cognitive Function After Stroke. MGH= Massachusetts General Hospital. N/A=not applicable. N/S= not stated. MMSE= mini mental state examination.*median values †Data from (non-overlapping) cohorts from same study group included. **Patients with prior Alzheimer's disease were excluded, ‡=Patients with MMSE<15 were excluded.

Study	Date of cohort collection	Study type	Mean age (years)	Female (%)	Stroke type	First ever stroke	Exclusion criteria	Pre-stroke dementia excluded	Pre-stroke dementia quantified	Follow-up	Post-stroke dementia diagnosis
Rochester, Minnesota[90]	1960-1984	L, RPS	..	50	IS	Y	Previous stroke or dementia	Y	Y	Up to 25 years	Review of medical records
Prospective Population Study of Women in Gothenburg[91]	1974–2011	L,V	78	100	IS, H	Y	Prior stroke or TIA, dementia before 1968,	N	Y	up to 44 years	DSM III-R
Framingham[92,93]	1982-2001	L, V	79	61	IS, H	Y	Previous stroke or dementia	Y	Y	10 years	DSM-III MMSE DSM-IV
The Rotterdam Study[94-96]	1990-2013	L,V	80	60	IS, H, TIA	Y	≥55 years, previous stroke or dementia	Y	N	Mean 9.9 person years	DSM III-R
Canadian Study of Health and Aging[97]	1991-1997	L,V	72**	59*	IS, H	Y	≥65 years, previous stroke or dementia	Y	N	5 years	DSM III-R
Melbourne, Australia (NEMESIS)[98-100]	1996-1999	X, L, PPS	74	56	IS, H, TIA, SAH	Y	Recurrent stroke, aphasia, non-English-speaking, inadequate vision or hearing	N	Y	3 months, 1, 2 years	DSM-IV
OxVasc, UK[10]	2002-12	L, PPS	74	51	IS, H, TIA	N	None	N	Y	5 years	DSM-IV

Table 6.2: Population-based studies of post-stroke dementia *mean of total volunteer sample. **Median values. L=longitudinal study. X=Cross-sectional. V=volunteer cohort. RPS=retrospective patient study. PPS=prospective patient study. H=intracerebral haemorrhage. IS=ischaemic stroke. Y=yes. N=no. DSM=diagnostic and statistical manual of mental disorders. MMSE=Mini-mental state examination. NEMESIS=North East Melbourne Stroke Incidence Study. LATCH= Lothian Audit of the Treatment of Cerebral Haemorrhage, †LATCH is a study of first intracerebral haemorrhage. OxVasc=Oxford Vascular Study.

Study	Date of cohort collection	Study setting/ type	Mean age (yrs)	Female	Stroke type	First ever stroke	Exclusion criteria	Pre-stroke dementia excluded	Pre-stroke dementia quantified	Follow-up	Score, cut-off	% < cut off
Oxford (OCSP), UK[101]	1990	P, X,L	71	55%	IS, H	Y	None stated	N	N	1, 6, 12 months	MMSE <24	26/122 (21%) at 6 months, 24/115 (21%) at 1 year
South London Stroke registry, UK[102-106]	1995-2011	P, X,L	69	47%	IS, H	Y	Prior stroke, severe aphasia/dysphasia/ dysarthria/deafness/visual impairment	N	N	3 months, annually up to 10 years	MMSE<24 or AMT<8	529/1682 (31%) at 3 months, 67/239 (15%) at 10 years.
Erlangen Stroke Project, Germany[107]	1998-2006	P, L	70	51%	IS, H, TIA	Y	Pre-stroke dementia, recurrent stroke	Y	N	3,12,36 months	MMSE<24	93/630 (15%) at 3 months, 53/456 (12%) at 3 years
ERMANCIA, French West Indies[108]	1998-99	P, L	73	45%	IS, H, SAH	Y	Prior stroke	N	N	5 years	MMSE<19	30/229 (13%), (135/229, 59%)† at 5 years
Orebro, Sweden[109,110]	1999- 2000	P, X	74	50%	IS, H	Y	aphasia	N	Y	1 year	MMSE <24	67/232 (29%) at 1 year
Utrecht, The Netherlands[&,111]	2000-10	H, X	65	58%	IS, TIA	N	Post event rankin >4, not atherosclerotic, not on secondary prevention, ICH, prior head injury, prognosis months, non-fluent in Dutch, unable to have an MRI	N	N	3.8y (median)	TICS ≤26 or IQCODE≥3.6	48/282 (15%) at median of 3.8 years follow up
Lund Stroke Register, Sweden[112]	2001-02	P, L	77*	43%	IS, H, SAH	Y	General health precluded testing, severe dysphasia / aphasia, poor vision/hearing	N	N	10 years	MMSE≤22, MoCA≤19	24/127 (19%) by MMSE, 35/122 (29%) by MoCA at 10 years
MGH ICH Longitudinal Study[113]	2006-2013	H, L	71	47%	H	N	Seizure disorder prior to index ICH, non-primary cause of ICH	Y	Y[£]	6 monthly	TICS-m<20 and/or coding	140/738 (19%) at 6 months
ARCOS, New Zealand[114]	2002-03	P, L	67	48%	H, IS, SAH,	N	None stated	N	N	5 years	HMT≤6	94/418 (22%) at 5 years
Mumbai, India[115]	2004-06	H, L	63	37%	IS	Y	History of cognitive dysfunction, DSM-4 depression at 3 months	Y	N	3 months	MMSE≤24	24/164 (15%) at 3 months
BASIC, Nueces County, Texas, USA[116]	2008-18	P, L	65, 72*	53%	IS	N	Race other than Mexican-American or Non-Hispanic White, language dysfunction	N	N	90 days	3MSE<80	135/469 (29%) at 90 days
Lothian, UK[&, 117-119]	2010-12	H, L	67*	42%	IS	N	Unable to consent (dementia, aphasia), contraindication to MRI, disabling stroke, unlikely to survive a year, TIA, ICH	Partly[$]	N	1,3,12 months, up to 3 years	ACE-R <88	29/151 (19%) at 12 months, 66/151 (44%) at 3 years
Nanjing, China[120]	2013	H, X	64	38%	IS	N	Age<50 years, lack of informant, severe motor/language disabilities, prior ICH, traumatic brain injury, Parkinson's disease, psychiatric disorders, pre-existing cognitive impairment	Y	N	3-12 months	MMSE[‡]	11/56 (20%) at 3 months
Brazil[&,121]	N/S	H, L	68	47%	IS	N	Embolic strokes, age <55 years, severe disability at baseline, bedridden	N	N	12 months	MMSE**	21/171 (12%)at 12 months
Nottingham, UK[122]	N/S	H, X	69	49%	IS, H	N	Aphasia, reduced conscious level, poor English	N	N	6 months	MMSE<21	22/189 (12%)

Table 6.3 Studies of post-stroke cognitive assessments with cut-off scores in keeping with dementia *median values. **MMSE cut off varies depending on education (illiterate <17, 1-4yrs of schooling <21, 5-8 schooling <24, 9 or more years <26). †for MMSE≤24 (defined as cognitive impairment in study). $Had to have capacity to consent and after recruitment no patients were found to have a diagnosis of pre-stroke dementia or mild cognitive impairment. ‡> MMSE cut off varies depending on education (illiterate<18, 1-6 years of education <21, >6 years of education <25). H=hospital-based; P=population-based; X=cross-sectional; L=longitudinal; FU=follow-up; OCSP=Oxford Community Stroke Project, IS=ischaemic stroke, H/ICH=haemorrhagic stroke. TIA=Transient Ischaemic Attack. ARCOS=Auckland Regional Community Stroke Study. ERMANCIA=Epidemiology of Stroke in Martinique, French West Indies. BASIC= Brain Attack Surveillance in Corpus Christi. MGH ICH=Massachusetts General Hospital Intracerebral Haemorrhage Longitudinal Study. MMSE=Mini-mental state examination. HMT=Hodkinson Mental Test. ACE-R=Addenbrooke's Cognitive Examination-Revised. MoCA=Montreal – Cognitive Assessment. N/S=not specified & Restricted populations: Brazil: excludes cardio-embolic strokes, Utrecht: only atherosclerosis related TIA/minor strokes, Lothian: ischaemic strokes with NIHSS<7. £Pre-stroke dementia prevalence rate excludes patients with history of seizure disorders pre-event which may lead to incomplete capture of pre-event dementia cases so not included in meta-analysis.

Cohort setting	Dementia / total	Prev (%)	95% CI	mean age	mean NIHSS
Hospital recurrent stroke including pre-stroke dementia	13 / 40	32.5	18.0-47.0	80	6.0
Hospital any stroke including pre-stroke dementia	116 / 453	25.6	21.6-29.6	74	5.4
Hospital first stroke including pre-stroke dementia	103 / 413	24.9	20.8-29.1	73	5.3
Hospital recurrent stroke excluding pre-stroke dementia	7 / 34	20.6	7.0-34.2	79	5.8
Hospital any stroke excluding pre-stroke dementia	84 / 421	20.0	16.1-23.8	73	5.3
Hospital first stroke excluding pre-stroke dementia	77 / 387	19.9	15.9-23.9	72	5.3
Population recurrent stroke including pre-stroke dementia	34 / 128	26.6	18.9-34.2	77	4.1
Population any stroke including pre-stroke dementia	203 / 1166	17.4	15.2-19.6	72	3.5
Population first stroke including pre-stroke dementia	169 / 1038	16.3	14.0-18.5	72	3.4
Population recurrent stroke excluding pre-stroke dementia	16 / 110	14.5	8.0-21.1	76	3.8
Population any stroke excluding pre-stroke dementia	131 / 1094	12.0	10.1-13.9	72	3.4
Population first stroke excluding pre-stroke dementia	115 / 984	11.7	9.7-13.7	71	3.3

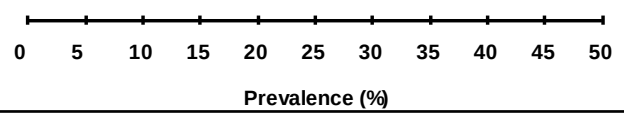


Figure 6.2: Post-stroke dementia prevalence at 1-year in the longitudinal population-based study (OxVasc). Stratified by cohort: hospital, population, first stroke, any (first or recurrent) stroke, recurrent stroke, and including and excluding pre-stroke dementia patients.

	Number of studies	Dementia / total		Pooled prev (%)	95% CI	p het*
A) Hospital-based						
Recurrent stroke inc pre-stroke dementia	5	182 /	449	**40.5**	26.4-54.7	<0.001
Any stroke inc pre-stroke dementia	15	1028 /	4054	**25.4**	20.4-30.4	<0.001
First stroke inc pre-stroke dementia	4	297 /	1256	**23.6**	21.8-25.5	0.530
Recurrent stroke exc pre-stroke dementia	2	21 /	99	**21.2**	20.6-21.8	0.994
Any stroke exc pre-stroke dementia	18	901 /	5523	**16.3**	8.9-23.7	<0.001
First stroke exc pre-stroke dementia	11	314 /	2720	**11.5**	3.5-19.6	<0.001
B) Population-based						
Recurrent stroke inc pre-stroke dementia	1	34 /	128	**26.6**	18.9-34.2	n/a
Any stroke inc pre-stroke dementia	1	203 /	1166	**17.4**	15.2-19.6	n/a
First stroke inc pre-stroke dementia	2	180 /	1126	**16.0**	14.6-17.4	0.594
Recurrent stroke exc pre-stroke dementia	1	16 /	110	**14.5**	8.0-21.1	n/a
Any stroke exc pre-stroke dementia	1	131 /	1094	**12.0**	10.1-13.9	n/a
First stroke exc pre-stroke dementia	3	139 /	1352	**10.3**	6.5-14.1	<0.001

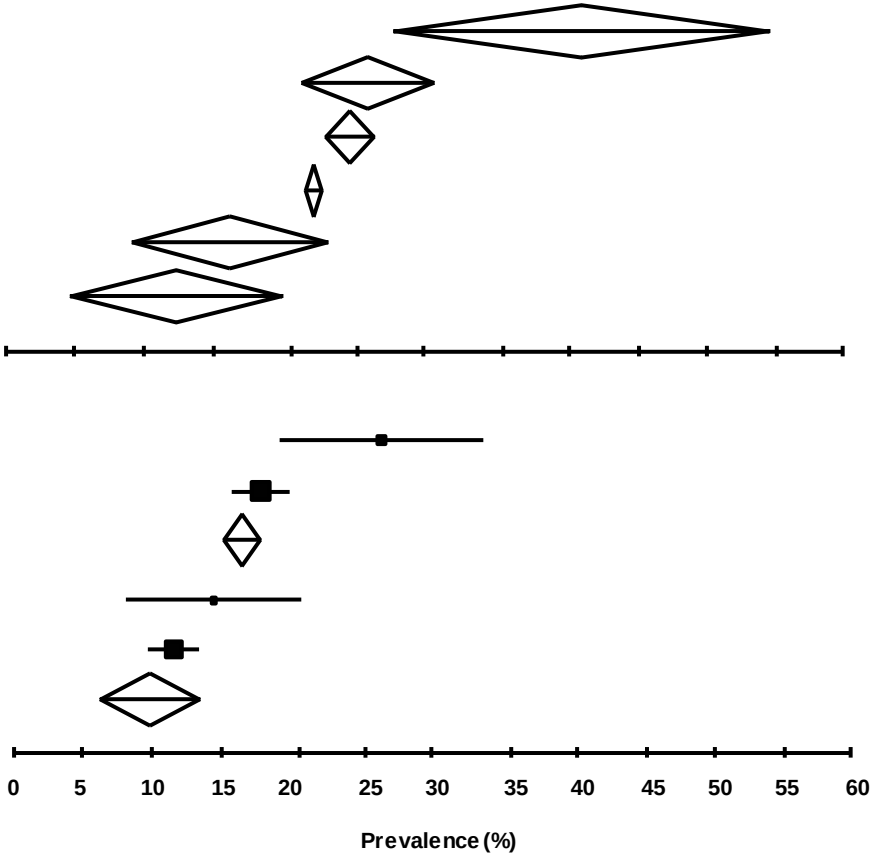
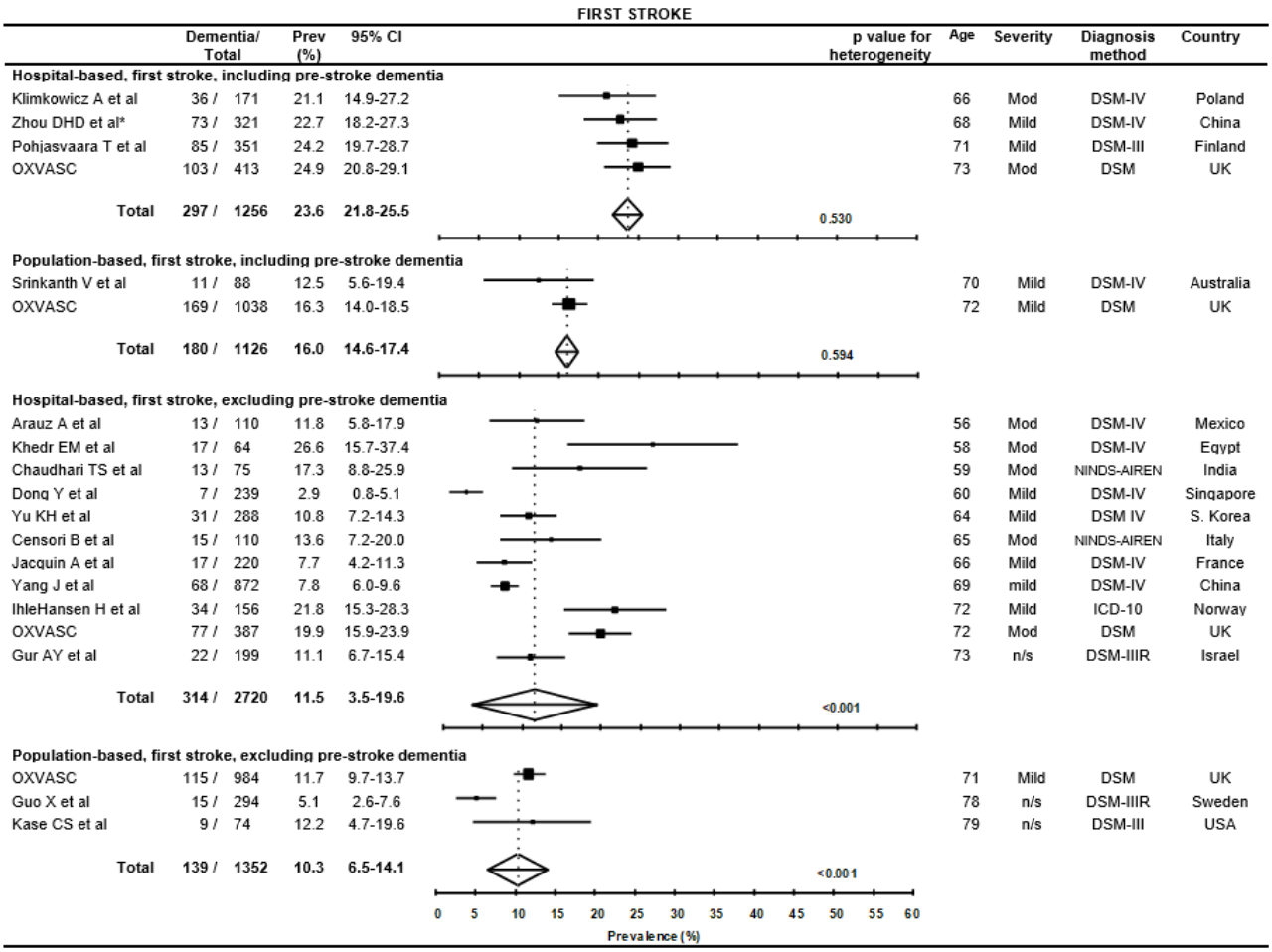
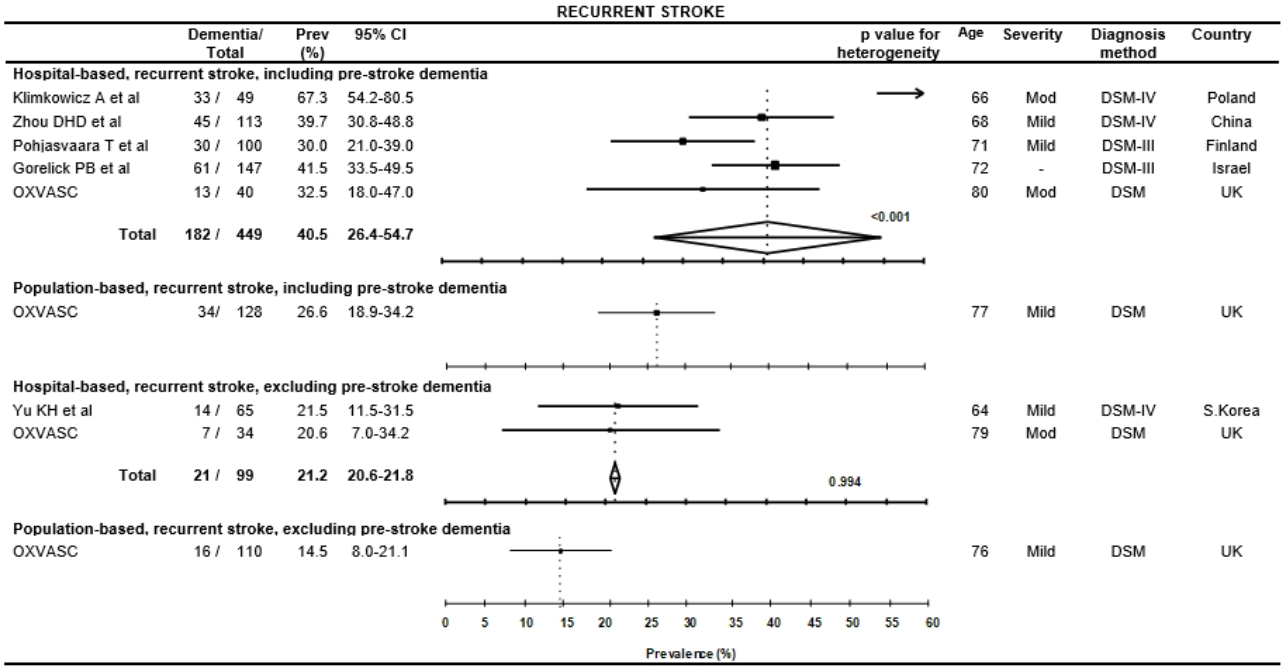


Figure 6.3: Summary of pooled prevalence rates of post-stroke dementia (up to 1-year) after a stroke stratified by A) hospital-based and B) population-based studies. For each the pooled prevalence is further stratified by stroke type (recurrent, vs any (first or recurrent) vs first stroke) and inclusion or exclusion of pre-stroke dementia. Studies are based on point prevalence in survivors at time points up to 1 year with post-stroke diagnosis made by DSM (or similar) criteria. Inc=including. Exc=excluding. n/a=not applicable. *p het = p value for heterogeneity of studies. Prev=prevalence. Details of meta-analyses can be found in figure 6.4.


FIRST STROKE
Dementia/ Total
Prev (%)
95% CI
p value for heterogeneity
Age
Severity
Diagnosis method
Country
Hospital-based, first stroke, including pre-stroke dementia
Klimkowicz A et al 36 / 171 21.1 14.9-27.2 66 Mod DSM-IV Poland
Zhou DHD et al* 73 / 321 22.7 18.2-27.3 68 Mild DSM-IV China
Pohjasvaara T et al 85 / 351 24.2 19.7-28.7 71 Mild DSM-III Finland
OXVASC 103 / 413 24.9 20.8-29.1 73 Mod DSM UK
Total 297 / 1256 23.6 21.8-25.5 0.530
Population-based, first stroke, including pre-stroke dementia
Srinkanth V et al 11 / 88 12.5 5.6-19.4 70 Mild DSM-IV Australia
OXVASC 169 / 1038 16.3 14.0-18.5 72 Mild DSM UK
Total 180 / 1126 16.0 14.6-17.4 0.594
Hospital-based, first stroke, excluding pre-stroke dementia
Arauz A et al 13 / 110 11.8 5.8-17.9 56 Mod DSM-IV Mexico
Khedr EM et al 17 / 64 26.6 15.7-37.4 58 Mod DSM-IV Egypt
Chaudhari TS et al 13 / 75 17.3 8.8-25.9 59 Mod NINDS-AIREN India
Dong Y et al 7 / 239 2.9 0.8-5.1 60 Mild DSM-IV Singapore
Yu KH et al 31 / 288 10.8 7.2-14.3 64 Mild DSM IV S. Korea
Censori B et al 15 / 110 13.6 7.2-20.0 65 Mod NINDS-AIREN Italy
Jacquin A et al 17 / 220 7.7 4.2-11.3 66 Mild DSM-IV France
Yang J et al 68 / 872 7.8 6.0-9.6 69 mild DSM-IV China
IhleHansen H et al 34 / 156 21.8 15.3-28.3 72 Mild ICD-10 Norway
OXVASC 77 / 387 19.9 15.9-23.9 72 Mod DSM UK
Gur AY et al 22 / 199 11.1 6.7-15.4 73 n/s DSM-IIIR Israel
Total 314 / 2720 11.5 3.5-19.6 <0.001
Population-based, first stroke, excluding pre-stroke dementia
OXVASC 115 / 984 11.7 9.7-13.7 71 Mild DSM UK
Guo X et al 15 / 294 5.1 2.6-7.6 78 n/s DSM-IIIR Sweden
Kase CS et al 9 / 74 12.2 4.7-19.6 79 n/s DSM-III USA
Total 139 / 1352 10.3 6.5-14.1 <0.001
0 5 10 15 20 25 30 35 40 45 50 55 60
Prevalence (%)


RECURRENT STROKE
Dementia/ Total
Prev (%)
95% CI
p value for heterogeneity
Age
Severity
Diagnosis method
Country
Hospital-based, recurrent stroke, including pre-stroke dementia
Klimkowicz A et al 33 / 49 67.3 54.2-80.5 66 Mod DSM-IV Poland
Zhou DHD et al 45 / 113 39.7 30.8-48.8 68 Mild DSM-IV China
Pohjasvaara T et al 30 / 100 30.0 21.0-39.0 71 Mild DSM-III Finland
Gorelick PB et al 61 / 147 41.5 33.5-49.5 72 - DSM-III Israel
OXVASC 13 / 40 32.5 18.0-47.0 80 Mod DSM UK
Total 182 / 449 40.5 26.4-54.7 <0.001
Population-based, recurrent stroke, including pre-stroke dementia
OXVASC 34/ 128 26.6 18.9-34.2 77 Mild DSM UK
Hospital-based, recurrent stroke, excluding pre-stroke dementia
Yu KH et al 14 / 65 21.5 11.5-31.5 64 Mild DSM-IV S.Korea
OXVASC 7 / 34 20.6 7.0-34.2 79 Mod DSM UK
Total 21 / 99 21.2 20.6-21.8 0.994
Population-based, recurrent stroke, excluding pre-stroke dementia
OXVASC 16 / 110 14.5 8.0-21.1 76 Mild DSM UK
0 5 10 15 20 25 30 35 40 45 50 55 60
Prevalence (%)

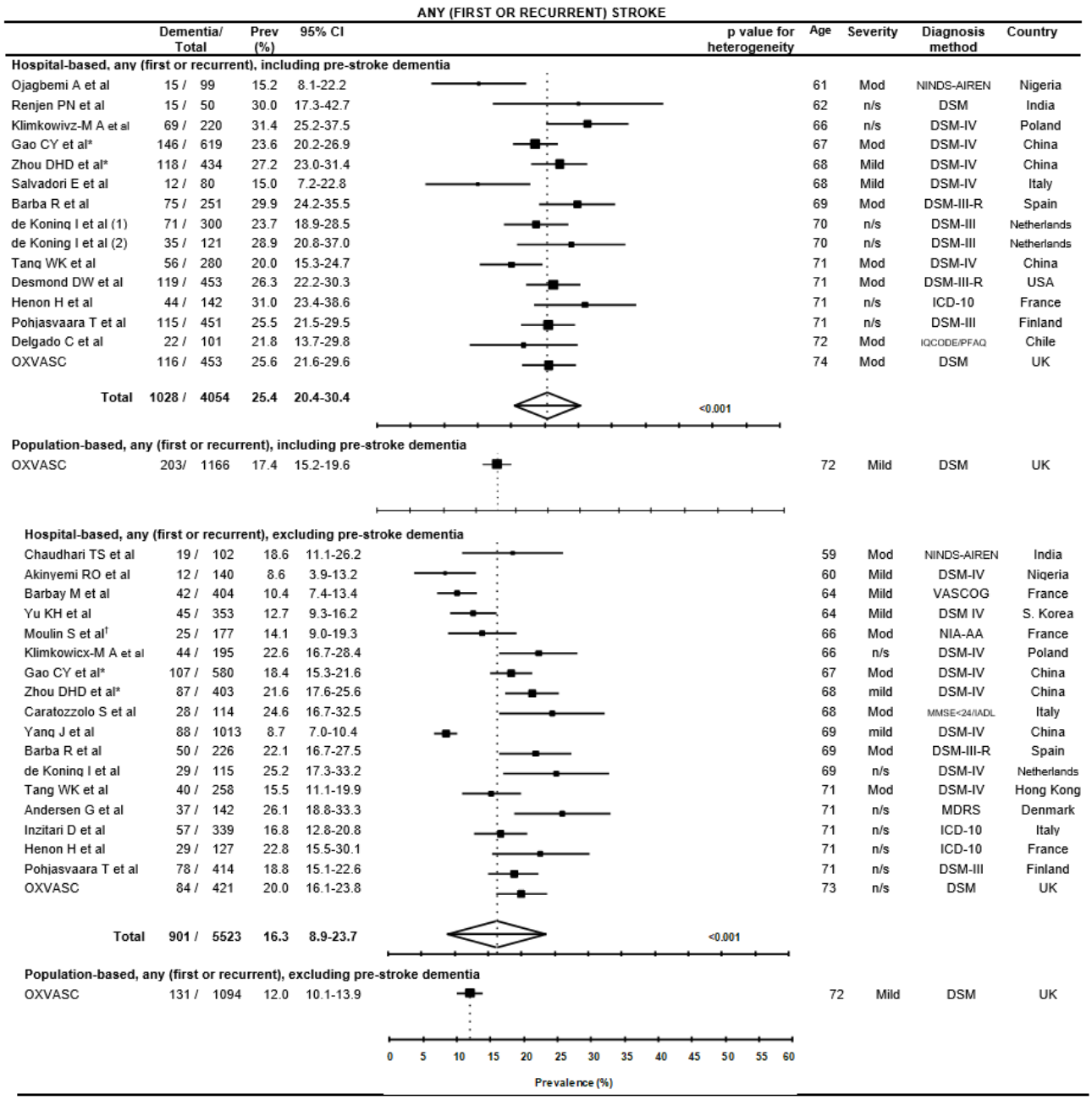


Figure 6.4: Prevalence of post-stroke dementia. Pooled prevalence (%) of post-stroke dementia up to 1 year after stroke stratified by study setting (hospital-based vs population-based), and by first-ever versus any (first or recurrent) versus recurrent stroke. Mean age of the patients in each study, the average severity of the strokes in each study, the method of dementia diagnosis and country of study are also shown. Bars indicate 95% confidence interval (CI). DSM=diagnostic and statistical manual of mental disorders. NINDS-AIREN=National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences. ICD=International Statistical Classification of Diseases and Related Health Problems. IQCODE=informant questionnaire on cognitive decline in the elderly. PFAQ=Pfeffer Functional Activities Questionnaire. VASCOG=Vascular Behavioural and Cognitive Disorders. NIA-AA=National Institute on Aging and Alzheimer's Association. MMSE=Mini-Mental State Examination. IADL=Instrumental activities of daily living. MDRS=Mattis Dementia Rating Scale. TICS=Telephone Interview for Cognitive Status. n/s=not stated. Mod=moderate *Gao CY et al and Zhou DHD are both from the Chongqing Stroke Study but different cohorts. †Studies of only primary intracerebral haemorrhages.

	Dementia/total		Pooled OR	95% CI	p value
	Single tool studies*	DSM studies			
Population-based, first stroke, including pre-stroke dementia	620/2029	180/1126	2.31	1.92-2.78	<0.001
Hospital-based, first stroke, excluding pre-stroke dementia	24/164	314/2720	1.31	0.84-2.06	0.233
Population-based, first stroke, excluding pre-stroke dementia	93/630	124/1058	1.30	0.98-1.74	0.072
Hospital-based, any stroke, excluding pre-stroke dementia	11/56	979/6036	1.26	0.65-2.45	0.490
Population-based, any stroke, excluding pre-stroke dementia	135/469	131/1094	2.97	2.27-3.89	<0.001
Overall			1.80	1.27-2.54	0.001

Table 6.4: Odds ratio of diagnosis of post-stroke dementia using a screening cognitive assessment tool versus a standard diagnostic criteria in studies of (up to 1 year) post-stroke dementia. Stratified by setting, stroke type (any or first) and including / excluding pre-stroke dementia. *Studies include studies where a widely accepted cut-off value for a brief single cognitive assessment tool was used (for example MMSE <24) was used in isolation to identify cases of dementia. MMSE=mini-mental state examination. DSM=Diagnostic and statistical manual of mental disorders. OR=odds ratio.CI=confidence. Not all cohort stratifications are presented due to lack of comparison studies.

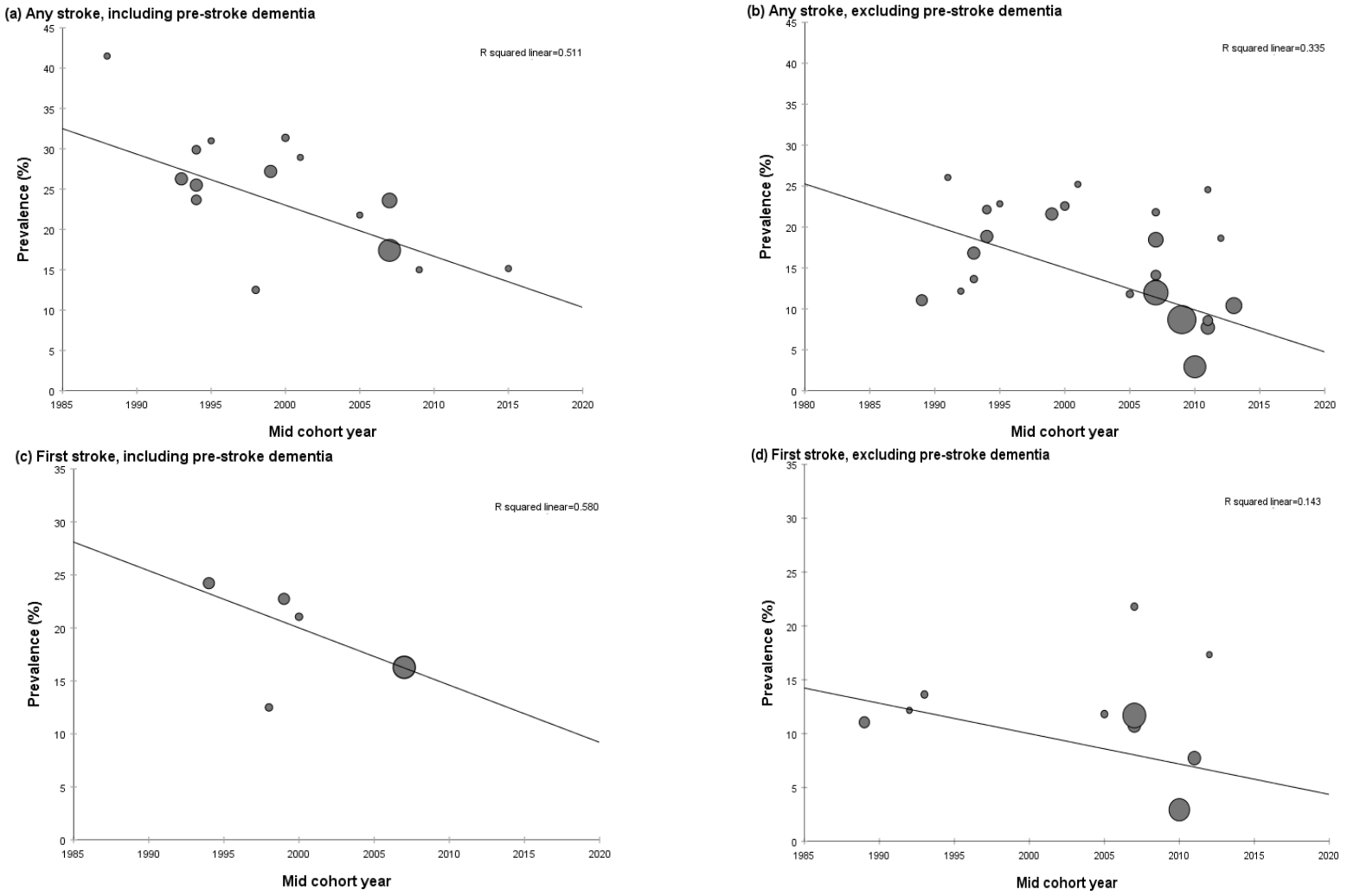


Figure 6.5: Time trends in post-stroke prevalence rates in studies. (a) studies of any stroke including pre-stroke dementia, (b) studies of any stroke excluding pre-stroke dementia, (c) studies of first stroke including pre-stroke dementia and (d) studies of first stroke excluding pre-stroke dementia. Symbol size is proportional to the inverse of the variance for each study. The line is linear regression weighted by inverse variance.

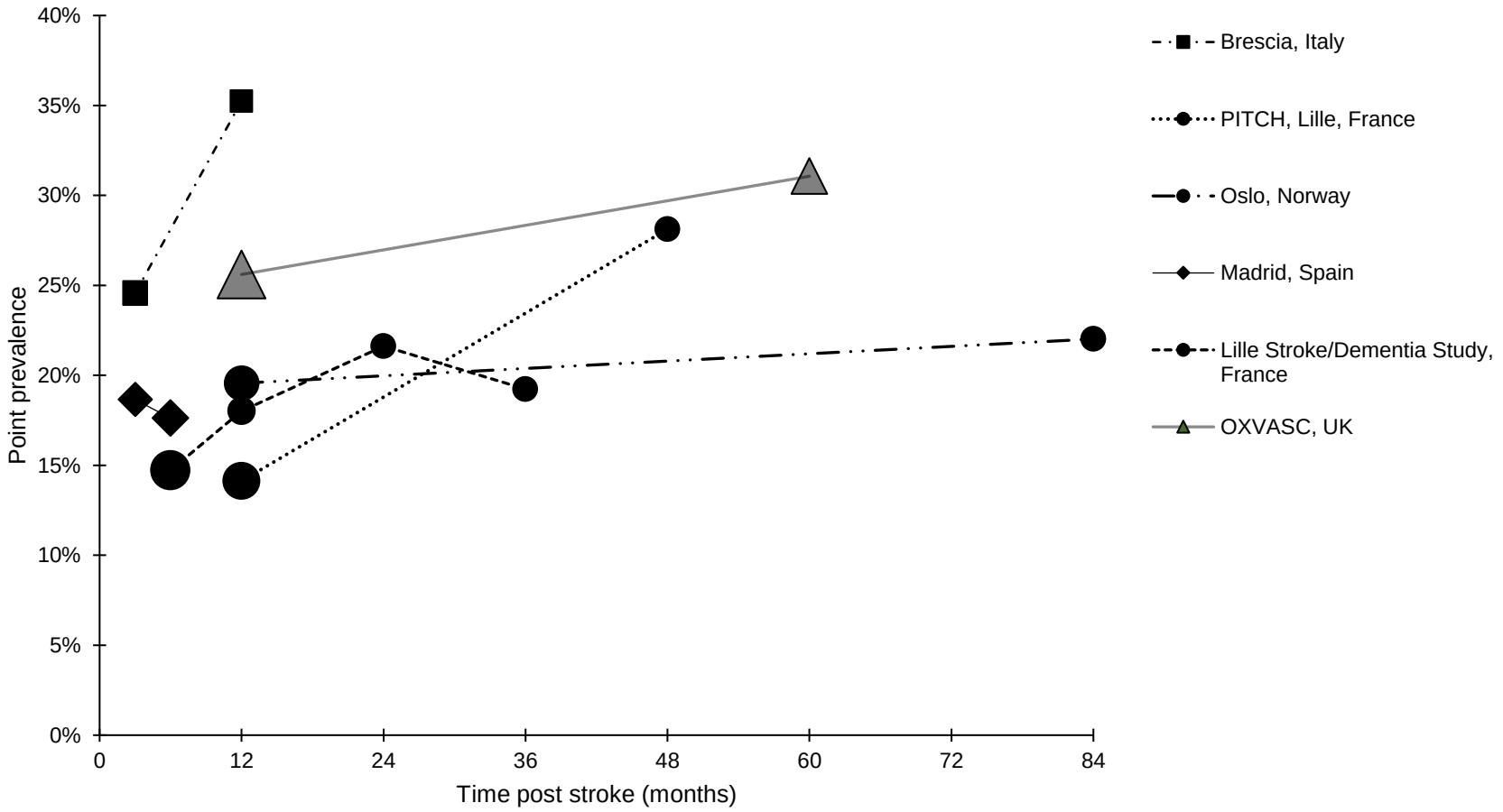


Figure 6.6: Point prevalence of post-stroke dementia in hospital-based studies reporting at more than one follow-up point. Symbol size is proportional to the inverse of the variance for study at each time point. Studies excluding pre-stroke dementia: PITCH, Oslo, Brescia. Studies excluding previous stroke: Oslo. PITCH is intracerebral haemorrhages only.

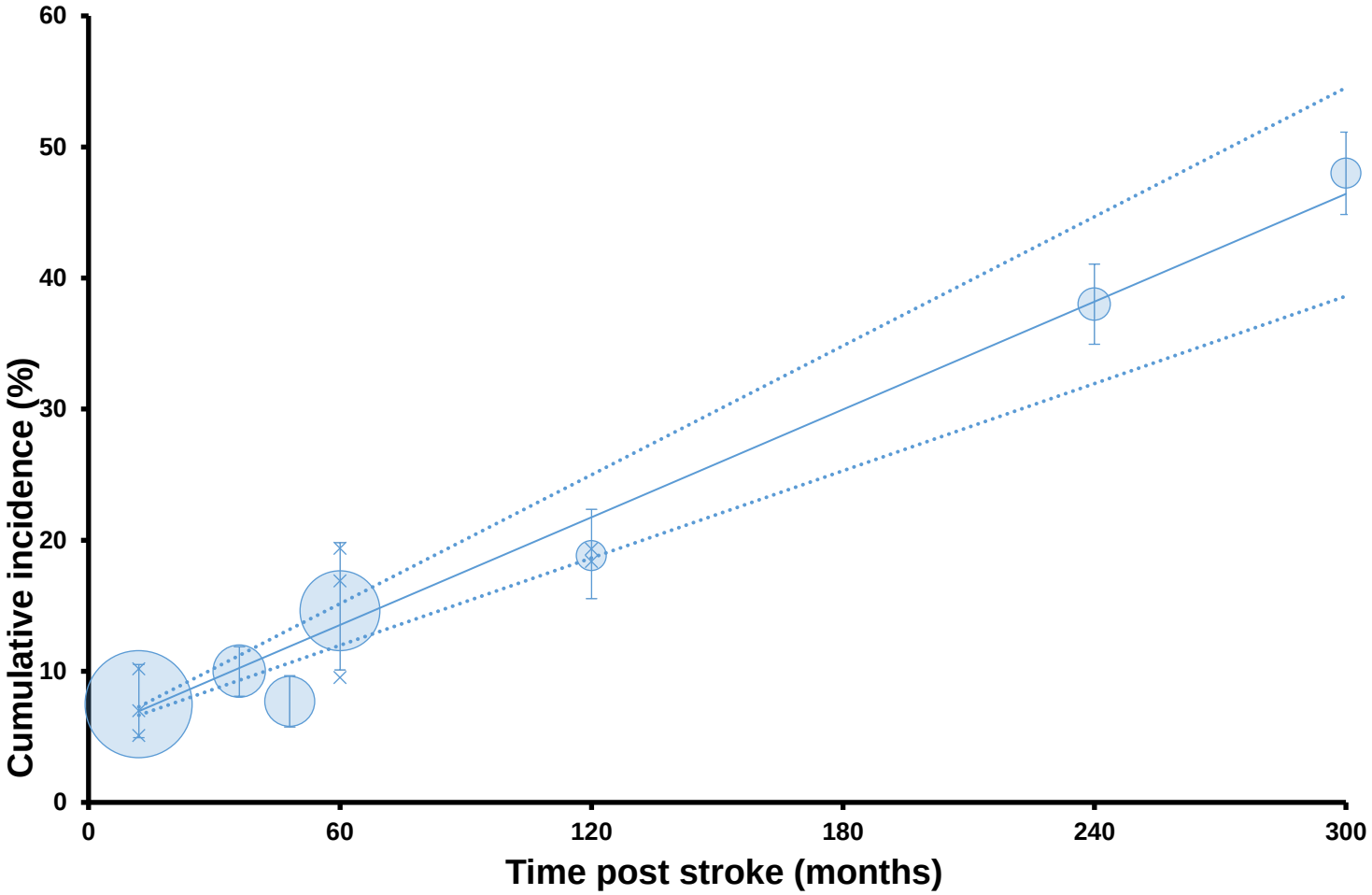


Figure 6.7 Pooled cumulative incidence (up to 25 years) of post-stroke dementia in population-based studies of first-ever stroke, excluding pre-stroke dementia. Solid line indicates linear regression, broken lines indicate 95% confidence interval. Symbol size is proportional to the inverse of the variance for each time point, error bars indicate 95% confidence interval at each point. Individual studies are denoted by crosses.

	Number of studies	Patients with factor/total		OR (95% CI)	p value for OR	p value for heterogeneity
		With dementia	Without dementia			
Demographic factors						
Female sex	34	1182/2309	3120/7265	1.36 (1.18-1.60)	<0.001	0.007
White	5	464/898	1364/2174	0.58 (0.49 – 0.70)	<0.001	0.564
Low education	18	725/1181	1783/3763	2.02 (1.55-2.65)	<0.001	<0.001
Family history of dementia	3	12/96	18/247	1.87 (0.79-4.40)	0.153	0.260
Low socio-economic status	5	326/933	941/2646	1.24 (1.05-1.47)	0.013	0.612
Vascular risk factors						
Diabetes	25	490/1967	1195/5956	1.42 (1.25-1.61)	<0.001	0.142
Atrial fibrillation	16	327/1704	636/4671	1.75 (1.33-2.30)	<0.001	0.002
Ischaemic Heart Disease	19	293/1802	772/4985	1.07 (0.87-1.31)	0.540	0.092
Peripheral Vascular Disease	6	57/598	158/1726	1.11 (0.66-1.87)	0.696	0.098
Previous TIA	14	221/1571	547/4413	1.21 (1.02-1.43)	0.031	0.193
Hypertension	27	1347/1999	3846/6103	1.19 (1.07-1.33)	0.002	0.198
Smoking	25	538/2013	2012/6458	0.92 (0.74-1.15)	0.477	<0.001
Moderate alcohol	15	360/986	994/2609	0.78 (0.66 – 0.93)	<0.001	0.225
Hypercholesterolaemia	13	311/1356	991/3832	1.04 (0.78-1.40)	0.776	0.002
Carotid stenosis	3	31/105	72/369	1.81 (0.71-4.63)	0.216	0.035
Stroke factors						
Haemorrhagic	16	177/1496	501/4928	1.29 (1.06-1.56)	0.009	0.107
Dysphasia	9	367/1297	504/3397	3.12 (2.19-4.43)	<0.001	0.002
Visual field deficit	5	173/676	191/1657	2.57 (2.03 – 3.24)	<0.001	0.310
Left hemisphere	22	703/1504	2278/4922	1.48 (1.22-1.79)	<0.001	0.012
Brainstem/posterior	13	237/1491	935/4082	0.64 (0.43-0.95)	0.029	<0.001
TOAST: Large artery atherosclerosis	7	125/841	325/2328	1.11 (0.87-1.43)	0.403	0.399
TOAST: Cardio-embolic	7	200/841	500/2328	1.17 (0.97-1.42)	0.104	0.458
TOAST: Lacunar	14	234/1138	1085/3473	0.80 (0.68-0.95)	0.011	0.339
TOAST: Cryptogenic	7	337/841	851/2328	1.13 (0.95-1.33)	0.157	0.690
Previous stroke	18[†]	296/1247	570/4027	1.94 (1.65-2.28)	<0.001	0.967
Multiple strokes	10	209/1025	511/2854	2.16 (1.53-3.05)	<0.001	0.052
Recurrent (interim) strokes	9	128/629	291/2153	1.85 (1.20-2.84)	0.005	0.025
Silent strokes	6	81/194	178/673	1.92 (1.35 – 2.72)	<0.001	0.112
Stroke complications						
Incontinence	9	511/1167	438/2844	6.08 (4.03 – 9.17)	<0.001	<0.001
Hypoxic - Ischaemic episodes	2	24/108	42/395	2.41 (1.38-4.21)	0.002	0.414
Acute confusion	6	192/458	220/1475	4.46 (3.50-5.68)	<0.001	0.426
Early seizures	2	22/52	22/183	5.70 (2.76 – 11.75)	<0.001	0.755
Abnormal EEG	1	45/71	43/109	2.66 (1.43-4.92)	0.002	N/A
Brain imaging factors						
White matter disease	12	1446/2381	4387/9446	2.14 (1.72-2.67)	<0.001	0.054
Atrophy	6	216/303	476/908	2.99 (1.33-6.72)	<0.001	<0.001
Medial temporal lobe atrophy	3	127/229	359/1265	3.62 (2.16-6.05)	<0.001	0.092

Table 6.5: Pooled odds ratios for factors associated with post-stroke dementia. TOAST= trial of ORG 10172 in acute stroke treatment classification system. N/A=not applicable. OR=odds ratio (95% confidence interval). Previous stroke is history of a stroke before the event that occurred at study entry with [†]3 of the 18 studies also including previous TIA. Recurrent stroke is a stroke occurring on follow-up.

Study	Mean (sd) (n)		WMD	95% CI
	Dementia	No dementia		
Post-stroke dementia including pre-stroke dementia				
Pohjasvaara et al	72.9 (7.6) (115)	70.4 (7.6) (336)	2.5	0.9-4.1
Gorelick et al	75.5 (9.7) (61)	69.6 (9.1) (86)	5.9	2.8-9.0
Lin et al	74.0 (8.4) (26)	64.0 (8.4) (257)	10.0	6.6-13.4
Zhou et al	73.8 (7.5) (118)	65.3 (6.8) (316)	8.5	7.0-10.0
Rasquin et al	78.2 (6.6) (17)	67.0 (12.5) (159)	11.2	7.5-14.9
Barba et al	76.9 (13.6) (75)	65.4 (9.3) (176)	11.5	8.1-14.9
De Koning 1	74.9 (8.8) (35)	68.1 (8.3) (86)	6.8	3.4-10.2
De Koning 2	73.0 (7.3) (55)	68.2 (8.0) (229)	4.8	2.6-7.0
Linden et al	83.0 (5.3) (41)	81.0 (5.3) (142)	2.0	0.2-3.8
Patel et al	73.0 (12.0) (248)	68.0 (13.8) (397)	5.0	3.0-7.0
Srinkanth et al	80.0 (8.2) (11)	68.0 (13.1) (77)	12.0	6.3-17.7
Lim J-S et al	69.1 (10.4) (50)	63.3 (13.4) (258)	5.8	2.5-9.1
Khedr EM et al	65.5 (9.2) (17)	56.9 (5.3) (64)	8.6	4.0-13.2
OxVasc	80.8 (9.0) (203)	70.5 (13.1) (963)	10.3	8.8-11.8
Total			**7.3***	6.6-8.0
Post-stroke dementia excluding pre-stroke dementia				
Desmond et al	76.6 (8.3) (119)	70.4 (8.3) (334)	6.2	4.5-7.9
Censori et al	65.9 (5.9) (15)	64.8 (9.6) (89)	1.1	-2.5-4.7
Altieri et al	71.0 (6.9) (41)	63.0 (9.5) (150)	8.0	5.4-10.6
Inzitari et al	76.2 (9.4) (57)	70.0 (11.5) (281)	6.2	3.4-9.0
Tang et al	75.0 (8.5) (55)	69.9 (9.6) (224)	5.1	2.5-7.7
Klimkowicz et al	72.3 (11.3) (44)	64.3 (10.5) (151)	8.0	4.3-11.7
Cordoliani-M et al	76.0 (21.0) (34)	71.0 (43.0) (110)	5.0	-5.7-15.7
Sachdev et al	74.9 (7.4) (36)	71.0 (9.1) (130)	3.9	1.0-6.8
Madureira et al	67.5 (12.7) (13)	58.5 (12.7) (207)	9.0	1.9-16.1
Bornstein et al	73.3 (5.3) (56)	71.2 (8.5) (101)	2.1	-0.1-4.3
Ivan et al	79.2 (6.6) (41)	80.3 (6.6) (212)	-1.1	-3.3-1.1
Yang J et al	79.9 (9.0) (88)	68.2 (11.4) (925)	11.7	9.7-13.7
Chaudhari TS et al	60.3 (9.1) (19)	59.2 (11.5) (83)	1.1	-3.7-5.9
Arauz A et al	70.7 (11.6) (13)	54.0 (17.5) (97)	16.7	9.5-23.9
Barbov I et al	73.3 (5.3) (33)	71.2 (8.5) (59)	2.1	-0.7-4.9
Akinyemi RO et al	65.4 (10.2) (12)	60.0 (9.3) (128)	5.4	-0.6-11.4
Caratozzolo S et al	72.4 (10.7) (37)	65.2 (12.0) (68)	7.2	2.7-11.7
Khedr EM et al	65.5 (9.2) (17)	56.9 (5.3) (64)	8.6	4.0-13.2
Garcia PY et al	65.0 (10.8) (18)	59.3 (14.0) (60)	5.7	-0.4-11.8
OxVasc	81.6 (9.0) (196)	72.7 (13.3) (1230)	8.9	7.4-10.4
Total			**5.9***	5.3-6.6

Table 6.6: Difference in mean age of patients with and without post-stroke dementia (including and excluding pre-stroke dementia). s.d=standard deviation, n=number of patients, WMD=weighted mean difference (years), *p<0.0001

Study	Mean (sd) (n)		WMD	95% CI
	Dementia	No dementia		
Censori et al	6.1 (3.8) (15)	6.6 (3.4) (89)	-0.5	-2.5-1.5
Altieri et al	6.5 (3.0) (41)	8.2 (4.0) (150)	-1.7	-2.8--0.6
Tang et al	2.4 (3.0) (55)	4.8 (4.4) (224)	-2.4	-3.4--1.4
Sachdev et al	9.4 (2.2) (36)	10.3 (2.7) (130)	-0.9	-1.8-0.0
Madureira et al	3.7 (2.0) (13)	4.9 (2.0) (207)	-1.2	-2.3--0.1
De Koning et al	8.7 (3.1) (55)	9.0 (3.0) (229)	-0.3	-1.2-0.6
De Koning et al	8.9 (4.1) (35)	9.6 (3.1) (86)	-0.7	-2.2-0.8
Srikanth et al	9.9 (2.4) (11)	9.9 (2.4) (77)	0.0	-1.5-1.5
Caratozzolo S et al	6.6 (2.9) (37)	8.3 (3.2) (68)	-1.7	-2.9--0.5
Akinyemi RO et al	5.9 (5.3) (12)	9.6 (5.5) (128)	-3.7	-6.8--0.6
Arauz A et al	2.0 (2.5) (13)	8.4 (5.0) (97)	-6.4	-8.1--4.7
Yang J et al	3.2 (3.9) (88)	5.8 (4.8) (925)	-2.6	-3.5--1.7
Total			**-1.6***	-2.0--1.3

Table 6.7: Difference in mean years of education between patients with and without post-stroke dementia. sd=standard deviation, n=number of patients in study, WMD=weighted mean difference (years), *p<0.001

Study	Mean (SD) IQCODE		Significance
	Dementia	No dementia	
Cordoliani-M. et al	86 (78-100)*	79 (78-102)*	OR 1.08
Barba et al	62 (12.4)	53 (3.2)	<0.001
Tang et al	3.6 (0.6)	3.2 (0.3)	<0.001
Sachdev et al	52.6 (6.9)	49.0 (2.6)	<0.001
Srikanth et al	RR 10.4 (3.3-32.9)		<0.001
Caratozzolo S et al	3.0 (0.2)	3.4 (0.8)	0.000
Selim HA	RR 1.79 (1.16-2.75)		<0.05
Lim J-S et al	9/50 (18.0%)**	13/258 (5.0%	<0.01
Moulin S et al	16/63 (29%)†	12/155 (8%)	n/s
Delgado C et al	OR 2.60 (0.9-7.0)‡		0.071

Table 6.8: Pre-event cognitive impairment in patients with and without post-stroke dementia. sd=standard deviation, RR=relative risk, *median (range), **proportion (and percentage) with premorbid cognitive decline defined as IQCODE≥3.6, †proportion (and percentage) of patients with IQCODE between 53 and 63 pre-stroke. ‡single-variable regression analysis for odds of previous cognitive impairment defined as IQCODE>57. Significance values are taken from individual papers. Higher IQCODE scores indicate greater cognitive decline pre-stroke.

Study	Measurement method	Disabled/Total or Mean (SD) score		Significance
		Dementia	No dementia	
Inzitari et al	Rankin>2	4/57	6/281	0.05
Barba et al	Barthel	87 (20.7)	98 (5.2)	<0.001
Tang et al	Rankin	0.6 (0.8)	0.3 (0.6)	<0.02
Patel et al	Barthel 15-20	218/248	345/397	0.002
House et al	Barthel			0.002*
	Rankin			0.001*
Delgado C et al	Rankin	OR 4.40 (2.2-8.6)**		<0.001
Caratozzolo S et al	IADL	1.5 (1.6)	0.5 (1.3)	0.000
	Barthel	96.0 (7.9)	95.4 (13.6)	NS
Moulin S et al	Rankin>2	19/63	19/155	0.002†
OxVasc	Rankin	2.0 (1.4)	0.8 (1.0)	<0.001
	Barthel	18.4 (9.4)	19.7 (3.0)	0.001

Table 6.9: Premorbid disability in patients with and without post-stroke dementia. SD=standard deviation, OR=odds ratio (and 95% confidence interval), IADL=Instrumental activities of daily living, NS=not significant, *correlated with MMSE, **single-variable regression analysis for higher score in patients with dementia. Significance values are taken from individual papers apart from †.

Study	Measurement method	Severe stroke/total or Mean (SD) score		Significance
		Dementia	No dementia	
Censori et al	NIHSS≥8	10/15	22/89	0.003
Pohjasvaara et al	SSS	54.6 (6.5)	55.9 (5.2)	0.05
Inzitari et al	Motor deficit scale	6.5 (1.39)	5.9 (1.46)	0.003
Barba et al	CNS	5.6 (2.5)	7.6 (1.9)	0.001
Henon et al	Orgogozo>50	21/36	86/133	OR 2.5 (95%CI 1.3-4.8)
Altieri et al	NIHSS	4.8 (4.5)	5.4 (4)	0.40
Lin et al	NIHSS>7	11/26	20/257	0.001
Zhou et al	NIHSS	1.96 (3)	1.85 (3)	0.70
Klimkowicz-M. et al	SSS	42.5 (14.6)	50.7 (9.2)	<0.001
Tang et al	NIHSS	18.8 (8.2)	5.7 (4.3)	<0.001
Srikanth et al	NIHSS	2.3 (2.1)	1.0 (1.7)	0.02
Moulin S et al	NIHSS*	10 (4-16)	7 (3-16)	n/s
Garcia PY et al	Discharge Rankin 0/1/2/3/4-5	0/0/5/4/9	17/18/10/7/8	0.0001
Khedr EM et al	SSS	35.4 (13.9)	42.9 (10.8)	0.019
Selim HA	Orgogozo's scale*	60 (20-100)	70 (5-100)	RR 0.63 (95%CI 0.4-0.97)
Caratozzolo S et al	NIHSS	6.3 (6.3)	5.6 (5.3)	Non-significant
Lim J-S et al	NIHSS	5.0 (5.1)	2.1 (2.5)	<0.01
Delgado C et al	NIHSS			OR1.20 (1.1-1.4)
OxVasc	NIHSS	6.0 (6.1)	4.8 (6.8)	0.004

Table 6.10: Stroke severity in patients with and without post-stroke dementia. SSS=Scandinavian stroke scale; CNS=Canadian neurological scale, NIHSS=National institute of health stroke scale, OR=odds ratio, RR=relative risk n/s=not stated. *median values (interquartile range), †no cognitive decline, ‡cognitive impairment with no dementia. Significance values are taken from individual papers.

Study	Atrophy measurement method	Measured atrophy		Significance
		Dementia	No dementia	
Altieri M et al	Number (%) with moderate or severe atrophy	21/41 (51%)	40/150 (27%)	0.001
Censori B et al	% with cortical atrophy	33.3	31.5	1.000
	% with subcortical atrophy	46.6	29.2	0.297
Pohjasvaara T et al	% with any cortical atrophy	62.7	59.1	0.52
	% with any central atrophy	64.8	47.7	0.004
	% with medial temporal atrophy	40.0	19.6	<0.001
	% with entorhinal atrophy	32.4	12.7	<0.001
	% with hippocampal atrophy	40.0	19.6	<0.001
Sachdev PS et al	Total intracranial volume (cm^3)	1391.72	1406.31†, 1454.51‡	0.854
Klimkowicz-M A et al	Number (%) with moderate or severe atrophy	17/44 (39%)	31/151 (21%)	0.001
Rasquin SMC et al	Presence of cortical atrophy	OR 7.8 (0.9-66.5, p=0.006)		
Cordoliani-M MA et al	Median (range) cerebral atrophy score 0-3	2 (0-3)	1 (0-3)	RR 2.19 (1.5-3.17)
de Koning I et al	% with cerebral atrophy	26%	16%	0.24
Moulin S et al*	Number (%) with moderate or severe atrophy	33/63 (52%)	44/155 (28%)	<0.001$
Yang J et al	Number (%) with global atrophy	49/88 (55.7%)	204/925 (22.1%)	<0.001
Selim HA	Median (range) cerebral atrophy score 0-3	2 (0.3)	1 (0-3)	RR 1.95 (1.12-3.4, p<0.05)

Table 6.11: Cerebral atrophy in patients with and without post-stroke dementia. Studies of post-stroke dementia exclude patients with pre-stroke dementia. OR=odds ratio (95% confidence interval), SD=standard deviation, RR=relative risk. See individual papers for details of atrophy scoring methods. Significance values are taken from individual papers or $calculated from data provided. *Intracerebral haemorrhage study, †no pre-stroke cognitive decline, ‡cognitive impairment with no dementia.

	Number of studies	Patients with factor/total		OR (95% CI)	p value for OR	p value for heterogeneity
		With dementia	Without dementia			
Demographic factors						
Female sex	20	520/1017	1587/3790	1.45 (1.26-1.67)	<0.001	0.398
Low education	12	458/712	1329/2484	1.69 (1.40-2.04)	<0.001	0.163
Family history of dementia	2	4/47	14/169	1.06 (0.33-3.41)	0.926	0.392
Low socio-economic status	3	203/393	695/1416	1.18 (0.94-1.48)	0.158	0.688
Vascular risk factors						
Diabetes	18	224/931	685/3512	1.61 (1.27-2.05)	<0.001	0.144
Atrial fibrillation	10	161/717	401/2415	1.49 (1.21-1.84)	<0.001	0.247
Ischaemic Heart Disease	13	131/857	431/2802	1.02 (0.72-1.47)	0.897	0.012
Peripheral Vascular Disease	4	44/462	127/1468	1.46 (0.68-3.12)	0.329	0.059
Previous TIA	7	87/606	264/2132	1.32 (1.01-1.72)	0.043	0.395
Hypertension	20	1023/1491	3050/4812	1.25 (1.10-1.25)	<0.001	0.106
Smoking	18	254/1010	1223/4124	0.95 (0.71-1.27)	0.733	0.002
Moderate alcohol	10	90/330	466/1332	0.75 (0.56-1.00)	0.048	0.948
Hypercholesterolaemia	10	271/1119	324/1078	1.19 (0.83-1.70)	0.348	0.001
Carotid stenosis	3	31/105	72/369	1.81 (0.71-4.63)	0.216	0.035
Stroke factors						
Haemorrhagic	11	76/747	320/3060	1.11 (0.84-1.46)	0.462	0.171
Dysphasia	6	172/551	321/1751	2.61 (1.69-4.03)	<0.001	0.084
Visual field deficit	3	18/103	37/328	1.82 (0.97-3.42)	0.064	0.966
Left hemisphere	14	362/734	1567/3013	1.65 (1.27-2.14)	<0.001	0.057
Brainstem/posterior	8	82/554	499/1926	0.49 (0.33-0.73)	<0.001	0.246
TOAST: Large artery atherosclerosis	4	44/383	152/1154	0.80 (0.49-1.32)	0.389	0.784
TOAST: Cardioembolic	4	107/383	288/1154	1.15 (0.88-1.49)	0.304	0.829
TOAST: Lacunar	9	139/570	655/2037	0.94 (0.74-1.20)	0.635	0.711
TOAST: cryptogenic/unknown	4	167/383	450/1154	1.18 (0.93-1.49)	0.181	0.323
Previous stroke	18[†]	159/783	325/2663	1.93 (1.56-2.39)	<0.001	0.866
Multiple strokes	3	78/394	187/1225	1.96 (1.02-3.76)	0.043	0.036
Recurrent (interim) strokes	8	111/557	269/1891	1.31 (1.01-1.72)	0.046	0.121
Silent strokes	5	73/181	152/532	1.70 (1.18-2.45)	0.005	0.156
Stroke complications						
Incontinence	4	84/197	93/774	6.92 (4.62-10.35)	<0.001	0.338
Hypoxic Ischaemic episodes	2	24/108	42/395	2.41 (1.38-4.21)	0.002	0.414
Acute confusion	4	161/382	174/1189	4.58 (3.51-5.99)	<0.001	0.405
Early seizures	1	5/16	3/50	7.12 (1.48-34.4)	0.015	n/a
Abnormal EEG	1	45/71	43/109	2.7 (1.4-4.9)	0.002	n/a
Brain imaging factors						
White matter disease	9	315/630	635/1986	2.39 (1.66-3.42)	0.039	0.039
Atrophy	3	128/148	309/451	2.86 (1.14-7.21)	0.025	0.057
Medial temporal lobe atrophy	2	84/122	314/1035	4.20 (2.09-8.44)	<0.001	0.129

Table 6.12: Pooled odds ratios for factors associated with post-stroke dementia for those studies where pre-stroke dementia was excluded.
TOAST= trial of ORG 10172 in acute stroke treatment classification system. N/A=not applicable. OR=odds ratio (95% confidence interval). Previous stroke is history of a stroke before the event that occurred at study entry with [†]3 of the 18 studies also including previous TIA. Recurrent stroke is a stroke occurring on follow-up.

	Age (per year, unless stated)	**Sex / race**	**Low Education**	**Prior stroke**	**Recurrent stroke**	**Vascular risk factors**	**Pre-stroke disability**	**Pre-stroke cognitive impairment**
Desmond et al[26]	**7.8** (3.2-19.3) ≥80 vs 60-65		**3.6** (1.2-10.9)	**1.9** (1.0-3.6)		Diabetes: **2.2** (1.1-4.1)		
Gorelick et al[21]	**1.1** (1.0-1.2)							
Kokmen et al[90]	**2.5** (2.1-2.9) per 10 years	Males: **1.6** (1.2-2.1)			**1.8** (1.2-2.6) [+] **3.8** (1.1-12.9) [++]			
Treves et al[24]	**1.5** (0.7-3.5) age ≥73		**2.3** (1.0-5.5)			Diabetes: **2.6** (1.0-7.2) AF: **2.5** (0.5-20)		
Censori et al[37]	**45.8** (2.9-73) 60-69yrs					Diabetes:**59.4** (4.2-821)		
Pohjasvaara et al[41]			**1.1** (1.0-1.2)	**2.2** (1.1-4.5)				
Inzitari et al[38]	**2.8** (1.4-5.7) age≥72			**2.5** (1.0-6.4)		AF: **2.3** (1.1-5.0)	Rankin>2: **1.5** (1.0-2.2)	
Henon et al[50]	**1.05** (1.0-1.1)					Diabetes: **2.7** (1.1-6.2)		**1.1** (1.0-1.1)
Barba et al[47]	**1.1** (1.03-1.1)					AF: **4.4** (1.4-14.3)		**1.1** (1.03-1.3)
Altieri et al[55]	**3.3** (1.4-7.8) age >65							
Lin et al[56]	**6.6** (1.6-26.6) age ≥65			**3.1** (1.1-8.8)				
Zhou et al[61]	**1.2** (1.1-1.2)		**2.2** (1.2-4.1)	**3.3** (1.72-6.2)		AF: **3.5** (1.6-7.5)		
Klimkowicz-M. et al[65]	**1.1** (1.1-1.2)					Diabetes: **3.3** (1.2-9.0)		
Tang et al[89]			**1.2** (1.0-1.3) Per year less					**14.7** (2.3-93.3)
Sachdev et al[57]	**1.06** (1.0-1.1)							**1.3** (1.0-1.6)
Rasquin et al[67]	**3.1** (0.6-15.6) age >70 years		**8.7** (1.3-60.3)	**7.4** (1.1-47.2)[+]				
Patel et al[102]	**2.5** (1.51-4.25) age ≤75 vs ≤65	Race: **1.9**[#] (1.2-3.2) **3.4**[##] (1.1-10.2)						
Srikanth et al[98]	**2.5 (1.4-5.5)** per 10 years				**13.3** (1.7-107.8)			**12.4** (3.5-44.3)
Moulin S et al[†,70]	**1.84** (1.43-2.38) per 10 years			**2.75** (1.43-4.62)**	**3.22** (1.27-8.15)			
Mirza SS et al[95]			**1.46** (1.18-1.81)					
Delgado C et al[72]							**4.08** (1.6-10.0)	
Lim J-S et al[76]								**3.56** (1.17-10.83)
Caratozzolo S et al[85]	**1.1** (1.0-1.2)							**0.05** (0.0-0.9)
Yang J et al[81]	**1.13** (1.09-1.17)					Diabetes: **1.90** (1.15-3.16)		
Selim HA[$,77]								**1.87** (1.09-2.45)
OxVasc[10]	**1.08** (1.07-1.10) per year. **4.58** (3.62-5.80) for age ≥ 75 years		**1.63** (1.30-2.05)			Diabetes: **1.53** (1.18-1.98)	**1.63** (1.29-2.05) for mRS≥3. **1.50** (1.20-1.87) for Barthel<20.	

Table 6.13 (a): Independent factors associated with post-stroke dementia: Demographic factors. Odds Ratio (95% confidence interval) *Correlated to Mattis dementia rating scale, [+]for second stroke, [++]for fourth stroke, [#]for black vs white, [# #]for Asian (Indian subcontinent origin) vs white, **prior stroke or TIA, [†]intracerebral haemorrhage study, [$]adjusted hazard ratios presented instead of odds ratios. CI=cognitive impairment, mRS=modified Rankin Score

	Left hemisphere	Major hemisphere syndrome	Aphasia	Acute confusion	Bilateral / multiple lesions	Incontinence	Stroke severity	White matter disease	Atrophy	Early post stroke seizures
Desmond et al[26]	**3.6** (1.4-9.3)	**3.4** (1.6-7.6)								
Kokmen et al[90]										
Treves et al[24]			**5.0** (1-21)	**5.7** (1.3-22.8)						
Censori et al[37]		**30.0** (2.7-334.0)	**14.8** (2.0-111.0)							
Pohjasvaara et al[41]		**3.5** (1.2-10.7) (dominant)	**7.2** (2.5-23.7)							
Inzitari et al[38]			**2.23** (1.1-4.4)			**3.3** (1.6-6.6)				
Henon et al[50]					**2.2** (1.0-4.5)[+]		**0.98** (0.97-0.99) Orgogozo <50	**1.6** (1.1-2.2)		
Barba et al[47]							**0.5** (0.4-0.6) CNS			
Altieri et al[55]					**2.5** (1.2-4.8)			**1.5** (0.5-3.1)	Global atrophy: **3.4** (1.5-7.9)	
Lin et al[56]	**12.5** (1.4-110.2)						**3.4** (1.1-10.9) NIHSS>7			
Zhou et al[61]	**2.0** (1.1-3.6)		**8.1** (3.4-19.0)							
Klimkowicz-M. et al[65]							**0.9** (0.9-1.0) SSS			
Tang et al[89]					**2.9** (1.2-7.5)			**1.2** (1.0-1.5)		
Sachdev et al[57]							**0.94** (0.88-0.99) ESS			
Patel et al[102]	**1.6** (1.0-2.4)					**4.8** (3.2-7.3)				
Moulin S et al[†,70]							**1.20** (1.05-1.36) per 5 point increase in NIHSS	**2.88** (1.63-5.07) for score ≥3**		
Delgado C et al[72]		**6.90** (1.2-40.0)[#]						**1.30** (1.05-1.53)		
Lim J-S et al[76]							**1.16** (1.05-1.28)			
Caratozzolo S et al[85]									MTLA: **0.6** (0.4-0.9)	
Yang J et al[81]								**1.08** (1.02-1.16)	MTLA: **2.24** (1.25-4.01)	
Selim HA[$,77]							**0.9** (0.85-0.99) Orgogozo's score			**1.95** (2.31-11)
Garcia PY[†,69]							**3.5** (1.7-6.9) for discharge Rankin			
OxVasc[10]				**3.22** (2.53-4.10)	**1.78** (1.16-2.71)		**1.12** (1.10-1.13) per NIHSS point	**1.49** (1.22-1.82)		

Table 6.13 (b): Independent factors associated with post-stroke dementia: Stroke/imaging factors. Odds Ratio (95% confidence interval) *correlated with Mattis dementia rating scale, [+]silent infarcts, **Fazekas scale, [†]intracerebral haemorrhage study, [#]left hemispheric large vessel occlusion . CNS=Canadian neurological scale, NIHSS=National institutes of health stroke scale, ESS=European stroke scale, SSS=Scandinavian stroke scale, CI=cognitive impairment, MTLA = medial temporal lobe atrophy

	Dementia / total	Prev (%)	95% CI	p value for heterogeneity	Age (yr)	P/H	Diagnosis Method	Country
First TIA								
Yang J et al	6 / 141	4.3	0.9-7.6		69*	H	DSM-IV	China
Ihle-Hansen H et al	2 / 28	7.1	-2.4-16.7		72*	H	ICD-10	Norway
OxVasc	20 / 529	3.8	2.2-5.4		71	P	DSM	UK
Total	**28 / 698**	**4.1**	**2.7-5.7**	0.570				

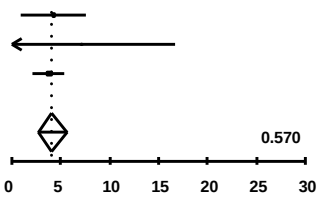


Figure 6.8 (a): Prevalence of post-TIA dementia (up to the first year) after their first event (excluding pre-stroke dementia). The mean age of the patients in each study, the method of dementia diagnosis and country of study are also presented. Bars indicate 95% confidence interval (CI). n/s=not stated. P=population-based study. H=hospital-based study. *age of TIA patients alone not stated, so overall mean age of cohort presented.

	Study cohort	Time	Dementia / total		Odds Ratio (95%CI)	p value	p value for heterogeneity
			TIA	Ischaemic stroke			
Yang J et al	H,F,E	3-6m	6/141	68/800	0.48 (0.20-1.12)	0.091	
Ihle-Hansen H et al	H,F,E	12m	2/28	27/140	0.32 (0.07-1.44)	0.138	
de Koning*	H,A,I	3-9m	0/25	27/77	0.04 (0.00-0.61)	0.022	
de Koning**	H,A,I	3-9m	3/46	39/203	0.29 (0.09-1.00)	0.049	
OxVasc	P,F,E	12m	20/529	134/1051	0.27 (0.17-0.44)	<0.001	
Total			**36/841**	**310/2370**	**0.28 (0.19-0.41)**	**<0.001**	**0.132**

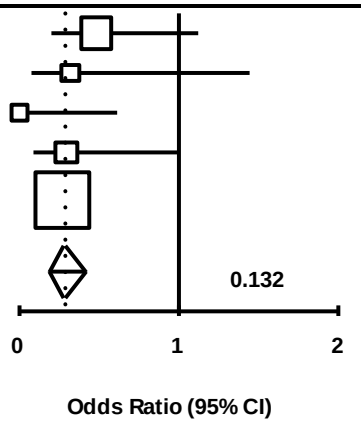


Figure 6.8 (b): Odds ratio of post-event dementia (up to 1 year) for Transient Ischaemic Attack (TIA) patients compared with ischaemic stroke patients. Studies exclude pre-event dementia. H=hospital-based study, P=population-based study, F=first stroke, A=any (first or recurrent) stroke, I=includes pre-stroke dementia, E=excludes pre-stroke dementia, m=months. Mean age (standard deviation) of OxVasc TIA patients = 72.5 (12.8) years vs 74.1 (76.4) years for ischaemic stroke patients (p=0.007). Breakdown of ages for the two cohorts in Yang J et al, de koning* and **, and Ihle-Hansen H et al not provided. *de Koning 2005, **de Koning 1998.

CHAPTER 7

POTENTIAL IMPEDIMENTS TO TELEPHONE COGNITIVE ASSESSMENTS: A SYSTEMATIC REVIEW AND OBSERVATIONS FROM THE TIME-COG STUDY

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7.1 Abstract

Introduction: Telephone forms of cognitive assessment are a convenient and cost-effective method of screening and monitoring cognition. However, there is little literature on the possible difficulties and limitations of using these tools.

Methods: I completed a systematic review in order to assess the reporting of potential impediments, the feasibility and the reliability of telephone cognitive assessments. Studies were eligible for inclusion if they used a standardised cognitive assessment that was administered via the telephone to adults. I then assessed the prevalence and impact of potential impediments reported during a study of older adults (age ≥70 years) who had completed both the modified - Telephone Interview for Cognitive Status (TICS-m) and the Telephone – Montreal Cognitive Assessment (T-MoCA) during an ongoing trial of blood pressure lowering (TIME-COG).

Results: Overall, 206 studies that utilised a telephone based cognitive assessment were included (including 16 feasibility studies and 70 validation studies). Only 17% (n=35) of studies reported any potential impediments and 74% of studies did not report a hearing requirement for inclusion in the study. Where reported hearing impairment accounted for up to 8% of participants subsequently excluded and was associated with lower cognitive scores when compared with face-to-face assessment. In the 1003 older adults who completed the TICS-m and T-MoCA in the TIME-COG study a potential impediment was reported during 10% of the baseline assessments. However, apart from hearing impairment being associated with a longer duration of the T-MoCA no other association with the overall scores or study withdrawal was detected.

Conclusion: Telephone cognitive assessment tools provide a pragmatic method of screening cognition though caution should be applied in using such tools in older populations with high rates of hearing impairment. However, whilst there is limited reporting of the other

impediments in using these tools, at least in TIME-COG, other potential impediments do not appear to have a significant impact upon the recruitment, retention or overall scores obtained.

7.2 Introduction

Telephone forms of cognitive assessments are increasingly being recognised as a convenient method for studying larger populations. Utilisation via telephone potentially facilitates testing across greater geographical areas, often at increased convenience to both examiner and examinee. Decreasing mobility, increasing frailty, carer constraints, lack of public transport, lack of personal finances, cognitive impairment and other medical comorbidities all could impact upon the ability to physically bring a patient to the clinic. Most recently the novel coronavirus-19 has led to dramatic changes in the delivery of healthcare worldwide and a need for better understanding of the potential and limitations of remote assessments. Furthermore, face-to-face assessments can be particularly burdensome when required to be repeated serially such as in longitudinal research studies. Telephone based assessments potentially provide a more convenient, and cost effective, way for studies and hospitals to assess cognition.

Yet, whilst there are multiple reviews on the different telephone based screening tools for cognitive impairment, there is little literature on the possible difficulties and limitations of using these tools.[1-5] Hearing impairment may have a different impact when the ability to read lips or write down instructions such as in a face-to-face assessment is removed. Similarly, during a telephone assessment the assessor has limited ability to control the participant's environment such as removing temporal cues and ensuring no interruptions and this also limits the ability to detect participants cheating by writing down notes during the test therefore impeding the test accuracy.

Therefore, within this chapter, firstly I aim to describe the reporting of impediments, together with the feasibility and reliability of telephone cognitive assessments in the published literature. Secondly I aim to describe the prevalence and the impact of potential impediments in

telephone testing in an ongoing longitudinal study (TIME-COG) utilising telephone cognitive assessment tools.

7.3 Methods

7.3.1 Systematic Review

To identify studies that used a telephone cognitive assessment I searched Ovid Medline (1946- 5th November 2020), EMBASE (1974 – 5th November 2020) and PsychInfo (1806 – 5th November 2020) using a comprehensive search strategy (figure 7.1). Relevant review articles were hand-searched for further studies. Studies were included if they used a standardised cognitive assessment tool administered via a telephone to assess cognitive function in adults. All types of studies were eligible: randomised controlled trials, cohort studies, case-control studies, cross-sectional studies and qualitative studies. Studies were excluded if the telephone cognitive assessment was administered face-to-face, if it involved video or other remote assessment tools or if a proxy or informant interview was used. Studies in which only a proportion of the assessments were performed via telephone were included only if the telephone data could be extracted from the whole dataset. Studies for which an English translation was not available were also excluded. Where there were multiple papers reporting on the same dataset the paper reporting in greatest detail on the method of delivery of the telephone cognitive assessment was included. Where available the study protocol or standard operating procedure was also reviewed.

Data on assessment tool used, hearing assessments, participant eligibility, reporting of impediments in telephone cognitive assessments encountered and measures taken by the study to reduce impediments, were extracted. Where the study involved serial telephone cognitive assessments, data on whether they were performed under the same circumstances (e.g. same time-of-day, same assessor) were extracted.

7.3.2 TIME-COG Study

TIME is an ongoing study to assess whether nocturnal dosing of antihypertensive medication reduces cardiovascular events compared with conventional morning dosing.[6] The study was advertised at collaborating general practitioners and participants were directly contacted through registered research network practices. All participants aged over 18 years who were both diagnosed and treated for hypertension (all forms) and had a valid email address were eligible for inclusion. Exclusion criteria included twice daily antihypertensive therapy, shift work pattern that included a night shift, those unwilling to be followed up, those who did not permit review of their medical records and those who had participated in another clinical trial of an investigational medicinal product within the last 3 months. Participants of all cognitive levels (whether known or unknown impairment) were eligible for enrolment, however, due to the trial design it was suspected that those with significant cognitive impairment would not volunteer. There were no exclusion criteria specifically related to a participants' medical history and details regarding prior cerebrovascular and cardiovascular events were collected at baseline. Participants participated by self-registering on a study-specific website (www.timestudy.co.uk) and were then randomised to a dosing time (morning versus evening). The feasibility of the largely automated system was validated in a pilot study of 355 participants.[7] In the pilot study the participants had a mean age at randomisation of 61 years, and a 10 year risk of cardiovascular events of 21%.[7]

The TIME-Cognitive function (TIME-COG) sub-study aims to detect any potential temporal change in cognition which may occur as a result of evening-dosing. Participants recruited to TIME, and who were over the age of 70 years, were invited to participate in the sub-study at the time of entry to the main trial (Appendix X, XI). All were eligible, though as it was advertised as a telephone study it was suspected that those with significant hearing impairment would not volunteer for the sub-study. Telephone cognitive assessments including Montreal Cognitive Assessment (T-MoCA) and the Modified Trends in Cognitive Sciences (TICS-M) were performed at baseline, 6 months, 1 year, then annually until the conclusion of the study

(Appendix VIII, IX).[8,9] The T-MoCA and TICS-M have both been validated in general and in post-TIA / stroke populations.[8-10] Reliability of diagnosis for multi-domain mild cognitive impairment for a post TIA/stroke population is good (area under the ROC curve: T-MoCA=0.85, 95% CI 0.75-0.96; TICS-M=0.83, 0.70-0.96).[9] The T-MoCA is scored out of 22 points (delayed recall: 5, orientation: 6, attention: 6, language: 3, abstraction 2) with a cut off of <19 for the detection of multi-domain mild cognitive impairment.[9] The TICS-M is scored out of 39 points (immediate memory:10, delayed recall: 12, orientation: 7, attention: 6, language: 1, abstraction: 3) with a cut-off of <25 for detection of multi-domain mild cognitive impairment.[9]

The assessments were performed on a participant each time by the same assessor and at the same time-of-day as the previous assessments in order to minimise confounders. Telephone assessments were performed by researchers experienced in both telephone cognitive and face-to-face cognitive assessments (S.W, F.C, A.M.H, S.C) blinded to the timing of the drug dosing. The assessor was asked to record any potential impediment they noted, or the participant reported, that occurred during the assessments. No formal hearing assessment was performed for the study and the description of whether a participant was hearing impaired was left to the discretion of the assessor. Low education was defined as self-reporting 12 years or less of formal education. Further details about TIME-COG including the power calculation used to determine the sample size are detailed in Chapter One. As TIME is an ongoing study additional baseline variables and treatment allocation were not available at the time of this analysis.

7.3.3 Statistical Analysis

As it was qualitative in nature no statistical analysis was performed for the systematic review.

For the TIME-COG analysis the baseline characteristics and cognitive scores of the participants in the different groups were compared with $\chi 2$ or independent T tests. To adjust for potential confounders on the impact of a potential impediment on cognitive scores multivariate linear regression modelling was used. To adjust for potential confounders on the

impact of a potential impediment on whether a participant withdrew from the study after their baseline assessment multivariate logistic regression modelling was used.

7.4 Results

7.4.1 Systematic Review

The literature search provided 9874 articles (including 716 duplicates) with a further 9 articles identified through hand-searching of review articles. 8413 were not relevant based on title review. However, after abstract and subsequent full text review, 206 were eligible for inclusion.[8,9,13,14,16-23,25-30,32-218] Reasons for exclusion (after title review) included: 196 (35%) reporting from a duplicate cohort, 144 (25%) no cognitive assessment performed, 109 (19%) assessment performed face-to-face, and 35 (6%) involving other forms of cognitive assessment (such as video-conferencing or computerised assessment) (figure 7.2).

Of the 206 studies, 88 were cohort studies, 70 validation studies, 16 feasibility studies, 12 cross-sectional studies, 11 randomised control trials, 7 case-control studies and 2 multiple purposes (1 validation / cohort study, 1 feasibility / cohort study) (table 7.1)

In the feasibility studies, where reported, the proportion of eligible recruited ranged from 69% to 88%.[32,34,65,68,69,75,102,131,137,162,171,173,186,193,218]

Choice of Cognitive Assessment Tool

79% (164/206) of studies used a single form of telephone cognitive assessment whereas 21% used more than one or a detailed neuropsychological battery. The different (single) cognitive assessment tools and their relevant validation studies are shown in table 7.2 and 7.3. The most commonly used assessment tool was the Telephone Interview for Cognitive Status (including TICS, TICS-M, translated versions, abbreviated versions) accounting for 43% (89/206) of all studies. Other commonly used single cognitive assessment tools included the Brief Test of Adult Cognition by Telephone (BTACT, 3/206 studies), telephone versions of the Mini-Mental State Examination (MMSE, 11/206 studies), and telephone versions of the Montreal Cognitive Assessment (MoCA, 7/206) (table 7.4). However, randomised control trials

were more likely to use a neuropsychological battery (7/11 studies) rather than a single screening tool.

Reporting of (Potential) Impediments

74% (153/206) of studies made no mention of a hearing requirement in their participant selection criteria (table 7.5). Of these only 5 studies reported using a proxy interview where the participant's hearing was insufficient to permit telephone assessment.[14,38,59,86,216] When hearing was mentioned in the participant selection criteria the requirements were diverse with 15 studies[56,82,91,106,149,158,165,167,183,189,193,196,202,213,214] requiring adequate hearing for telephone assessment but 5 studies[29,50,116,152,191] requiring adequate hearing only for face-to-face assessments. 15 studies[23,33,48,58,55,93,113,121,154,160,180,181,185,198,208] excluded participants with severe hearing impairment or deafness but 11 studies[28,32,36,97,118,151,153,155,166,194] excluded participants with any hearing impairment. Only 8 studies used a hearing test prior to their telephone cognitive assessment ranging from face-to-face screening of hearing to the ability to accurately repeat 3 words.[20,27,69,79,83,114,126,196] One of the studies that used a hearing test was specifically to assess the impact of hearing impairment on a telephone cognitive assessment and therefore performed a detailed audiometric test.[79]

Where reported the proportion of participants that subsequently had to be excluded due to hearing difficulties on testing ranging from 0.1% to 11% of participants.[68,82,118,130,140,151,153,166,181] Four studies reported the proportion of participants with subjective hearing impairment, who completed assessments, ranging from 21% to 50%.[30,75,127,173] Four studies reported no correlation between T-MMSE, TICS-M, T-MoCA and SPMSQ scores and subjective hearing impairment.[17,18,93,173] However, one study compared ALFI-MMSE scores completed over the telephone to face-to-face assessments and found that telephone scores were on average approximately 1 point less in those with self (or informant) reported hearing impairment.[30] Another study correlated the self-reported hearing impairment with neuropsychological battery sub-domains and reported that subjective hearing impairment negatively correlated with

scores on episodic memory, reasoning, verbal fluency and working memory and positively correlated with reaction time latencies.[19] In a study specifically on hearing impairment the percentage hearing loss on audiometric testing was found to correlate with lower cognitive screening scores and accounted for significant proportion of the variance between face-to-face and telephone assessments.[79]

Overall 17% (35/206) of studies reported on (some) impediments encountered during completion of telephone cognitive assessments (table 7.1). Where mentioned, aside from hearing impairment there were few other impediments reported.[30,38,42,71,83,135,118,188] In a large population-based study of 14,435 individuals aged 65 years and over they found that 5% of interviews could not be completed over the telephone due to deafness, illness or dementia.[71] In the secondary analysis of the ADAPT randomised controlled trial, 8% of participants were excluded as at least one of the telephone cognitive assessments were rated as of questionable validity (e.g. hearing problems, interruptions during testing, physical or emotional illness that interfered with completion of testing).[135] In a post-stroke study, 29% of interviews could not be completed over the telephone (11% aphasia, 7% not native language, 5% frailty / fatigue, 4% confused, 2% hearing impaired).[38] Other issues identified by studies including access to a telephone (accounting for 10% of excluded participants in a study on rehabilitation), and the participant inappropriately receiving assistance from other people (affecting up to 5% of tests in a population study of participants aged 65 years and older).[42,118]

Only 9% (19/206) of studies reported on the measures taken to reduce potential impediments to the telephone cognitive assessment.[18,22,29,34,37,49,61,94,101,102,127,155,161,180,189,194,197,204,218] These included asking participants not to write anything down, asking them to use a hardwired telephone line, sit in a quiet room, ensure no temporal information within easy reach, turn off media and ignore call-waiting. Two studies used family members to reduce potential impediments for example by asking them to confirm the environment was suitable for testing, remove any distractions / aids (such as clocks) and/or sit beside to ensure the participant didn't cheat.[29,127]

31% (64/206) of studies involved repeat telephone cognitive testing as part of their study protocol of which none reported ensuring the same test conditions (e.g. same time-of-day, same environment) for their serial tests. Four of the 64 did report using the same assessor for the repeat tests.[88,97,198,208]

Validity and Test-Retest Reliability of Telephone Cognitive Screening Assessments

(A) Telephone Interview for Cognitive Status (TICS, TICS-M)

25 studies were identified which were used to validate the TICS, TICS-M or a translation version.[8-10,13,39,49,53,56,64,73,76,78,79,82,92,93,98,105,107,113,116,117,125,161,182] Overall, TICS (and its modified and translated versions) demonstrated high sensitivity to detect participants with dementia. In the original validation cohort of 100 participants with Alzheimer's disease and 33 control participants the TICS showed strong correlation with face-to-face MMSE scores (0.94, $p<0.001$).[8] Even when limiting the analysis to participants with mild dementia the TICS still showed good discriminatory ability (sensitivity 94%, specificity 100%).[8] However, it is was slightly less sensitive in its ability to detect mild cognitive impairment with sensitivity of 82% and specificity of 87%.[93] With a large population-based screening to enrol participants in a subsequent clinical trial reporting that the TICS had a positive predictive value of 51% for mild cognitive impairment (subsequently diagnosed by a face-to-face neuropsychological and clinical assessment).[78] Five validation studies reported on the test re-test reliability of the TICS (or one of its versions) with good agreement when the test was repeated between 1 to 6 weeks later (coefficient of reliability values ranging from 0.73 to 0.97).[8,39,73,88,116] The TICS has been validated in German, Hebrew, Italian, Japanese, Korean and Portuguese languages and additionally in post-stroke patients.[9,39,53,73,82,88,116,117, 161]

(B) Brief Test of Adult Cognition by Telephone (BTACT)

BTACT is a battery of neuropsychological tests that have been adapted for telephone administration including immediate recall of a 15-word list, backward digit span, category fluency test, number series completion, backward counting task and delayed recall of the 15-word list.[27] Two studies were identified that have validated the BTACT.[27,115] In the original

validation study of 75 community-dwelling individuals the BTACT reported an average correlation across cognitive sub-domains with face-to-face neuropsychological testing of 0.74.[27] However, the BTACT correlated less well (correlation coefficient = 0.32–0.51) when compared to a face-to-face neuropsychological battery in participants with traumatic brain injury.[115] When the test was repeated within 4 weeks the test-retest correlation coefficients ranged from 0.84 to 0.87.[27]

(C) Telephone Mini Mental State Exam (T-MMSE, ALFI-MMSE, TCogS, T3MS)

Nine studies were identified that were used to validate a telephone version of the MMSE (T-MMSE, ALFI-MMSE, TCogS, T3MS, translated versions).[25,30,43,48,97,114,143,208] In the original validation study of 100 participants referred to a geriatric assessment centre, the ALFI-MMSE demonstrated good correlation with a face-to-face MMSE (Pearson's r=0.85) and good sensitivity for detection of dementia compared with face-to-face neuropsychological screening (sensitivity 67%, specificity 100%).[30]Two validation studies reported on the re-test reliability of a telephone version of the MMSE with good agreement when the test was repeated within 4 weeks (both reporting coefficient of reliability values of 0.99).[97,208]The T-MMSE has been validated in Turkish, Brazilian, Italian, and Cantonese languages.[48,97,114,208]

(D) T-Montreal Cognitive Assessment (T-MoCA, 5 minute MoCA, MoCA-BLIND)

Four studies were identified that were used to validate a telephone version of the MoCA.[9,29,182,217] The T-MoCA and MoCA-Blind are similarly scored out of 22 with the 5-minute MoCA scored out of 30. Three of the studies[9,29,182] were in post-stroke participants and one study[217] in participants with Parkinson's disease. For the T-MoCA, a score of less than 18 gave a sensitivity for detecting mild cognitive impairment at 81% and specificity 59% in post-stroke patients and 56% and 92% respectively in Parkinson's disease participants.[9,217] No study was identified on the test re-test reliability, validation in an unselected population nor on a translated version.

7.4.2 Findings from the TIME-COG study

Of the 1027 participants enrolled in TIME-COG 24 (2.3%) withdrew prior to their baseline assessments and a further 91 (8.9%) withdrew or failed to complete their 6-month assessment. The most common reason reported for failing to complete the assessments was patient choice with the reasons shown in figure 7.3. Three (0.3%) participants were excluded prior to the baseline assessment as their hearing was deemed by the assessor as insufficient to complete the assessments.

Of the 1003 participants that completed a baseline assessment in 97 (9.7%) one or more potential impediments were reported. There were no differences in age, sex or education level for those participants with or without a potential impediment (table 7.5). The most frequently reported potential impediment was hearing impairment affecting 7.0% of assessments overall, followed by a significant bereavement (0.8%) and a first language other than English (0.6%) (table 7.6).

Whilst increasing age, male gender and low education were associated with lower baseline assessment T-MoCA and TICS-M scores (T-MoCA all $p<0.001$, TICS-M all $p<0.001$), even after adjusting for these factors, the presence of a potential impediment was not (T-MoCA: $p=0.514$, TICS-M: $p=0.358$) (table 7.5 & 7.7). Furthermore, the presence of a potential impediment was not associated with whether a participant withdrew from the study after the baseline assessment (age / sex / education / baseline T-MoCA score adjusted OR: 0.41, 96% CI 0.15-1.15, $p=0.089$) (table 7.8).

A sub-group analysis of the 70 participants in whom hearing impairment was recorded was performed comparing with the 906 participants in whom no impediment was reported. No difference in the overall baseline scores was detected (table 7.8). There were small differences noted in sub-domains with those with a hearing impairment scoring lower on TICS-M abstraction (mean (s.d) = 2.91 (0.41) vs 2.97 (0.16), $p=0.015$) but higher on T-MOCA orientation (5.94 (0.23) vs 5.84 (0.39), $p=0.030$). Those with a hearing impairment took longer to complete the T-MOCA assessment compared with those without an impediment (mean

duration (s.d) = 7.48 (1.38) mins vs 6.88 (1.13) mins, p<0.001). However, this difference was not noted on the TICS-M assessment (hearing impairment: 2.99 (0.71), no impairment: 2.84 (0.79), p=0.148) (table 7.9).

7.5 Discussion

Overall, the majority of studies utilising telephone cognitive assessments did not report on the prevalence or impact of impediments. However, the TIME-COG study suggests that about 10% of telephone assessments are afflicted by a potential impediment, which as this was a volunteer-based study is likely to be lower estimation of what should be expected in a population-based study. Fortunately, in general, in the TIME-COG study the presence of a potential impediment during a participant's telephone assessment (such as interruptions, poor phone line, fatigue) did not have a significant impact upon the study results overall. Therefore, at least in a highly selective volunteer study population it does not appear to be a major problem. The most frequently reported potential impediment in the TIME-COG study was subjective hearing impairment. This is unsurprising given that hearing loss affects around 40% of those aged 71-80 years in the UK.[11] Despite this three quarters of studies in the systematic review failed to report any mention of a hearing requirement in their selection criteria. For studies where participants volunteer for a telephone based assessment if their hearing was sufficiently impaired it is likely they would self-select to not participate. Though, even in the TIME-COG study three participants had to be excluded at baseline due to hearing impairment that prohibited telephone assessments. Where the study is, for example, population-based screening, or for subsequent follow-up of a previously recruited cohort, participants with hearing impairment are likely to be more prevalent. Furthermore, both the systematic review and the TIME-COG study suggested an impact of hearing impairment upon score results. In the systematic review face-to-face scores were higher than telephone scores in those with an impairment and telephone scores correlated with percentage hearing loss. In TIME-COG whilst there was no significant effect on the TICS-M and T-MoCA scores hearing impairment was associated with a longer duration of testing for the T-MoCA. No impact on duration was

seen for the TICS-M though this was likely due to its shorter nature and suggests that perhaps a more significant impact of hearing impairment may be detectable on lengthier telephone neuropsychological testing.

Both the systematic review and the TIME-COG study demonstrated that telephone cognitive assessments are a feasible method of assessing cognition with good recruitment and retention rates. Studies that did report on the proportion of participants that were unable to complete the telephone assessments gave similar reasons to studies of face-to-face assessments such as aphasia, loss of contact or physical illness. This suggests that, apart from hearing impairment, telephone cognitive assessments provide no additional barrier to assessment than a face-to-face assessment would. However, a telephone cognitive assessment by its nature requires a telephone[12] and whilst almost ubiquitous, certain populations may be disadvantaged such as those of no fixed abode and in certain countries, e.g Nigeria, ownership being skewed towards those of higher education.[12]

The most commonly utilised single cognitive assessment tool in the systematic review was the TICS. Originally designed in 1988, this has now been validated in the general population, in participants with mild cognitive impairment, Alzheimer's dementia and post-stroke and in translated and adapted into multiple languages.[8] Other tools, including the telephone versions of the MMSE and MoCA have been validated in fewer studies and for the MoCA in particular require validating in a general population. Furthermore, all of the telephone cognitive assessment tools are limited in their ability to assess visuospatial deficits. This is perhaps why in the T-MoCA validation study for mild cognitive impairment in some conditions the sensitivity was found to be only around 50%.[217]

This study has numerous limitations. With regards to the systematic review it must be noted that it is a review of what is reported and as such is biased towards what is written rather than what occurred. Whilst only 9% of studies reported on measures implemented to reduce the impact of potential impediments many studies may have had protocols in place but did not include them in their final draft. Protocol papers were found for less than 10% of studies

reviewed. Many of the studies included did not validate against a face-to-face assessment of the same tool but instead against a neuropsychological battery which limited the assessment of the impact of the telephone modality itself. With regards to the TIME-COG study no formal hearing assessment was undertaken. As such, varying degrees of impairment may have been collated potentially nullifying the impact of more significant hearing impairment. Furthermore, no face-to-face assessment was undertaken so their validation could be assessed. Due to the TIME-COG protocol the serial telephone assessments were all completed by the same assessor which means that the impact of a different assessor on the scores could not be assessed. Finally, the TIME-COG study is a volunteer based study and as such is likely to attract participants who possess sufficient cognitive, communication and hearing ability in order to complete a telephone assessment and may not be wholly representative of the general older population.

7.6 Conclusion

Telephone cognitive assessment tools provide a feasible and, in general, reliable method of screening cognition. However, potential impediments may be encountered during telephone assessments but there remains limited reporting of these impediments in studies. Particular attention should be given to the presence of a hearing impairment as whilst participants with severe hearing impairment may chose not to complete a telephone assessment, even the presence of milder impairments may still impact upon the score and time to complete the assessment.

7.7 References

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Embase
exp telephone interview/ or exp telephone/ or exp telephone telemetry/
exp cognition assessment/ or exp cognition/
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cognitive impairment.mp.
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MEDLINE
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telephone interview.mp.
exp Remote Consultation/
Cognition Disorders/ or Cognition/ or cognition.mp.
exp Neuropsychological Tests/ or exp Cognitive Dysfunction/ or exp Cognition Disorders/ or exp Cognition/
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PSYCHINFO
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exp cognition/ or exp cognitive impairment/
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Figure 7.1: Search strategy for systematic review on the reporting of potential impediments to telephone cognitive assessments.

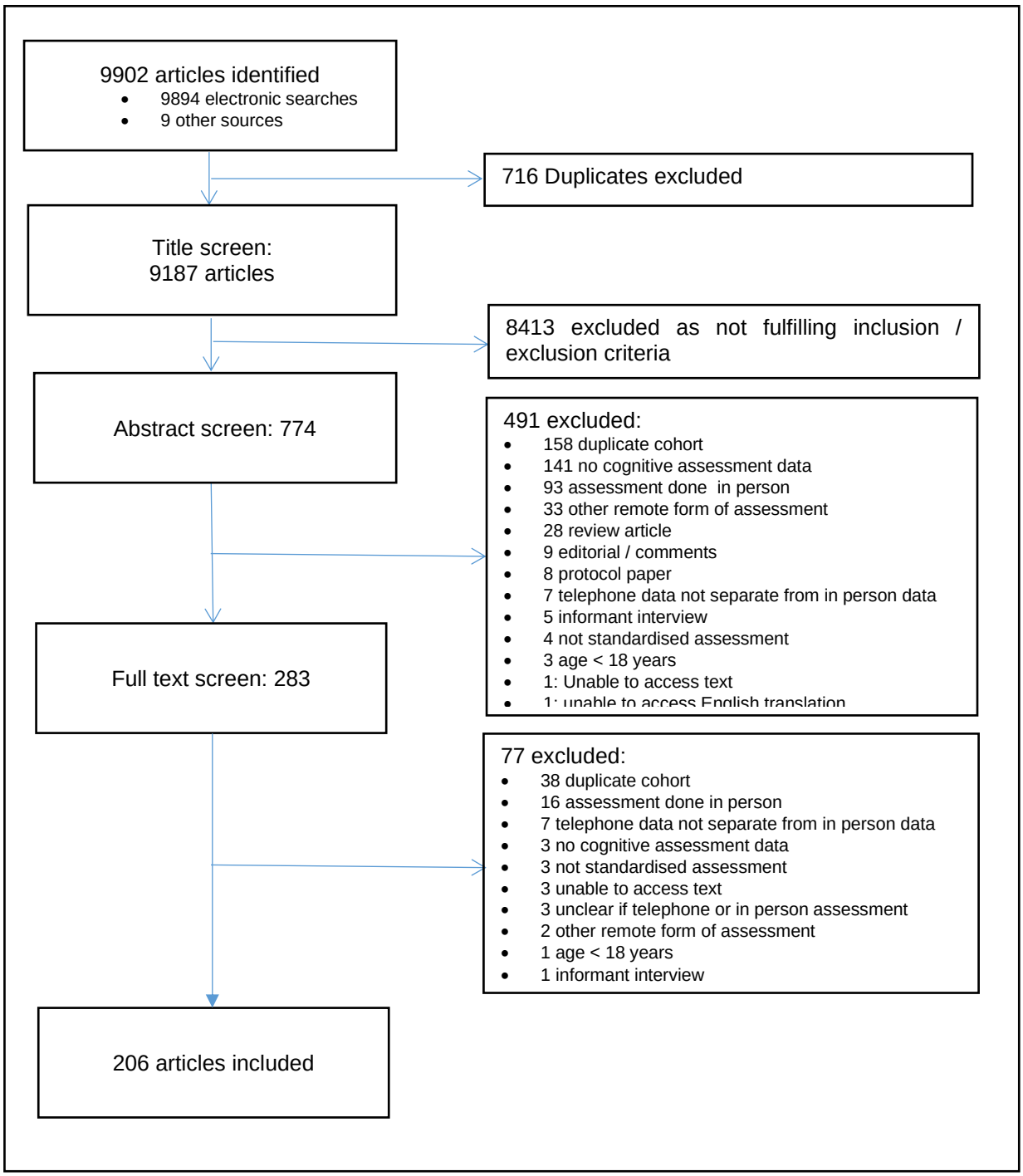

Figure 7.2: Literature search results.

	Year of publication	Longitudinal Study (if appropriate)	Type of study	Tool used	Potential impediment reported
The telephone interview for cognitive status.[8]	1988		V	TICS	N
Validation of a telephone version of the mini-mental state examination.[30]	1992		V	ALFI-MMSE	Y
Detection of dementia in the elderly using telephone screening of cognitive status.[13]	1993		V	TICS-M	N
Telephone-Assessed Mental State.[21]	1993		V	TAMS	N
Health-related information post discharge: Telephone versus face-to- face interviewing.[38]	1994		X	SPMSQ	Y
Reliability and validity of the Short Portable Mental Status Questionnaire administered by telephone.[17]	1994		V	SPMSQ	Y
The telephone interview for cognitive status (TICS): Reliability and validity in a stroke sample.[39]	1994		V	TICS	N
An empirical test of telephone screening to identify potential dementia cases.[14]	1995	From Southern California Alzheimer's Disease Research Center registry	V	TELE	N
Reliability of the blessed telephone information-memory-concentration test.[22]	1995		V	Blessed IMC	N
Intermodal agreement of follow-up telephone functional assessment using the Functional Independence Measure in patients with stroke.[40]	1996		X	FIM-COGNITION	N
Telephone and in-person proxy agreement between stroke patients and caregivers for the functional independence measure.[35]	1996		V	FIM-COGNITION	N
Development and validation of a structured telephone interview for dementia assessment (STIDA): The NIMH genetics initiative.[16]	1997		V	STIDA	N
Validation of a telephone cognitive assessment battery.[23]	1997	From University Alzheimer Centre Research Registry	V	TCAB	N
Diagnosing delirium by telephone.[41]	1998		C	T-MMSE	N
Recovery and rehabilitation following subarachnoid haemorrhage: Part II. Long-term follow-up.[42]	1998		X	TICS	Y
Reliability of routine clinical instruments for the assessment of Alzheimer's disease administered by telephone.[43]	1998		V	T-MMSE, BRCS	Y
Telephone adaptation of the Modified Mini-Mental State Exam (3MS). The Cache County Study.[25]	1999	The Cache County Study	V	T-MMSE	N
Association of Alzheimer's disease and smoking: the case for sibling controls.[44]	2000		C	TCAB	N
Development and standardization of a new telephonic cognitive screening test: The Minnesota Cognitive Acuity Screen (MCAS).[19]	2000		C	MCAS	N
Assessing traumatic brain injury outcome measures for long-term follow-up of community-based individuals.[45]	2001		C	FIM-COGNITION	N
Impact of maintenance ECT on concentration and memory.[46]	2001		C	Battery	N
Reliability of a telephone-administered cognitive test battery (TACT) between telephone and face-to-face administration. [47]	2001		V	TACT	N
Telephone screening of older adults using the orientation-memory-concentration test.[36]	2001		V	OMC	N

The ITEL-MMSE: An Italian telephone version of the Mini-Mental State Examination.[48]	2001		V	Itel-MMSE	N
Characteristics of two telephone screens for cognitive impairment.[49]	2002		V	TELE, TICS	N
Telephone screening to identify potential dementia cases in a population-based sample of older adults.[50]	2002	Swedish Adoption/Twin Study of Aging	V	TELE	Y
Evaluation of rehabilitation outcomes in older patients with hip fractures.[51]	2002		C	FIM-COGNITION	N
Concordance for cognitive impairment: A study of 50 community-dwelling elderly female-female twin pairs.[52]	2003	From Institute of Psychiatry Volunteer Twin Register	C	TICS	N
Utility of TICS-M for the assessment of cognitive function in older adults.[10]	2003		V	TICS-M	N
Validation of the modified Telephone Interview for Cognitive Status (TICS-m) in Hebrew.[53]	2003	Israel Ischaemic Heart Disease Cohort study	V	TICS-M	Y
Cataract extraction and cognitive function in older women.[54]	2003	Nurses' Health Study	C	Battery	N
Diabetes mellitus and cognitive performance in older women.[55]	2003		C	TICS-M	N
Telephone screening for amnestic mild cognitive impairment.[56]	2003	PRAISE study	V	TICS-M & CFT	N
A brief Telephonic Instrument to Screen for Cognitive Impairment in a Managed Care Population.[57]	2003		V	BCSI	N
Validity of the Telephone Interview for Cognitive Status (TICS) in post-stroke participants.[58]	2004		F	TICS-M and TICS	N
Physician recognition of cognitive impairment: Evaluating the need for improvement.[59]	2004	Womens' Memory Study	C	TICS-M	N
Telephone word-list recall tested in the Rural Aging and Memory Study: Two parallel versions for the TICS-M.[60]	2004	Rural Aging and Memory Study	C	Battery	N
Telephone administration of neuropsychological tests can facilitate studies in schizophrenia.[61]	2004		V	Battery	N
Diabetes mellitus in midlife and the risk of dementia three decades later.[62]	2004	Israeli Ischemic Heart Disease project	C	TICS-M (Hebrew)	N
Validation of a 26-point telephone version of the Mini-Mental State Examination.[18]	2004		V	T-MMSE	Y
Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage.[63]	2005		C	TICS	N
Validation of multi-stage telephone-based identification of cognitive impairment and dementia.[64]	2005	University of Southern California Alzheimer Disease Research Centre Study	V	TICS-M	N
Measuring stroke impact with the stroke impact scale: Telephone versus mail administration in veterans with stroke.[65]	2005		F	"cognitive screen"	N
Validation of a brief telephone battery for neurocognitive assessment of patients with pulmonary arterial hypertension.[66]	2005		V	Battery	N
Assessment of cognitive decline in old age with brief tests amenable to telephone administration.[67]	2005	Sub-study of the Religious Orders Study.	V	Battery	N
Correlation analysis of the In-Clinic and Telephone Batteries from the AREDS Cognitive Function Ancillary Study. AREDS report no. 15.[68]	2005	Age-Related Eye Disease Study	F	Battery	Y
Validation of a brief screen for cognitive impairment (BSCI) administered by telephone for use in the Medicare population.[26]	2005		V	BCSI	N
Assessment of cognitive status in the elderly using telephone interviews.[69]	2005	Heidelberger Langzeitstudie zu Risikofaktoren und	F	Battery	N

		Diagnose chronischer Erkrankungen Study			
Associations between dementia/mild cognitive impairment and cognitive performance and activity levels in youth.[70]	2005	Cleveland Longitudinal Aging Studies of Students	C	TICS-m	N
Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study.[71]	2005	HARMONY (Swedish Twin Study)	C	TELE	Y
Neurological, neuropsychological, and functional outcome following treatment for unruptured intracranial aneurysms.[72]	2005		CC	TICS	N
Use of an Italian version of the Telephone Interview for Cognitive Status in Alzheimer's disease.[73]	2006		V	TICS (Italian)	N
Formation and validation of a telephone battery to assess cognitive function in acute respiratory distress syndrome survivors.[74]	2006		V&C	Battery	N
A cost effective method of identifying and recruiting persons over 80 free of dementia or mild cognitive impairment.[75]	2006		F	TICS-m	Y
Telephone assessment of cognitive function in adulthood: The Brief Test of Adult Cognition by Telephone.[27]	2006		V	BTACT	N
Detection of memory impairment in the general population: Screening by questionnaire and telephone compared to subsequent face-to-face assessment.[76]	2006		V	TICS	N
ADCS Prevention Instrument Project: Development of a brief verbal memory test for primary prevention clinical trials.[77]	2006		V	Four Word Delayed Recall Test	Y
Utility of the telephone interview for cognitive status for enrollment in clinical trials.[78]	2006	The Alzheimer's Disease Cooperative Study	V	TICS-M	N
A comparison of the MMSE and the TICS-m in hearing-impaired older adults.[79]	2006		V	TICS-M	N
Cognitive functioning in patients with cerebral aneurysms measured with the mini mental state examination and the telephone interview for cognitive status.[80]	2007		C	TICS	N
Duke Twins Study of Memory in Aging in the NAS-NRC Twin Registry.[81]	2007	Duke Twins Study of Memory in Aging in the NAS-NRC Twin Registry.	C	TICS-M	N
Validation of the Telephone Interview for Cognitive Status (TICS) in Japanese.[82]	2007		V	TICS (Japanese)	Y
Memory impairment among primary care veterans.[83]	2007		C	MIS-T	Y
The Indiana University Telephone-Based Assessment of Neuropsychological Status: A new method for large scale neuropsychological assessment.[37]	2007		V	Battery	N
A randomized trial of a screening, case finding, and referral system for older veterans in primary care.[84]	2007		C	short OMC	N
Development and validation of the Cognitive Telephone Screening Instrument (COGTEL) for the assessment of cognitive function across adulthood.[28]	2007		V	COGTEL	N
Low dose aspirin and cognitive function in the women's health study cognitive cohort.[85]	2007	Subset from Women's Health Study	C	Battery	N
Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease.[86]	2007	Rochester Epidemiology Project	CC	TICS-M	N
The Memory and Aging Telephone Screen: development and preliminary validation.[20]	2007		V	MATS	N
Validation of the Cognitive Assessment of Later Life Status (CALLS) instrument: a computerized telephonic measure.[33]	2007		V	CALLS	N

Measures of cognitive functioning in the 1994-2000 Second Longitudinal Study of Aging.[87]	2008	Longitudinal Study of Aging II	C	(abbreviated) TICS	N
Reproducibility of a telephone interview assessing cognitive function and depressive symptoms in older adults in Germany.[88]	2008		V	battery	N
The long-term effects of oophorectomy on cognitive and motor aging are age dependent.[89]	2008	The Mayo Clinic Cohort Study of Oophorectomy and Aging	X	TICS-M	N
Type 2 diabetes mellitus and cognitive decline in two large cohorts of community-dwelling older adults.[90]	2008	Physicians Health Study and Women's Health Study	C	Battery	N
Use of the telephone-administered Minnesota Cognitive Acuity Screen to detect mild cognitive impairment.[91]	2008		V	MCAS	N
Using telephone and informant assessments to estimate missing modified mini-mental state exam scores and rates of cognitive decline.[92]	2009	Cardiovascular Health Study	V	TICS	N
The use of the modified telephone interview for cognitive status (Tics-M) in the detection of amnestic mild cognitive impairment.[93]	2009		V	TICS-M	Y
Cognitive, mood and quality of life impairments in a select population of ARDS survivors.[94]	2009		C	Battery	N
Level and change in cognitive test scores predict risk of first stroke.[95]	2009	From Health and Retirement Study	C	TICS-M	N
Outcome after emergency surgery without angiography in patients with intracerebral haemorrhage after aneurysm rupture.[96]	2009		C	TICS	N
Reliability and validity of the telephone version of the Cantonese Mini-mental State Examination (T-CMMSE) when used with elderly patients with and without dementia in Hong Kong.[97]	2009		V	T-MMSE (Cantonese)	N
Validation of the modified telephone interview for cognitive status in amnestic mild cognitive impairment and intact elders.[98]	2009		V	TICS-M	N
Validation study of a French version of the modified telephone interview for cognitive status (F-TICS-m) in elderly women.[99]	2010	EtudeEpide´miologique de Femmes de l'Education Nationale study	V	Battery	N
Telephone assessment of cognitive function in the late-onset Alzheimer's disease family study.[100]	2010	Late Onset Alzheimer's Disease Family Study	C	Battery	N
Relationship Between Depression, Fatigue, Subjective Cognitive Impairment, and Objective Neuropsychological Functioning in Patients With Multiple Sclerosis.[101]	2010		C	Battery	N
Evaluating cognition in an elderly cohort via telephone assessment.[102]	2010		F	Battery	N
Telephone administration of the Mental Alternation Test: sensitivity to cognitive decline and practice effects across midlife and late life.[103]	2010	Canadian Longitudinal Study of Aging	V	MATS	N
Two simple questions to assess neurologic outcomes at 3 months after out-of-hospital cardiac arrest: experience from the public access defibrillation trial.[104]	2010		C	T-MMSE	N
Validation of the telephone interview for cognitive status-modified in participants with normal cognition, mild cognitive impairment, or dementia.[105]	2010	Mayo Clinic Study of Aging	V	TICS-M	N
Identification of community-residing individuals with dementia and their unmet needs for care.[106]	2011	Follow up study of "Aging in Place in the Baltimore Jewish Community" Study	C	TICS	N
Telephone-based identification of mild cognitive impairment and dementia in a multicultural cohort.[107]	2011		V	TICS	Y
Incident cognitive impairment is elevated in the stroke belt: The REGARDS Study.[108]	2011	Reasons for Geographic and Racial Differences in Stroke Study	C	battery	N

Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial.[109]	2011	SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids Study	C	TICS-M (French)	Y
Cognitive impairment and outcomes in older adult survivors of acute myocardial infarction: findings from the translational research investigating underlying disparities in acute myocardial infarction patients' health status registry.[110]	2011	TRIUMPH sub-study	C	TICS-M	N
Dispositional optimism and outcome following traumatic brain injury.[111]	2011		X	TICS	N
Emotion and cognitive function assessment of patients with central neurocytoma resection through transcortical frontal approach: a 5-year postoperative follow-up study.[112]	2011		CC	Battery	N
Telephone Interview for Cognitive Status (TICS) screening for clinical trials of physical activity and cognitive training: The seniors health and activity research program pilot (SHARP-P) study.[113]	2011	Seniors Health and Activity Research Program-Pilot	V	TICS	N
Validation of a telephone screening test for Alzheimer's disease.[114]	2011		V	Braztel-MMSE	N
Validity of the Brief Test of Adult Cognition by Telephone (BTACT) in Level 1 Trauma Center Patients 6 Months Post-Traumatic Brain Injury: A TRACK-TBI Study.[115]	2011	Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study	V	BTACT	N
Validity of the telephone interview for cognitive status (TICS) and modified TICS (TICSm) for mild cognitive impairment (MCI) and dementia screening.[116]	2011		V	TICS, TICS-M	N
[Screening for dementia using telephone interviews. An evaluation and reliability study of the Telephone Interview for Cognitive Status (TICS) in its modified German version].[117]	2012		V	TICS	Y
Association of prion protein with cognitive functioning in humans.[118]	2012		C	COGTEL	Y
Personality stability is associated with better cognitive performance in adulthood: are the stable more able?[119]	2012	MIDlife In the United States Study	C	BTACT	N
Cognitive function in the community setting: the neighbourhood as a source of 'cognitive reserve'?.[120]	2012	Chicago Community Adult Health Survey	C	TICS-M	N
Mediterranean diet and cognitive decline in women with cardiovascular disease or risk factors.[121]	2012	Women's Antioxidant Cardiovascular StudY	C	TICS-M (French)	N
Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms--the Beyond Ageing Project: a randomized controlled trial.[122]	2012	Beyond Ageing Project	RCT	BTACT & TICS	N
Predicting current memory with the modified telephone interview for cognitive status.[123]	2012		X	TICS	N
Race and cognitive decline among community-dwelling elders with mild cognitive impairment: Findings from the Memory and Medical Care Study.[124]	2012	Memory and Medical Care Study	C	TICS	N
The Telephone Interview for Cognitive Status (Modified): relation with a comprehensive neuropsychological assessment.[125]	2012	From Utrecht Diabetic Encephalopathy Study and Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care	V	TICS-M	N
Validation of a cognitive assessment battery administered over the telephone.[126]	2012		V	Battery	N
A feasibility study of a telephone-based screening service for mild cognitive impairment and its uptake by elderly people.[127]	2013		V	Battery	Y
A human volunteer study to identify variability in performance in the cognitive domain of the postoperative quality of recovery scale.[128]	2013		V	Postoperative Quality of Recovery Scale	N
Cognitive outcomes of patients undergoing therapeutic hypothermia after cardiac arrest.[129]	2013		C	TICS-M	N

Cognitive, physical, and psychological status after intracranial aneurysm rupture: A cross-sectional study of a Stockholm case series 1996 to 1999.[130]	2013		X	TICS	Y
Feasibility, internal consistency and covariates of TICS-m (telephone interview for cognitive status - Modified) in a population-based sample: Findings from the KORA-Age study.[131]	2013	KORA-Age Study	F	TICS-M	N
History of lifetime smoking, smoking cessation and cognitive function in the elderly population.[132]	2013	ESTHER	C	COGTEL	N
In-hospital acute stress symptoms are associated with impairment in cognition 1 year after intensive care unit admission.[133]	2013		C	TICS-M	N
Midlife cardiovascular risk factors and late cognitive impairment.[134]	2013	Older Finnish Twin Cohort*	C	TELE (Finnish)	N
Screening by telephone in the Alzheimer's disease anti-inflammatory prevention trial.[135]	2013	ADAPT	V	TAB	Y
Telephone assessment of cognition after transient ischemic attack and stroke: modified telephone interview of cognitive status and telephone Montreal Cognitive Assessment versus face-to-face Montreal Cognitive Assessment and neuropsychological battery.[9]	2013		V	T- MoCA,TICS-m	N
Telephone-based cognitive screening for stroke patients in China.[32]	2013		F	NINDS-CSN and SIS	N
The Adult Respiratory Distress Syndrome Cognitive Outcomes Study: Long-Term Neuropsychological Function in Survivors of Acute Lung Injury.[136]	2013	Adult Respiratory Distress Syndrome cognitive outcomes study	C	Battery	N
Utility and acceptability of the modified Telephone Interview for Cognitive Status in a longitudinal study of Australian women aged 85 to 90.[137]	2013	Australian Longitudinal Study on Women's Health	F	TICS-M	Y
150 minutes of vigorous physical activity per week predicts survival and successful ageing: a population-based 11-year longitudinal study of 12 201 older Australian men.[138]	2014	Health In Men Study	C	TICS	N
Arizona Alzheimer's Registry: Strategy and Outcomes of a Statewide Research Recruitment Registry.[139]	2014	Arizona Alzheimer's Registry	C	battery	N
Cerebral microbleeds are not associated with long-term cognitive outcome in patients with transient ischemic attack or minor stroke.[140]	2014		C	TICS (Dutch)	Y
Cognitive complaints correlate with depression rather than concurrent objective cognitive impairment in the successful aging evaluation baseline sample.[141]	2014	Study on global AGEing and adult health	C	TICS-M	N
Cognitive function and quality of life after successful resuscitation from cardiac arrest.[142]	2014	AmsteRdam REsuscitation Study	C	TICS	Y
Comparison of in-person and telephone administration of the Mini-Mental State Examination in the University of Alabama at Birmingham Study of Aging.[143]	2014	University of Alabama at Birmingham Study of Aging II	V	T-MMSE	N
Correcting for demographic variables on the modified telephone interview for cognitive status.[144]	2014	Risk Factors for Progressive Supranuclear Palsy	C	TICS-M	N
Episodic memory impairment in Addison's disease: results from a telephonic cognitive assessment.[145]	2014		CC	BTACT	N
Personality Traits, Facets and Cognitive Performance: Age Differences in Their Relations.[146]	2014		X	BTACT	N
Relationship between post-stroke cognition, baseline factors, and functional outcome: data from "efficacy of nitric oxide in stroke" trial.[147]	2014	Efficacy of Nitric Oxide in Stroke Trial	RCT	Battery	N
Telephone screening for mild cognitive impairment in Hispanics using the Alzheimer's Questionnaire.[148]	2014	Texas Alzheimer's Research Consortium and Care Study	C	Battery	N
Association Between Cognitive Function and Health Care Costs 3 Months and 6 Months After Initiating Antidepressant Medication for Depressive Disorders.[149]	2015		C	Battery	N
Cognitive and Physical Function by Statin Exposure in Elderly Individuals Following Acute Myocardial Infarction.[150]	2015		C	TICS-M	N

Cognitive function in adults aging with fabry disease: a case-control feasibility study using telephone-based assessments.[151]	2015		CC	Battery	Y
Correcting Bias Caused by Missing Data in the Estimate of the Effect of Apolipoprotein epsilon4 on Cognitive Decline.[152]	2015	Einstein Aging Study	C	MIS-T	N
Dietary glycemic load and risk of cognitive impairment in women: findings from the EPIC-Naples cohort.[153]	2015	European Prospective Study into Nutrition and Chronic disease - Naples	C	TICS	Y
Factors related to long-term post-stroke cognitive impairment in young adult ischemic stroke.[154]	2015		C	TICS-M	N
Montreal Cognitive Assessment 5-minute protocol is a brief, valid, reliable, and feasible cognitive screen for telephone administration.[29]	2015	STRIDE	V	5 min MoCA	N
Patient-reported cognitive functioning and daily functioning in chronic dialysis patients.[155]	2015		C	BTACT	N
Patients Experience High Levels of Anxiety 2 Years Following Aneurysmal Subarachnoid Hemorrhage.[156]	2015		C	TICS	N
Post-discharge outcomes after resuscitation from out-of-hospital cardiac arrest: A ROC PRIMED substudy.[157]	2015	Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance valve and Early vs Delayed analysis sub-study	C	ALFI-MMSE	N
Clinically Meaningful Rehabilitation Outcomes of Low Vision Patients Served by Outpatient Clinical Centers.[158]	2015	Low Vision Rehabilitation Outcomes Study	C	TICS-M	N
Baseline subjective memory complaints associate with increased risk of incident dementia: the PREADVISE trial.[159]	2015	Prevention of Alzheimer's Disease with Vitamin E and Selenium Trial	RCT	TICS-M	N
A randomized trial of videoconference-delivered cognitive behavioural therapy for survivors of breast cancer with self-reported cognitive dysfunction.[160]	2016		RCT	TBANS	Y
Applicability of the Telephone Interview for Cognitive Status (Modified) in a community sample with low education level: association with an extensive neuropsychological battery.[161]	2016		V	TICS-M (Portuguese)	N
Assessing Cognitive Function in Older Adults Using a Videoconference Approach.[162]	2016		F	TICS-M (Portuguese)	N
Associations between retinal markers of microvascular disease and cognitive impairment in newly diagnosed type 2 diabetes mellitus: A case control study.[163]	2016		CC	TICS-m	N
Depression as a risk factor for cognitive impairment in later life: the Health In Men cohort study.[164]	2016	Health In Men cohort study	C	TICS-M	N
Omega-3 fatty acid status enhances the prevention of cognitive decline by B vitamins in mild cognitive impairment.[165]	2016	VITACOG	RCT	TICS-M and HVLT-DR	N
Peripheral glucose levels and cognitive outcome after ischemic stroke-Results from the Munich Stroke Cohort.[166]	2016	Munich Stroke Cohort	C	TICS	Y
Prediction of Cognitive and Functional Decline Using the Telephone-Administered Minnesota Cognitive Acuity Screen.[167]	2016		V	MCAS	N
Predictors of Optimal Cognitive Aging in 80+ Women: The Women's Health Initiative Memory Study.[168]	2016	The Women's Health Initiative Memory Study.	C	TICS-M	N
Stroke Symptoms With Absence of Recognized Stroke Are Associated With Cognitive Impairment and Depressive Symptoms in Older Adults With Diabetes.[169]	2016		X	TICS-M	N
Telephone based cognitive-behavioural screening for frontotemporal changes in patients with amyotrophic lateral sclerosis (ALS).[170]	2016		V	Battery	N
Feasibility study for remote assessment of cognitive function in multiple sclerosis.[171]	2016	Kaiser Permanente MS Research Program	F	TICS-M	N

"Good Outcome" Isn't Good Enough: Cognitive Impairment, Depressive Symptoms, and Social Restrictions in Physically Recovered Stroke Patients.[172]	2017		C	T- MoCA	N
A pilot study of potential brain donor satisfaction and attitudes towards telephone assessment.[173]	2017	Sub-study from Brains for Dementia Research Study	F	TICS-M and MoCA-BLIND	Y
Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes.[174]	2017		C	BTACT	N
Change in Cognitive Function in the Month After Hospitalization for Acute Coronary Syndromes: Findings From TRACE-CORE (Transition, Risks, and Actions in Coronary Events-Center for Outcomes Research and Education).[175]	2017		C	TICS	N
Cognitive function and patient-reported memory problems after radiotherapy for cancers at the skull base: A cross-sectional survivorship study using the Telephone Interview for Cognitive Status and the MD Anderson Symptom Inventory-Head and Neck Module.[176]	2017		C	TICS	N
MRI markers predict cognitive decline assessed by telephone interview: The Northern Manhattan Study.[177]	2017	Northern Manhattan Study	C	TICS-M	N
Recovery, Risks, and Adverse Health Outcomes in Year 1 After Extracorporeal Membrane Oxygenation.[178]	2017		C	TICS	N
The Decisions, Interventions, and Goals in ImplaNtable Cardioverter-DefIbrillator TherapY (DIGNITY) Pilot Study.[179]	2017	Decisions, Interventions, and Goals in ImplaNtable Cardioverter-DefIbrillator TherapY	C	TICS	N
The quality of life of patients developed delirium after coronary artery bypass grafting is determined by cognitive function after discharge: A cross-sectional study.[180]	2017		C	TICS-M	N
The SAGES telephone neuropsychological battery: correlation with in-person measures.[181]	2017	Successful Ageing after Elective Surgery sub-study	C	Battery	Y
Validation of the telephone interview of cognitive status and telephone montreal cognitive assessment against detailed cognitive testing and clinical diagnosis of mild cognitive impairment after stroke.[182]	2017	Determinants of Dementia After Stroke Study	V	TICS and T-MoCA	N
Long-term Effects on Cognitive Trajectories of Postmenopausal Hormone Therapy in Two Age Groups.[183]	2017	WHIMS-ECHO and WHIMSY	C	Battery	N
Cognitive Outcomes After Anterior Communicating Artery Aneurysm Repair.[184]	2018		C	TICS-M	N
Midterm outcomes after postoperative delirium on cognition and mood in patients after cardiac surgery.[185]	2018		C	MIS	N
Remote assessment of verbal memory in MS patients using the California Verbal Learning Test.[34]	2018		F	CVLT-II	N
Status epilepticus associated with acute encephalitis: long-term follow-up of functional and cognitive outcomes in 72 patients.[186]	2018		C	TICS-M	N
Sustained quality-of-life improvements over 10 years after deep brain stimulation for dystonia.[187]	2018		X	T-MoCA	N
The Feasibility of Telephone-Administered Cognitive Testing in Individuals 1 and 2 Years after Inpatient Rehabilitation for Traumatic Brain Injury.[188]	2018	Traumatic Brain Injury Model Systems	F	BTACT	Y
The Modified Telephone-Administered Minnesota Cognitive Acuity Screen for Mild Cognitive Impairment.[189]	2018		V	MCAS	N
Triple versus guideline antiplatelet therapy to prevent recurrence after acute ischaemic stroke or transient ischaemic attack: the TARDIS RCT.[190]	2018	Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke Trial	RCT	Battery	N
A multicentre randomised controlled trial of the effect of intra-operative dexmedetomidine on cognitive decline after surgery.[191]	2019		RCT	Battery	N
A Prospective Association of Nut Consumption with Cognitive Function in Chinese Adults aged 55+ _ China Health and Nutrition Survey.[192]	2019	China Health and Nutrition Survey	C	TICS-M	N

A randomized clinical trial to evaluate home-based assessment of people over 75 years old.[193]	2019	Alzheimer's Disease Cooperative Study	F	Battery	N
A valid alternative for in-person language assessments in brain tumor patients: feasibility and validity measures of the new TeleLanguage test.[194]	2019		F/V	TeleLanguage Test	N
Association Between Postoperative Delirium and Long-term Cognitive Function After Major Nonemergent Surgery.[195]	2019		C	T-MoCA	N
Design and baseline characteristics of the cocoa supplement and multivitamin outcomes study for the Mind: COSMOS-Mind.[196]	2019	Cocoa Supplement and Multivitamins Outcomes Study for the Mind	RCT	Battery	N
Dispositional optimism and cognitive functioning following traumatic brain injury.[197]	2019		X	BTACT	N
Does stroke laterality predict major depression and cognitive impairment after stroke? Two-year prospective evaluation in the EMMA study.[198]	2019	Sub-study of EMMA (Stroke Mortality and Morbidity Study)	C	TICS-M	N
Effects of propofol, dexmedetomidine, and midazolam on postoperative cognitive dysfunction in elderly patients: a randomized controlled preliminary trial.[199]	2019		RCT	5 min MoCA	N
Interleukin-6 and Depressive Mood Symptoms: Mediators of the Association Between Childhood Abuse and Cognitive Performance in Middle-Aged Adults.[200]	2019		C	TICS	N
Liver Transplant Recipients Older Than 60 Years Show Executive and Memory Function Improvement Comparable to Younger Recipients.[201]	2019		C	BTACT	N
Long-term health outcomes in survivors after chronic subdural haematoma.[202]	2019		CC	COGTEL	N
Prehospital Transdermal Glyceryl Trinitrate for Ultra-Acute Intracerebral Hemorrhage: Data From the RIGHT-2 Trial.[203]	2019	Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial -2	RCT	Battery	N
Prevalence and correlates of dementia and mild cognitive impairment classified with different versions of the modified Telephone Interview for Cognitive Status (TICS-m).[204]	2019	Older Finnish Twin Cohort*	C	TICS-M	N
Sequelae and Quality of Life in Patients Living at Home 1 Year After a Stroke Managed in Stroke Units.[205]	2019		C	TICS-M	Y
Subjective cognitive functioning and associations with psychological distress in adult brain tumour survivors.[206]	2019		X	BTACT	N
Sugar-sweetened and artificially-sweetened beverages and changes in cognitive function in the SUN project.[207]	2019	Seguimiento Universidad de Navarra substudy	C	TICS-M (Spanish)	N
The Turkish Version of the Telephone Cognitive Screen for Detecting Cognitive Impairment in Older Adults.[208]	2019		V	T-CogS (Turkish TICS)	N
Validation and Normative Data for the Modified Telephone Interview for Cognitive Status: The Sydney Memory and Ageing Study.[209]	2019	Sydney Memory and Ageing Study	C	TICS-m	N
Association of cerebral small vessel disease and cognitive decline after intracerebral hemorrhage.[210]	2020		C	TICS-m	N
Cognition in the First Year After a Minor Stroke, Transient Ischemic Attack, or Mimic Event and the Role of Vascular Risk Factors.[211]	2020		C	TICS + verbal fluency task	N
Cognitive and psychosocial outcomes of mechanically ventilated intensive care patients with and without delirium.[212]	2020		C	TICS	Y
Diagnostic accuracy of cognitive screening tools under different neuropsychological definitions for poststroke cognitive impairment.[213]	2020		V	NINDS-CSN and SIS scale	N
Executive function but not episodic memory decline associated with visual hallucinations in Parkinson's disease.[214]	2020		C	BTACT	N
High-Sensitivity Cardiac Troponin T and Cognitive Function in Patients With Ischemic Stroke.[215]	2020	Prospective cohort with incident stroke Berlin	C	TICS-M	N

Randomized Pragmatic Trial of Stroke Transitional Care: The COMPASS Study.[216]	2020	Comprehensive Post-Acute Stroke Services Study	RCT	MoCA 5-min	N
Rapid communication: Preliminary validation of a telephone adapted Montreal Cognitive Assessment for the identification of mild cognitive impairment in Parkinson's disease.[217]	2020		V	T-MoCA	N
Telemedicine assessment of long-term cognitive and functional status in anti-leucine-rich, glioma-inactivated 1 encephalitis.[218]	2020		F	Battery	Y

Table 7.1: Studies that used a telephone-based cognitive assessment. The longitudinal study from which the study reported the data upon is presented where relevant. The year of publication, type of study (C = cohort, V=validation, F=feasibility, RCT=randomised control trial, X=cross-sectional), the telephone cognitive assessment tool used and whether or not they reported upon the presence of any potential impediments is also included. *duplicate cohort included but different telephone cognitive assessment tools used and performed by different study groups. TICS = telephone interview of cognitive status. TICs (Telephone Interview for Cognitive Status), TICS – m =Telephone Interview for Cognitive Status – modified, TELE =Telephone screening protocol, MIS-T = Memory Impairment Screen Telephone, STIDA = Structured Telephone Interview for Dementia Assessment, SPMSQ-T = Short Portable Mental Status Questionnaire, T-MMSE = 26-point version of the Mini-Mental State Examination, MCAS= Minnesota Cognitive Acuity Screen, MATS = Memory and Aging Telephone Screen, TAMS = Telephone Assessed Mental State, Blessed (T)IMC = Blessed Telephone Information Memory Concentration Test, TCAB = Telephone Cognitive Assessment Battery, HVLT = Hopkins Verbal Learning Test, T3MS = Telephone adaptation of the Mini-Mental State Exam, BSCI = Brief Screen for Cognitive Impairment, BTACT = Brief Test of Adult Cognition by Telephone, COGTEL = Cognitive Telephone Screening Instrument, T-MoCA = Telephone Montreal Cognitive Assessment, 5 minute MoCA = 5 minute Telephone Montreal Cognitive Assessment, ALFI-MMSE (Adult Lifestyles and Functions Interview - version of the MMSE, SIS = 6-item screener, CALLS = Cognitive Assessment of Later Life Status, NINDS-CSN 5 minute protocol = 5-minute National Institute of Neurological Disorders and Stroke and Canadian Stroke Network, CVLT-II = California Verbal Learning Test, 2nd edition, FIM-COGNITION = Functional Independence Measure – Cognitive subscale, OMC = Orientation-Memory-Concentration Test, IU-TBANS = Indiana University - Telephone-Based Assessment of Neuropsychological Status.

Name of Cognitive Assessment	Validation Sample	Paper
TICs (Telephone Interview for Cognitive Status)	100 individuals with mild Alzheimer's Dementia	Brandt et al, 1988[8]
TICS – m (Telephone Interview for Cognitive Status – modified)	109 individuals (ranging from healthy to dementia)	Welsh et al, 1993[13]
TELE (Telephone screening protocol)	30 (outpatient clinic) individuals (ranging from healthy to dementia)	Gatz et al, 1995[14]
MIS-T (Memory Impairment Screen Telephone)	27 individuals with dementia and 273 healthy individuals	Lipton RB et al, 2003[15]
STIDA (Structured Telephone Interview for Dementia Assessment)	15 individuals with cognitive impairment and 13 healthy individuals	Go et al, 1997[16]
SPMSQ-T (Short Portable Mental Status Questionnaire)	100 individuals with dementia	Roccaforte et al, 1994[17]
T-MMSE (26-point version of the Mini-Mental State Examination)	46 individuals with dementia	Newkirk et al, 2004[18]
MCAS (Minnesota Cognitive Acuity Screen)	99 mild to moderate dementia and 129 older adults	Knopman et al, 2000[19]
MATS (Memory and Aging Telephone Screen)	120 individuals with mild cognitive impairment and/or memory complaints	Rabin et al, 2007[20]
TAMS (Telephone Assessed Mental State)	30 individuals with dementia	Lanska et al, 1993[21]
Blessed (T)IMC (Blessed Telephone Information Memory Concentration Test)	84 individuals	Kawas et al, 1995[22]
TCAB (Telephone Cognitive Assessment Battery)	40 individuals with Alzheimer's Dementia and 40 healthy individuals	Debanne et al, 1997[23]
HVLT (Hopkins Verbal Learning Test)	129 healthy individuals	Brandt et al, 1991[24]
T3MS (Telephone adaptation of the Mini-Mental State Exam)	263 community dwelling older adults	Norton et al, 1999[25]
BSCI (Brief Screen for Cognitive Impairment)	35 individuals with dementia and 35 healthy individuals	Hill et al, 2005[26]
BTACT (Brief Test of Adult Cognition by Telephone)	84 healthy individuals	Tun et al, 2006[27]
COGTEL (Cognitive Telephone Screening Instrument)	81 younger individuals (19-37 years) and 83 older individuals (39-75 years)	Kliegel et al, 2007[28]
T-MoCA (Telephone Montreal Cognitive Assessment)	91 individuals with minor stroke or transient ischaemic attack	Pendlebury et al, 2013[9]
5 minute MoCA (5 minute Telephone Montreal Cognitive Assessment)	104 individuals with stroke or transient ischaemic attack	Wong et al, 2015[29]
ALFI-MMSE (Adult Lifestyles and Functions Interview - version of the MMSE)	100 (geriatric clinic) individuals	Roccaforte et al, 1992[30]
SIS (6-item screener)	*344 healthy individuals and 651 individuals referred to a dementia clinic 80 individuals with stroke	*Callahan et al, 2002[31] Chen et al, 2015[32]
CALLS (Cognitive Assessment of Later Life Status)	211 older adults	Crooks et al, 2007[33]
NINDS-CSN 5 minute protocol (5-minute National Institute of Neurological Disorders and Stroke and Canadian Stroke Network)	80 individuals with stroke	Chen et al, 2015[32]
CVLT-II (California Verbal Learning Test, 2nd edition)	180 individuals with Multiple Sclerosis and 90 healthy individuals	Barcellos et al, 2017[34]
FIM-COGNITION (Functional Independence Measure – Cognitive subscale)	25 individuals with stroke	Segal et al, 1996[35]
OMC (Orientation-Memory-Concentration Test)	12 (geriatric clinic) individuals	Dellasega et al, 2001[36]
IU-TBANS (Indiana University - Telephone-Based Assessment of Neuropsychological Status)	106 (female) individuals	Unverzagt et al, 2007[37]

Table 7.2: Telephone-based cognitive assessment methods and their (telephone) validation samples. (Adapted from Castanho et al, 2014[1]). *Original validation sample was face-to-face though was designed as a telephone tool.

Assessment tool	Number of studies using tool
TICS, TICS-M, abbreviated TICS	89
BTACT	14
T-MMSE, ALFI-MMSE, T3MS	11
T-MoCA, 5 minute MoCA	7
COGTEL	4
FIM-COGNITION	4
TELE	4
MCAS	4
MIS-T	3
TCAB	3
BSCI	2
MATS	2
NINDS-CSN	2
OMC	2
SPMSQ	2
Other*	10
Multiple/battery	44

Table 7.3: Choice of telephone cognitive assessment used in studies. Translated versions included with original tool (i.e. F-TICS-M included with TICS-M). *Other includes 1 x Blessed IMC, 1 x CALLS, 1 x CVLT-II, 1 x STIDA, 1 x TAMs, 1 x TBANS, 1 x four word delayed recall test, 1 Postoperative Quality of Recovery Scale, 1 x TeleLanguage Test and 1 not specified. Multiple includes studies that included more than one screening tool or a (unnamed) neuropsychological battery. TICS = telephone interview of cognitive status. TICs (Telephone Interview for Cognitive Status), TICS – m =Telephone Interview for Cognitive Status – modified, TELE =Telephone screening protocol, MIS-T = Memory Impairment Screen Telephone, STIDA = Structured Telephone Interview for Dementia Assessment, SPMSQ-T = Short Portable Mental Status Questionnaire, T-MMSE = 26-point version of the Mini-Mental State Examination, MCAS= Minnesota Cognitive Acuity Screen, MATS = Memory and Aging Telephone Screen, TAMS = Telephone Assessed Mental State, Blessed (T)IMC = Blessed Telephone Information Memory Concentration Test, TCAB = Telephone Cognitive Assessment Battery, HVLT = Hopkins Verbal Learning Test, T3MS = Telephone adaptation of the Mini-Mental State Exam, BSCI = Brief Screen for Cognitive Impairment, BTACT = Brief Test of Adult Cognition by Telephone, COGTEL = Cognitive Telephone Screening Instrument, T-MoCA = Telephone Montreal Cognitive Assessment, 5 minute MoCA = 5 minute Telephone Montreal Cognitive Assessment, ALFI-MMSE (Adult Lifestyles and Functions Interview - version of the MMSE, SIS = 6-item screener, CALLS = Cognitive Assessment of Later Life Status, NINDS-CSN 5 minute protocol = 5-minute National Institute of Neurological Disorders and Stroke and Canadian Stroke Network, CVLT-II = California Verbal Learning Test, 2nd edition, FIM-COGNITION = Functional Independence Measure – Cognitive subscale, OMC = Orientation-Memory-Concentration Test, IU-TBANS = Indiana University - Telephone-Based Assessment of Neuropsychological Status.

Description	Number of studies
Severe hearing impairment, deafness or bilateral hearing impairment	15
Adequate hearing for telephone assessment	15
Hearing impairment	10
Adequate hearing for cognitive assessment	5
Self-reported hearing difficulty beyond that associated with normal aging	1
Pass hearing screen / test	6
Not applicable*	1
Not mentioned	153

Table 7.4: Description of hearing requirement mentioned in the participant selection criteria of each study *1 study was specifically on participants who wore hearing amplification devices who had undergone an audiometric test information for total percentage hearing loss adjusted for age.

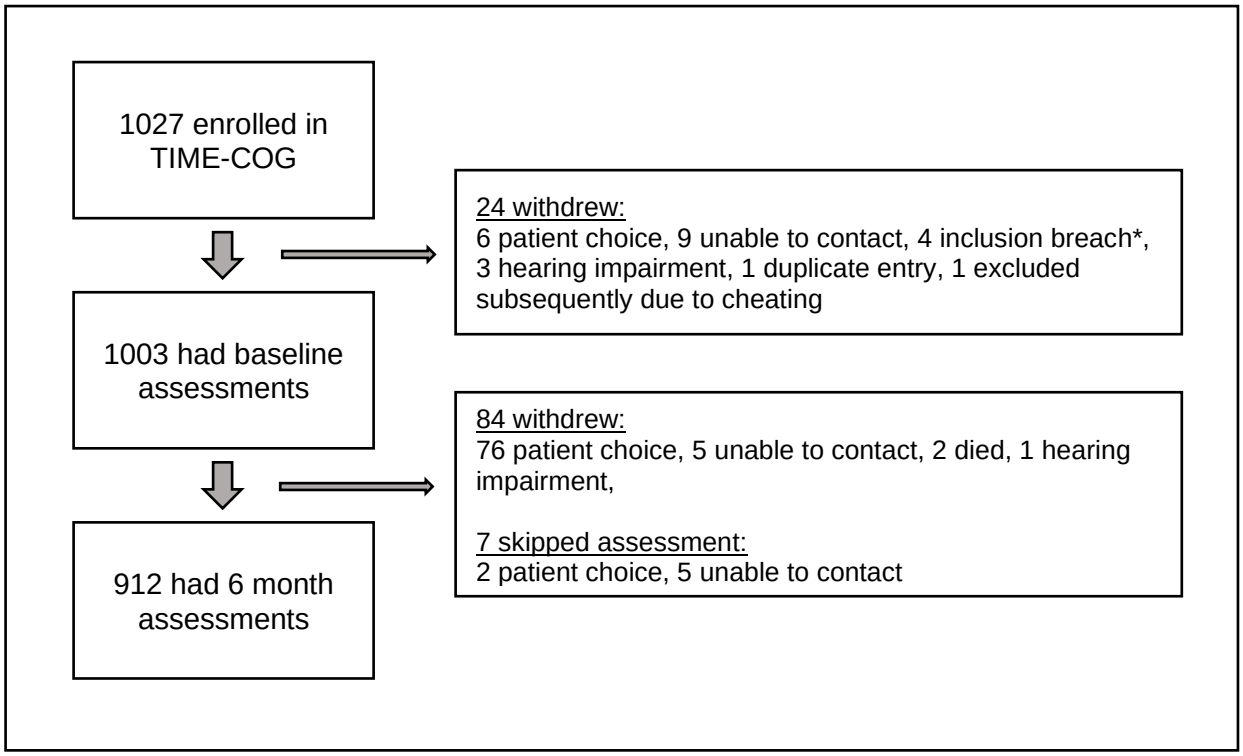

Figure 7.3: Flow chart showing the number of participants in TIME-COG at each stage and the reasons for withdrawal. *Inclusion criteria breach = 2 not on antihypertensives, 1 under the age of 70 years and 1 in another trial.

	All participants	Potential impediment reported	No potential impediment reported	p value*
Number of participants	1003	97	906	n/a
Age, mean (s.d)	74.0 (3.7)	74.7 (3.9)	74.0 (3.7)	0.075
Male sex, % (n)	57.6% (578)	59.8% (58)	57.4% (520)	0.650
Low education, % (n)	38.3% (384)	35.1% (34)	38.6% (350)	0.491
Baseline TICS-m score, mean (s.d)	25.3 (3.8)	25.0 (4.2)	25.4 (3.8)	0.425
Baseline T-MoCA score, mean, (s.d)	18.7 (2.1)	18.6 (2.2)	18.7 (2.1)	0.443

Table 7.5: Baseline characteristics of the 1003 participants who completed the baseline assessment and comparison of those in which a potential impediment was reported during the assessment compared to those in which no impediment was reported. *p value for comparison between the participants with a potential impediment in their baseline assessment compared with those without.

	Frequency of impediment	Proportion of all reported impediments (%)	Proportion of all baseline assessments affected (%)
Hearing impairment	70	70.0	7.0
Significant bereavement (<1 year)	8	8.0	0.8
English not first language	6	6.0	0.6
Poor phone line	4	4.0	0.4
Interruptions*	4	4.0	0.4
Speech impediment	3	3.0	0.3
Dyslexia	2	2.0	0.2
Recent poor sleep (affecting concentration)	1	1.0	0.1
Other significant illness**	1	1.0	0.1
Other***	1	1.0	0.1

Table 7.6: Potential impediments reported during the baseline telephone cognitive assessments. *Mobile phone ringing, post arrived, visitors arrived, distracted by partner. **Epilepsy with short term memory loss. ***stopwatch malfunction.

	T-MoCA		TICS-M	
	B (95% C.I)	p value	B (95% C.I.)	p value
Increasing age	-0.06 (-0.10 to -0.03)	**<0.001**	-0.16 (-0.22 to -0.09)	**<0.001**
Male sex	-0.76 (-1.01 to -0.50)	**<0.001**	-1.31 (-1.77 to -0.86)	**<0.001**
Low education	-0.84 (-1.11 to -0.58)	**<0.001**	-1.30 (-1.77 to -0.84)	**<0.001**
Potential Impediment	-0.14 (-0.58 to 0.29)	0.514	-0.36 (-1.13 to 0.409)	0.358

Table 7.7: Multivariate regression analysis for the impact of a (potential) reported impediment on cognitive screening assessment scores at baseline.

	T-MoCA		TICS-M	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Increasing age	0.98 (0.92-1.04)	0.426	0.98 (0.92-1.04)	0.429
Male sex	0.85 (0.54-1.32)	0.459	0.86 (0.55-1.34)	0.507
Low education	1.21 (0.78-1.90)	0.395	1.24 (0.80-1.93)	0.335
Baseline score	0.93 (0.84-1.03)	0.184	0.97 (0.91-1.03)	0.351
Potential Impediment	0.41 (0.15-1.15)	0.089	0.41 (0.15-1.15)	0.091

Table 7.8: Multivariate regression analysis for the impact of a (potential) reported impediment during the baseline assessment on whether a participant subsequently withdrew. OR = odds ratio (95% confidence interval).

	Hearing impairment (n=70)		No impairment (n=906)		p value
	Mean	**s.d**	**Mean**	**s.d**	
TICS-M					
Overall score	24.90	3.79	25.36	3.75	0.319
Attention	5.50	0.78	5.48	0.94	0.893
Language	0.86	0.35	0.89	0.32	0.463
Abstraction	2.91	0.41	2.97	0.16	**0.015**
Immediate recall	4.41	1.88	4.62	1.68	0.991
Delayed recall	4.34	1.86	4.65	2.05	0.229
Orientation	6.87	0.38	6.75	0.50	0.056
Duration (mins)	2.99	0.71	2.84	0.79	0.148
T-MoCA					
Overall score	18.61	2.20	18.72	2.13	0.685
Attention	5.57	0.71	5.63	0.65	0.436
Language	2.13	0.88	2.27	0.76	0.142
Abstraction	1.73	0.61	1.66	0.59	0.363
Delayed Recall	3.24	1.37	3.32	1.41	0.676
Orientation	5.94	0.23	5.84	0.39	**0.030**
Duration (mins)	7.48	1.38	6.88	1.13	**<0.001**

Table 7.9: Mean baseline T-MoCA and TICS-M scores and test duration depending on presence or absence of a hearing impairment. Overall score and subdomain scores presented. 27 participants for whom other impairments in their baseline assessment were reported (other than hearing impairment) were excluded from the analysis.

CHAPTER 8

IMPACT OF SEASON AND TIME-OF-DAY ON COGNITIVE SCREENING PERFORMANCE IN OLDER SUBJECTS WITH HYPERTENSION

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8.1 Abstract

Introduction: Cognitive screening tools, such as the MoCA and TICS-M, are commonly used in prevention trials in patients with TIA and stroke. Some studies have suggested that cognitive performance exhibits both diurnal and seasonal variation, being better in the morning than in the afternoon, and better in the Summer / Autumn than in the Winter / Spring. However, it is uncertain whether any such effects would influence the outcome of brief cognitive screening assessments or be sufficiently large to necessitate same time-of-day or same time-of-year testing for repeat assessments in clinical trials or other research studies. I therefore determined whether time-of-day or season affected the results of telephone cognitive testing in older individuals at risk of stroke

Methods: Older participants (≥ 70 years) with hypertension enrolled in an ongoing trial of blood pressure lowering completed telephone cognitive screening assessments (T-MoCA; TICS-M) between 9am and 6pm according to availability of the participant and assessor. The assessments were repeated at six-months. Assessments in the morning (before 12pm) and the afternoon (after 12pm) were compared after adjusting for age, sex and level of education. Then the difference between baseline and six month scores were compared in the participants that had baseline assessments in Winter/Spring (December-May) versus Summer/Autumn (June-November).

Results: Telephone cognitive assessments were completed for 1003 participants at baseline and 912 at 6-months. 399 (39.8%) baseline assessments were completed in the morning and 604 (60.2%) in the afternoon. Lower cognitive scores were associated with male gender, low education and increasing age (T-MoCA –all $p<0.001$, TICS-M - all $p<0.001$), but not with the time of day the test was undertaken (T-MoCA $p=0.190$, TICS-M $p=0.332$). Among the 745 participants who had baseline and 6-month assessments in different seasons 407 (54.6%) had their baseline in Winter / Spring and 338 (45.4%) in Summer / Autumn. On repeat testing after 6-months participants tested at baseline in Winter/Spring had a significantly greater improvement on testing in Summer/Autumn

compared with those first tested in Summer / Autumn for the T-MoCA alone: difference in mean change (T-MoCA – p=0.020; TICS-M – p=0.351).

Conclusion: Time-of-year but not time-of-day may affect the results of cognitive screening assessments in older participants. A larger study in more a cognitively diverse population should be undertaken including adjustment for seasonal variations in mood.

8.2 Introduction

Robust reproducibility of cognitive assessments is required in order to determine cognitive trajectories or to assess the impact of a treatment on cognition whether in an individual or in large-scale clinical trials. However, despite this the impact of changing seasons or of time-of-day on the re-test reliability of brief cognitive assessments is not known. Several studies have suggested that cognitive function fluctuates according to an individuals' circadian rhythm with older adults often performing better in the morning than the evening.[1-6] However, few studies have addressed the potential impact of this diurnal fluctuation on standardised cognitive screening assessments.[7] An earlier study in older patients with Transient Ischaemic Attack (TIA) and stroke suggested that afternoon testing was associated with increased rates of severe cognitive impairment in contrast to morning testing.[7] However, it is unclear whether this finding would be replicated in a general older population and if so, whether it would be sufficiently large to necessitate same time-of-day cognitive screening for repeat assessments in clinical trials or other research studies. Furthermore, data are emerging regarding the possible influence of season on cognitive processes but studies are limited and conflicting.[8-12] A recent study, in an older population with and without Alzheimer's Dementia, suggested that the Winter / Spring seasons were associated with clinically relevant lower cognitive scores in both cohorts, independent of any seasonal mood disorder.[13] However, this study was limited as the participants were only tested at one time point and repeated testing in an alternative season was not undertaken. A previous earlier study on younger adults found that seasonal variation in cognitive performance was only detectable in the presence of a seasonal affective disorder but this again was limited by a lack of repeated testing.[14]

The Treatment in Morning versus Evening Study (TIME) is an ongoing randomised trial of timing of dosing of antihypertensive medication in which a sub-group of older participants are required to have serial cognitive screening assessments.[15] Therefore, using these assessments, I aimed to determine whether the time-of-day or the season in which the

cognitive screening assessment is undertaken impacts upon the outcome in older individuals.

8.3 Methods

8.3.1 Participants and Procedures

TIME is an ongoing study to assess whether nocturnal dosing of antihypertensive medication reduces cardiovascular events compared with conventional morning dosing.[15] The study was advertised at collaborating general practitioners and participants were directly contacted through registered research network practices. All participants aged over 18 years who were both diagnosed and treated for hypertension (all forms) and had a valid email address were eligible for inclusion (Appendix X). Exclusion criteria included participants who take twice daily antihypertensive therapy, participants who work shift patterns that include a night shift, those unwilling to be followed up, those who do not permit review of their medical records and those who have participated in another clinical trial of an investigational medicinal product within the last 3-months. Participants of all cognitive levels (whether known or unknown impairment) were eligible for enrolment, however, due to the trial design it was suspected that those with significant cognitive impairment would not volunteer. There were no exclusion criteria specifically related to a participants' medical history and details regarding prior cerebrovascular and cardiovascular events were collected at baseline. Participants participated by self-registering on a study-specific website (www.timestudy.co.uk) and were then randomised to a dosing time (morning versus evening) (Appendix XII). The feasibility of the largely automated system was validated in a pilot study of 355 participants.[16] In the pilot study the participants had a mean age at randomisation of 61 years, and a 10-year risk of cardiovascular events of 21%.[16]

The TIME-Cognitive function (TIME-COG) sub-study aims to detect any potential temporal change in cognition which may occur as a result of evening-dosing. Participants recruited to TIME, and who were aged 70 years or older, were invited to participate in the sub-study at the time of entry to the main trial (Appendix XI). Telephone cognitive assessments

including Montreal Cognitive Assessment (T-MoCA) and the Modified Trends in Cognitive Sciences (TICS-M) were performed at baseline, 6-months, 1-year, then annually until the conclusion of the study (Appendix VIII, IX).[17,18] The T-MoCA and TICS-M have both been validated in general and in post-TIA / stroke populations.[17,18,19,20] Reliability of diagnosis for multi-domain mild cognitive impairment for a post TIA/stroke population is good (area under the ROC curve: T-MoCA=0.85, 95% CI 0.75-0.96; TICS-M=0.83, 0.70-0.96).[18] The T-MoCA is scored out of 22 points (delayed recall: 5, orientation: 6, attention: 6, language: 3, abstraction 2) with a cut off of 19 for the detection of mild cognitive impairment.[18] The TICS-M is scored out of 39 points (immediate memory:10, delayed recall: 12, orientation: 7, attention: 6, language: 1, abstraction: 3) with a cut-off of 25 for detection of mild cognitive impairment.[18]

The assessments were performed on a participant each time by the same assessor and at the same time-of-day as the previous assessments in order to minimise confounders. Telephone assessments were performed by researchers experienced in both telephone cognitive and face-to-face cognitive assessments (S.W, F.C, A.M.H, S.C) blinded to the timing of the drug dosing. The time-of-day (between 9am and 6pm) at which a participant was contacted was predominantly determined by the availability of the assessor and the participant. As TIME-COG baseline and 6-month assessments, by default, would fall in differing seasons these were used to assess the impact of season in this study. Previous studies have demonstrated that cognition is relatively stable in the first year of follow-up in antihypertensive trials so any change could be, in part, associated with the season change.[21,22] Seasons were defined meteologically (Winter: December 1st to Feb 28th, Spring: March 1st to May 31st, Summer: June 1st to August 31st, Autumn: September 1st to November 30th). Participants were grouped as to whether their baseline cognitive assessment was in Winter / Spring or Autumn / Summer. Low education was defined as self-reporting 12 years or less of formal education. Further details about TIME-COG including the power calculation used to determine the sample size are detailed in Chapter

2. As TIME is an ongoing study baseline variables and treatment allocation were not available at the time of this analysis.

8.3.2 Statistical Analysis

The baseline characteristics and cognitive scores of the participants in the different groups were compared with χ2 or independent T tests. To adjust for potential confounders on the impact of time-of-day on cognitive scores multivariate linear regression modelling was used. For the season analysis, in order to assess for regression to the mean a fitted linear regression of change in score against baseline score was performed. Where found, a Bland-Altman plot was performed to correct for regression to the mean.[23] The mean change in baseline to 6-month scores for the two season groups were compared by independent T tests. All statistical tests were completed using SPSS Statistics 26.

8.4 Results

Of 1027 participants recruited to TIME-COG 97.7% (n=1003) completed a baseline assessment and 88.8% (n=912) completed a 6-month assessment. Reasons for failing to complete the assessments are shown in figure 8.1. At baseline the mean age (s.d) was 74.0 (3.7) years, 57.6% were male and 38.3% reported less than 12 years of education. There were no differences in age, gender or education between those that continued and those that withdrew after the baseline assessment (table 8.1)

8.4.1 Impact of Time-of-Day on Cognitive Screening

Of the 1003 participants that completed a baseline assessment 399 (39.8%) completed it in the morning (<12pm) and 604 (60.2%) in the afternoon / evening (≥12pm). There were no differences in terms of age or gender between those that were assessed in the morning and those assessed in the afternoon / evening (table 8.2). However, there was a higher proportion of participants with low education tested in the morning (p=0.022).

Telephone cognitive assessments were initiated between 09:00 and 19:40 (median: 13:09, IQR 10:55 – 15:20) (figure 8.2).

Timing of the test did not impact the TICS-M or the T-MoCA score for the overall cohort nor when gender or level of education was taken into account (table 8.3 (a)). This finding was sustained at the 6-month assessment (table 8.3 (b)). In a multivariate analysis, a lower cognitive score was independently associated with male sex, having less than 12 years education and with increasing age (baseline and 6-months: T-MoCA all $p<0.001$, TICS-M all $p<0.001$) but not with the time-of-day the test was undertaken (baseline T-MoCA $p=0.190$, TICS-M $p=0.332$. 6-months: T-MoCA $p=0.466$, TICS-M $p=0.758$) (table 8.4).

On the individual cognitive assessment subdomains testing in the morning was associated with lower scores in the language domain on the baseline T-MoCA ($p=0.009$) and in the abstraction domain in the TICS-M ($p=0.035$). However, these findings represented a negligible clinical difference (mean difference: 0.02 points in the TICS-M abstraction domain and 0.13 points in the T-MoCA language domain) and were not replicated at the 6-month assessments (table 8.5).

8.4.2 Impact of Season on Cognitive Screening

Of the 1003 participants that completed a baseline assessment 571 (56.9%) were tested in the Winter / Spring and 432 (43.1%) in Summer / Autumn. Of the 912 participants that completed both a baseline and a 6-month assessment 81.6% (n=745) had their assessments in opposite seasons. 12.6% (n=115) had both their assessments in Winter / Spring and 5.7% (n=52) had both their assessments in Summer / Autumn and so were not included in the analysis.

There was no difference in age, sex and education between those that had their baseline assessments in Winter / Spring compared with Summer / Autumn (table 8.6). Despite regression to the mean being demonstrated, after correction by Bland and Altman plot, a mean improvement in the 6-month score from baseline, possibly attributable to a practice effect, was still seen across both season groups for both the T-MoCA and TICS-M (figures 8.3-8.5). However, the mean change in cognitive scores was greater for those who had their 6-month assessment in Summer / Autumn compared with Winter / Spring (T-MoCA:

+1.0 vs +0.6, TICS-M: +0.7 vs +0.4), (figure 8.4 & 8.5, table 8.7). The difference in mean change in scores between the two season groups was only significant for the T-MoCA assessment (p=0.021) and not the TICS-M assessment (p=0.351) (table 8.7). On subgroup analysis, for the T-MoCA alone, the difference in scores was significant for those who scored ≤ 19 on the baseline assessment (p=0.016) and for female participants (p=0.027) (table 8.7).

Of the individual subdomains of the cognitive assessments no association between sub-score and season of testing was seen for either the TICS-M nor the T-MoCA (table 8.7).

8.5 Discussion

In this study, time-of-day of the cognitive screening assessment did not appear to affect the cognitive scores in an older population. To my knowledge, this is the first study to assess the impact of time-of-day on telephone cognitive assessments, specifically the TICS-M and T-MoCA. This finding is reassuring as many clinical trial protocols do not have a requirement for consistent timing of their serial cognitive testing and it has been, until now, unclear as to whether this is a confounding factor.

A previous study on the impact of time-of-day on face to face cognitive assessments in a cohort of patients who had a recent cerebrovascular event identified higher proportions of cognitive impairment in the afternoon.[7] Whilst this aligns with previous studies, suggesting that optimal testing for older adults is the morning, that specific cohort were more vulnerable due to a degree of cognitive fragility conveyed by their cerebrovascular pathology.[24] In this study the cohort were cognitively more robust and therefore perhaps less susceptible to fatigue and circadian changes throughout the day.

In contrast, however, the time-of-year in which the cognitive screening assessment was undertaken may affect the outcome with worse scores occurring during the Winter / Spring seasons. The difference was small (+0.3 in the T-MoCA) which may imply limited clinical impact. However, as both the T-MoCA and TICS-M are only brief cognitive screening

assessments this raises the question as to whether the season has a more clinically relevant impact on more detailed neuropsychological assessments. This would have potentially significant ramifications for trials and other clinical studies in which repeat testing is undertaken and in which this possible source of bias has not been considered. This study reassuringly aligns with a recent study showing a decline in cognitive function in Winter / Spring but with the added benefit of demonstrating this by utilising serial cognitive assessments on the same individuals at different time points in the year.[13] Yet a seasonal variation in the TICS-M scores was not demonstrated. Similarly, the brief Cognitive Performance Scale recently failed to find an association between cognitive performance of older adults and season.[25] Therefore, further large scale studies are required in order to fully elucidate the impact of season on cognitive screening assessments.

Previous studies have suggested that the cognitive domains affected by season include working memory, attention, executive functioning, and verbal fluency with poorer performances in the Winter / Spring seasons.[11,13] In this study no association between season and the sub-domains were detected for either the T-MoCA or TICS-M. This may be a consequence of the brief screening nature of these tools and as such their lower discriminatory ability. Furthermore, the underlying mechanisms that may lead to fluctuations in cognition according to the season are as yet unknown. A previous study found no association between seasonal changes in (self-reported) sleep patterns, activity levels and mood with the cognitive changes but there is insufficient evidence to currently fully discount a potential influence of these factors on cognitive assessment scores.[13]

This study has numerous limitations. The population tested are required to be technologically literate in order to enrol and therefore may be in general higher functioning than some of their contemporaries. Furthermore executive dysfunction and, specifically, apathy are often early and prominent features of vascular cognitive impairment which may make participants with these symptoms less likely to volunteer to participate in a trial procedure, further biasing the population studied.[26] For the time-of-day analysis participants

were assessed during ‘9am to 5pm’ thereby limiting the evaluation of more extremes of time. However, given that most clinical consultations are completed during this time this is unlikely to be a significant limitation to interpretation with regards to clinical practice. Neither the timing of the assessment nor the season of the baseline assessment were randomised, and whilst for the majority it was determined by the availability of the assessor, it could not be established how much was also impacted by the availability of the participant. A repeat assessment at a different time-of-day may have yielded greater insight into any potential association but was not feasible due to the TIME-COG protocol. No assessment for mood or seasonal affective disorder was undertaken and as such it cannot be discounted that mood may have impacted upon the change in cognitive scores. Particularly given the finding that the seasonal variation was more pronounced in women than men who are proportionally more affected by seasonal affective disorder.[27] A significant proportion of participants (18.3%) had both their assessments in the same season group and as such were excluded from the season analysis. The reasons why and the potential impact of this was not assessed. Finally, only basic baseline variables are available for the participants so it is not possible to attest that they are equally matched for other factors known to impact cognition (such as history of previous stroke) or for the impact of the timing of their antihypertensive.

8.6 Conclusion

The time-of-year but not the time-of-day may affect the outcome of brief cognitive assessments in older adults. Further studies on a more diverse older population, including adjustment for seasonal variations in mood, are required in order to validate the findings.

8.7 References

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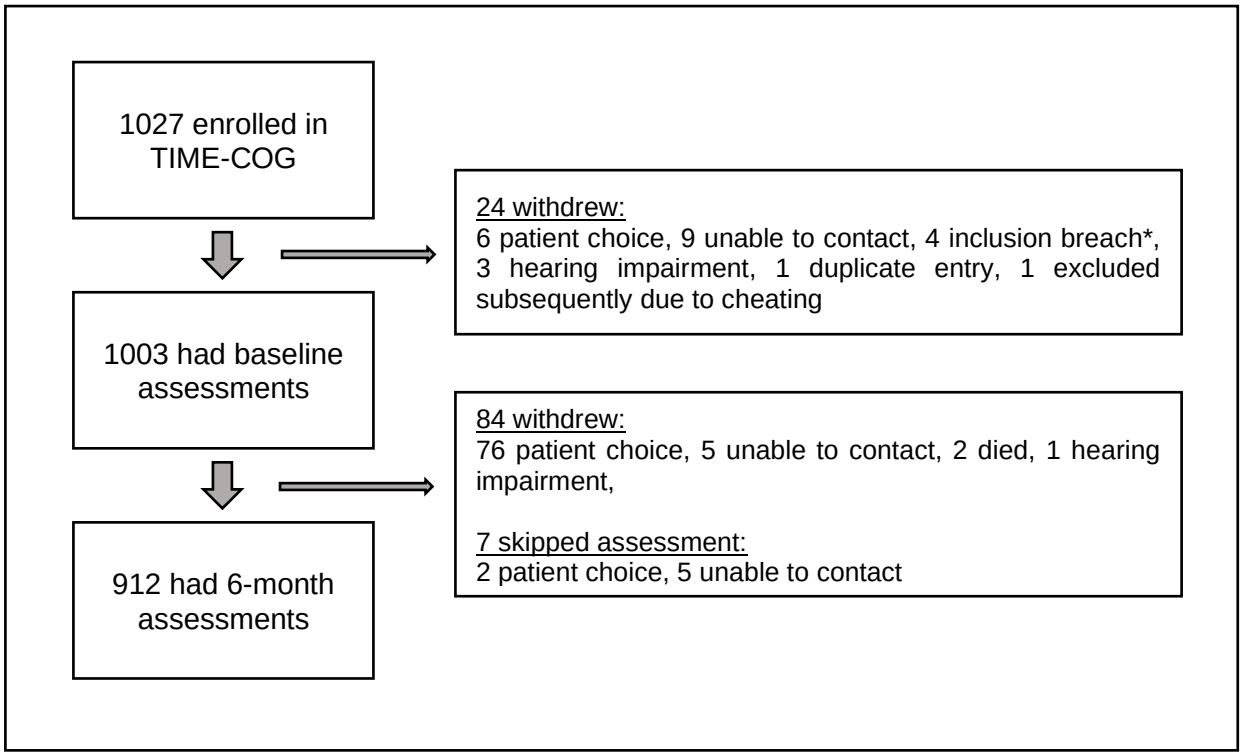

Figure 8.1: Flow chart showing the number of participants in TIME-COG at each stage and the reasons for withdrawal. *Inclusion criteria breach = 2 not on antihypertensives, 1 under the age of 70 years and 1 in another trial.

	Completed baseline assessment	Continued after baseline	Withdrew after baseline	p value*
Number of participants	1003	912	91	n/a
Age, mean (s.d)	74.0 (3.7)	74.1 (3.7)	73.8 (3.9)	0.475
Male sex, % (n)	57.6% (578)	57.9% (528)	54.9% (50)	0.587
Low education, % (n)	38.3% (384)	37.7% (344)	44.0% (40)	0.243

Table 8.1: Baseline characteristics of the 1003 participants who completed the baseline assessment and comparison of those that subsequently continued or withdrew in the study.
*p value for comparison between the participants that continued after baseline versus those that withdrew.

	Morning (n=399)	Afternoon / Evening (n=604)	p value
Age, mean (s.d)	74.3 (3.9)	73.9 (3.7)	0.067
Male sex, % (n)	53.9% (215)	60.1% (363)	0.051
Low education, % (n)	42.6% (170)	35.4% (214)	0.022

Table 8.2: Baseline characteristics of the 1003 participants that completed the initial assessment stratified by whether their assessment was in the morning (pre-12pm) or afternoon / evening (post-12pm).

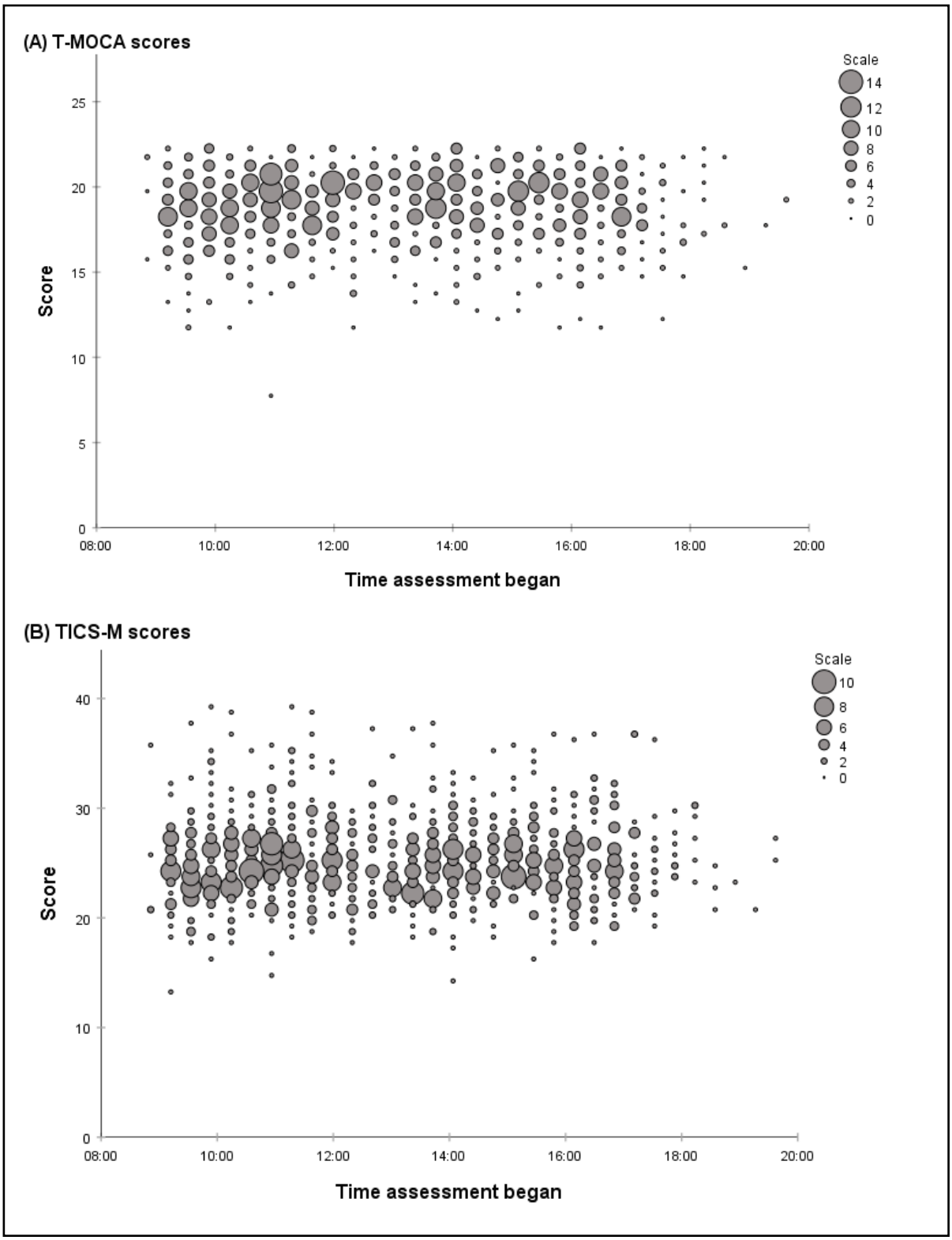

Figure 8.2: Baseline cognitive assessment scores according to time-of-day assessment began. (A) T-MoCA scores, (B) TICS-M scores.

	Morning			Afternoon / Evening			p value
	Mean	**s.d**	**Range**	**Mean**	**s.d**	**Range**	
(a) Baseline							
TICS-M							
Overall Cohort	25.42	4.01	13-39	25.27	3.64	14-38	0.550
Female	26.38	4.27	13-39	25.83	3.94	17-37	0.170
Male	24.60	3.58	17-39	24.91	3.39	14-38	0.307
>12 years Education	26.06	4.23	13-39	25.70	3.66	16-38	0.268
≤12 years Education	24.56	3.51	15-39	24.50	3.48	14-37	0.860
T-MoCA							
Overall Cohort	18.58	2.14	8-22	18.79	2.14	12-22	0.122
Female	19.03	2.19	8-22	19.21	1.92	12-22	0.361
Male	18.19	2.06	12-22	18.51	2.23	12-22	0.085
>12 years Education	18.97	1.92	12-22	19.06	1.98	12-22	0.543
≤12 years Education	18.05	2.30	8-22	18.29	2.32	12-22	0.320
(b) 6-months							
TICS-M							
Overall Cohort	25.91	4.22	16-39	26.05	4.11	14-39	0.616
Female	26.89	4.54	16-38	26.90	4.44	18-39	0.988
Male	25.09	3.76	17-39	25.48	3.80	14-38	0.259
>12 years Education	26.38	4.31	18-39	26.53	4.13	18-39	0.668
≤12 years Education	25.22	4.01	16-38	25.20	3.95	14-38	0.944
T-MoCA							
Overall Cohort	19.55	2.00	12-22	19.49	1.97	10-22	0.639
Female	19.93	1.82	12-22	19.76	1.86	13-22	0.392
Male	19.24	2.10	13-22	19.30	2.03	10-22	0.737
>12 years Education	19.88	1.85	14-22	19.78	1.78	14-22	0.538
≤12 years Education	19.07	2.13	12-22	18.97	2.19	10-22	0.659

Table 8.3: Cognitive scores according to the time-of-day the assessment was initiated for the overall cohort and subgroups at (a) baseline and (b) 6-months. Baseline assessments were performed in 1003 participants and 6-months assessments in 912 participants. Morning defined as pre 12pm and afternoon / evening as post 12pm.

	B (95% C.I)	p value
(a) Baseline		
TICS-M		
Increasing age	-0.16 (-0.22 to -0.10)	<0.001
Male sex	-1.30 (-1.76 to -0.85)	<0.001
Low education	-1.32 (-1.78 to -0.85)	<0.001
Afternoon / evening assessment	-0.23 (-0.69 to 0.23)	0.332
T-MoCA		
Increasing age	-0.06 (-0.10 to -0.03)	<0.001
Male sex	-0.77 (-1.03 to -0.51)	<0.001
Low education	-0.83 (-1.09 to -0.57)	<0.001
Afternoon / evening assessment	0.18 (-0.09 to 0.44)	0.190
(b) 6-months		
TICS-M		
Increasing age	-0.22 (-0.28 to -0.15)	<0.001
Male sex	-1.63 (-2.15 to -1.11)	<0.001
≤ 12 years education	-1.24 (-1.77 to -0.71)	<0.001
Afternoon / evening assessment	0.08 (-0.45 to 0.61)	0.758
T-MoCA		
Increasing age	-0.07 (-0.11 to -0.04)	<0.001
Male sex	-0.58 (-0.83 to -0.32)	<0.001
≤ 12 years education	-0.81 (-1.06 to -0.55)	<0.001
Afternoon / evening assessment	-0.10 (-0.35 to 0.16)	0.466

Table 8.4: Multivariate regression modelling for impact of baseline characteristics and time-of-day of assessment on cognitive score at (a) baseline and (b) 6-months. Afternoon / Evening defined as an assessment after 12pm.

	Morning			Afternoon / Evening			p value
	Mean	**s.d**	**Range**	**Mean**	**s.d**	**Range**	
(a) Baseline							
TICS-M							
Attention	5.46	1.00	1-6	5.49	0.89	1-6	0.558
Language	0.91	0.29	0-1	0.87	0.34	0-1	0.095
Abstraction	2.96	0.25	0-3	2.98	0.14	2-3	**0.035**
Immediate recall	4.61	1.62	1-10	4.61	1.63	0-10	0.924
Delayed recall	4.71	2.18	0-12	4.58	1.97	1-12	0.312
Orientation	6.78	0.45	5-7	6.75	0.52	4-7	0.339
T-MoCA							
Attention	5.59	0.70	1-6	5.66	0.63	3-6	0.120
Language	2.18	0.80	0-3	2.31	0.76	0-3	**0.009**
Abstraction	1.65	0.61	0-2	1.68	0.57	0-2	0.326
Delayed Recall	3.31	1.36	0-5	3.30	1.43	0-5	0.866
Orientation	5.85	0.37	4-6	5.84	0.39	3-6	0.831
(b) 6-months							
TICS-M							
Attention	5.56	0.80	2-6	5.53	0.78	1-6	0.599
Language	0.92	0.28	0-1	0.93	0.26	0-1	0.711
Abstraction	2.97	0.17	2-3	2.98	0.13	2-3	0.139
Immediate recall	4.82	1.85	0-10	4.88	1.87	1-10	0.609
Delayed recall	4.85	2.27	1-12	4.92	2.20	1-12	0.623
Orientation	6.80	0.43	5-7	6.81	0.43	5-7	0.865
T-MoCA							
Attention	5.70	0.61	2-6	5.69	0.69	2-6	0.736
Language	2.38	0.75	0-3	2.43	0.71	0-3	0.315
Abstraction	1.82	0.46	0-2	1.75	0.52	0-2	0.057
Delayed Recall	3.80	1.22	0-5	3.76	1.23	0-5	0.603
Orientation	5.85	0.37	4-6	5.86	0.36	4-6	0.730

Table 8.5: Effect of time-of-day on individual sub-domains for the TICS-M and T-MoCA at (a) baseline and (b) 6-months.

	Baseline: Winter / Spring 6-month: Summer / Autumn	Baseline: Summer / Autumn 6-month: Winter / Spring	p value
Age, mean (s.d)	74.2 (4.0)	73.9 (3.4)	0.219
Male sex, % (n)	60.4% (246)	54.4% (184)	0.099
Low education, % (n)	36.1% (147)	33.4% (113)	0.444

Table 8.6: Baseline characteristics of the 407 participants that completed the initial assessment in Winter / Spring and 6-month assessment in Summer / Autumn compared with the 338 participants that completed their initial assessment in Summer / Autumn and 6-month assessment in Winter / Spring.

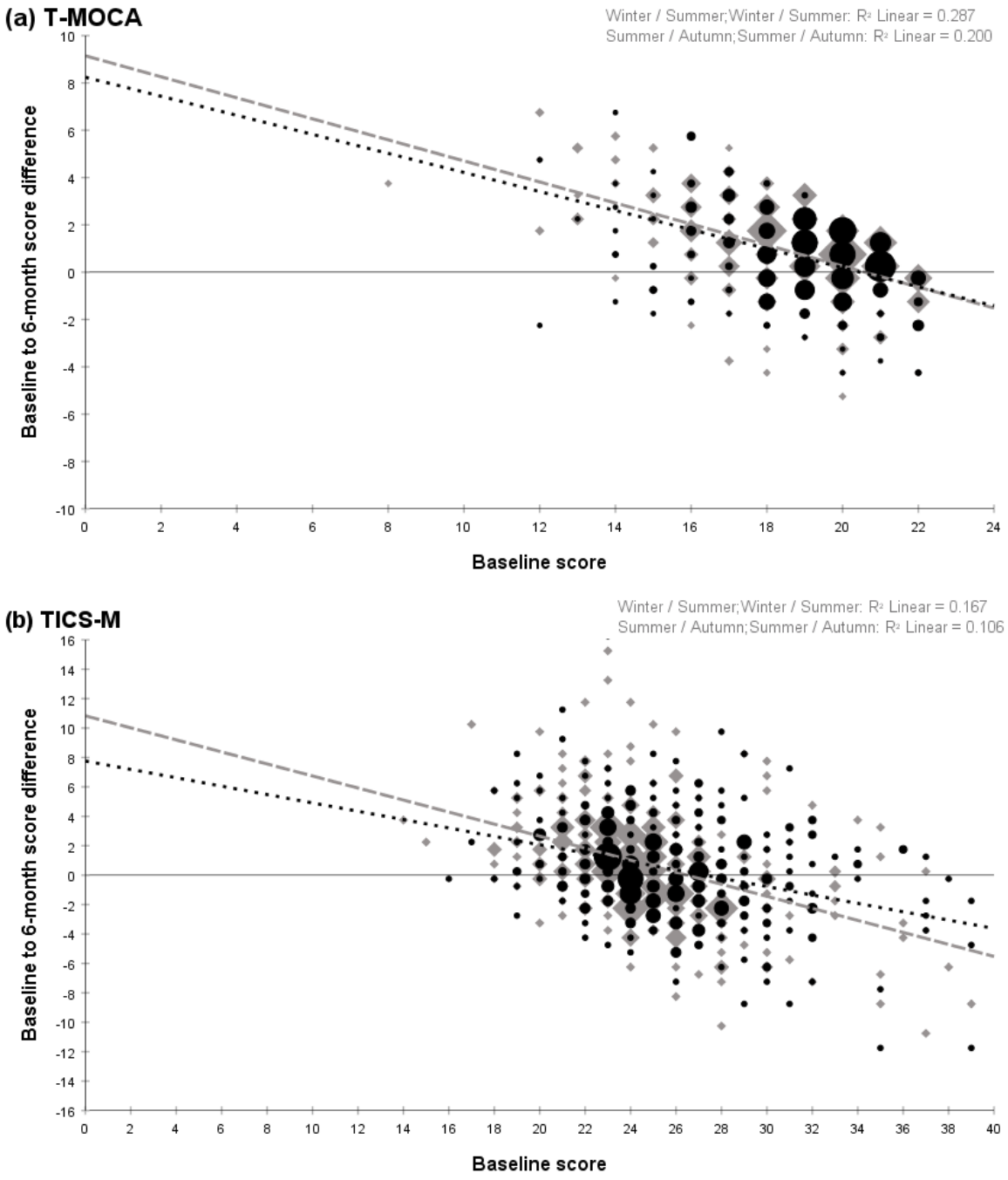

Figure 8.3: Scatter-plots of paired cognitive scores showing change (at 6-month assessment) against baseline for both (a) T-MoCA and (b) TICS-M assessments to demonstrate potential regression to the mean. The unbroken line represents perfect agreement (no change). The broken lines are fitted linear regression lines for those with baseline assessment in Winter / Summer (grey dashed line, diamonds) and those with their baseline assessment in Summer / Autumn (black, dotted line, circles).

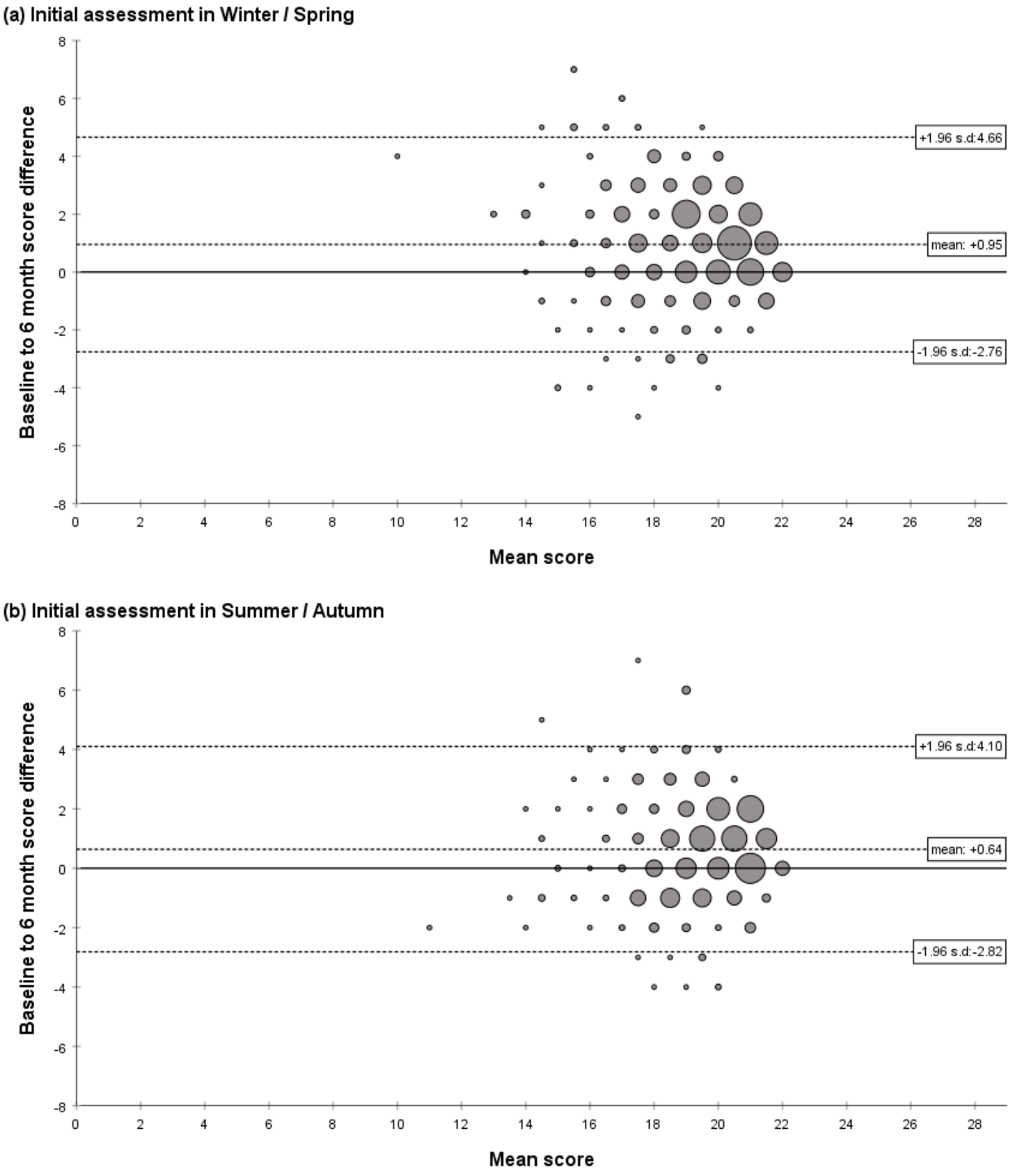

Figure 8.4: Bland-Altman plots of the change in cognitive score (at 6-month assessment) against mean score for the T-MoCA assessment for those assessed initially in (a) Winter / Spring and those assessed initially in (b) Summer / Autumn. The solid line represents perfect agreement (no change) and the dotted lines are the mean difference and 95% confidence interval.

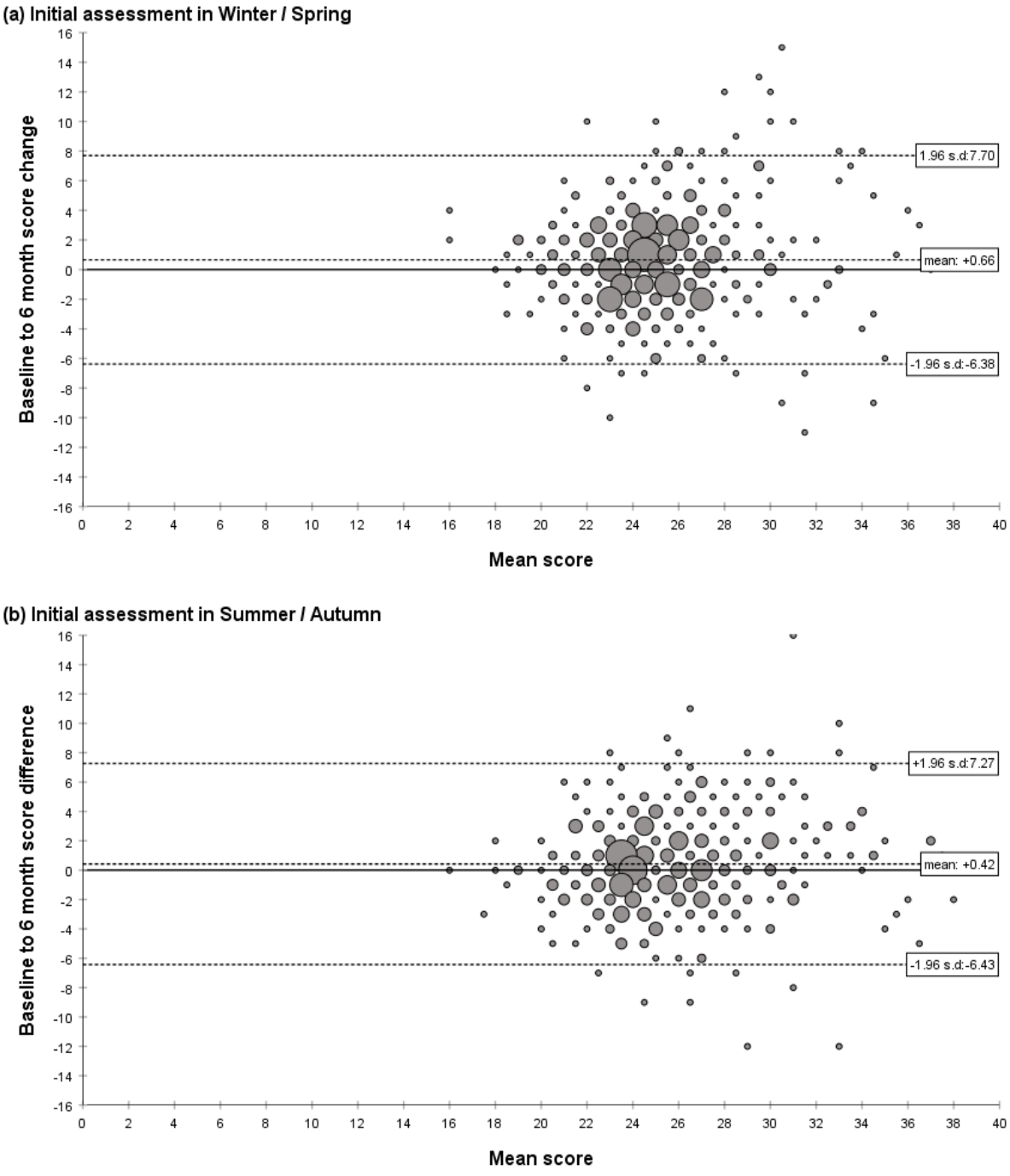

Figure 8.5: Bland-Altman plots of the change in cognitive score (at 6-month assessment) against mean score for the TICS-M assessment for those assessed initially in (a) Winter / Spring and those assessed initially in (b) Summer / Autumn. The solid line represents perfect agreement (no change) and the dotted lines are the mean difference and 95% confidence interval.

	Baseline: Winter/Spring 6-month: Summer/Autumn (n=407)		Baseline: Summer/Autumn 6-month: Winter/Spring (n=338)		Mean difference between the groups (95% C.I)	p value*
	Mean baseline score (s.d)	Mean change (s.d)	Mean baseline score (s.d)	Mean change (s.d)		
TICS-M						
Overall Cohort	24.9 (3.6)	+0.7 (3.6)	25.8 (4.0)	+0.4 (3.5)	0.2 (-0.3–0.8)	0.351
Female	25.2 (3.6)	+1.0 (4.0)	26.8 (4.4)	+0.6 (3.7)	0.4 (-0.4-1.3)	0.331
Male	24.6 (3.6)	+0.5 (3.3)	25.0 (3.5)	+0.3 (3.3)	0.2 (-0.5-0.8)	0.633
>12 years Education	25.4 (3.6)	+0.5 (3.7)	26.1 (4.0)	+0.5 (3.7)	0.1 (-0.6-0.7)	0.075
≤12 years Education	23.9 (3.4)	+0.9 (3.4)	25.1 (4.0)	+0.3 (3.0)	0.6 (-0.2-1.4)	0.174
Baseline score ≤ 25	21.4 (1.7)	+2.4 (3.1)	21.6 (1.6)	+2.0 (3.2)	0.5 (-0.4-1.3)	0.263
Baseline score > 25	26.7 (2.9)	-0.3 (3.5)	27.6 (3.3)	-0.2 (3.4)	0.0 (-0.6-0.6)	0.940
T-MoCA						
Overall Cohort	18.4 (2.3)	+1.0 (1.9)	18.9 (2.0)	+0.6 (1.8)	0.3 (0.0-0.6)	**0.020**
Female	18.9 (2.2)	+0.9 (1.8)	19.2 (1.8)	+0.5 (1.7)	0.4 (0.1-0.8)	**0.027**
Male	18.2 (2.3)	+1.0 (2.0)	18.6 (2.0)	+0.8 (1.8)	0.2 (-0.2-0.6)	0.260
>12 years Education	18.8 (2.1)	+0.9 (1.8)	19.2 (1.8)	+0.6 (1.7)	0.3 (-0.1-0.6)	0.099
≤12 years Education	17.9 (2.5)	+1.1 (2.0)	18.3 (2.2)	+0.6 (1.9)	0.4 (-0.1-0.9)	0.105
Baseline score ≤ 19	17.3 (1.8)	+1.6 (1.9)	17.6 (1.5)	+1.1 (1.8)	0.4 (0.1-0.8)	**0.016**
Baseline score > 19	20.7 (0.8)	-0.1 (1.4)	20.7 (078)	-0.1 (1.4)	0.0 (-0.3-0.3)	0.922

Table 8.7: Mean baseline and mean change in cognitive scores (at 6-months) according to the season in which the baseline and 6-month assessments were completed. Results are presented for overall cohort and stratified by sex and level of education. *p value for comparison of the mean difference in scores between the two season groups.

	Baseline: Winter/Spring 6-month: Summer/Autumn (n=407)		Baseline: Summer/Autumn 6-month: Winter/Spring (n=338)		Mean difference between the groups (95% C.I)	p value*
	Mean baseline score (s.d)	Mean change (s.d)	Mean baseline score (s.d)	Mean change (s.d)		
TICS-M						
Attention	5.5 (0.9)	+0.1 (0.9)	6.8 (0.5)	0.0 (1.0)	0.1 (-0.1-0.2)	0.454
Language	0.9 (0.3)	0.0 (0.3)	0.9 (0.3)	0.0 (0.3)	0.0 (-0.1-0.0)	0.462
Abstraction	3.0 (0.2)	0.0 (0.2)	3.0 (0.4)	0.0 (0.1)	0.0 (0.0-0.0)	0.663
Immediate recall	4.4 (1.6)	0.3 (1.8)	4.8 (1.8)	0.1 (1.7)	0.2 (-0.1-0.4)	0.150
Delayed recall	4.4 (1.9)	0.2 (2.0)	4.8 (2.2)	0.2 (2.0)	0.0 (-0.3-0.3)	0.915
Orientation	6.8 (0.5)	0.0 (0.6)	6.8 (0.5)	0.0 (0.6)	0.0 (-0.1-0.1)	0.961
T-MoCA						
Attention	5.6 (0.7)	+0.1 (0.7)	5.6 (0.6)	0.0 (0.7)	0.1 (0.0-0.2)	0.298
Language	2.2 (0.8)	+0.2 (0.7)	2.3 (0.7)	+0.1 (0.8)	0.1 (0.0-0.2)	0.199
Abstraction	1.6 (0.6)	+0.1 (0.6)	1.7 (0.5)	+0.1 (0.5)	0.1 (0.0-0.1)	0.208
Delayed recall	3.1 (1.5)	+0.6 (1.4)	3.4 (1.3)	+0.4 (1.3)	0.1 (0.0-0.3)	0.134
Orientation	5.8 (0.4)	0.0 (0.5)	5.9 (0.3)	0.0 (0.4)	0.0 (-0.1-0.1)	0.794

Table 8.8: Mean baseline and mean change (at 6-months) in the subdomains of the cognitive scores according to the season in which the baseline and 6-month assessments were completed. *p value for comparison of the mean difference in the subdomain scores between the two season groups.

CHAPTER 9

CONCLUSIONS AND FUTURE RESEARCH

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9.1 Introduction

This thesis presents data from the Oxford Vascular Study (OxVasc) and The Treatment In Morning versus Evening – Cognitive Function (TIME-COG) study. OxVasc is an ongoing population-based study of the incidence and outcome of all acute vascular events including stroke and transient ischaemic attacks. TIME-COG is an ongoing randomised, open-label study comparing morning dosing of usual antihypertensive medication with evening dosing to determine the impact upon simple cognitive screening tests in subjects aged 70 years and older.

The focus of this thesis has been to assess the psychological impact of a TIA or minor stroke, to study the relationship between stroke and dementia and to explore the feasibility and limitations of telephone cognitive assessments.

9.2 Depression after a TIA or minor stroke

Depression affects 1-in-3 patients in the first year after a stroke and is associated with a higher mortality, poorer outcomes and an increased risk of recurrent vascular events. Understanding the burden of depression and how to identify who is most at risk is therefore an important aspect of ongoing care after a stroke. However, the prevalence and risk factors for depression after a TIA are not known. Therefore, I assessed the prevalence, and risk factors, for depression one month and twelve months after a TIA and minor stroke in OxVasc. To complement this I undertook a meta-analysis of published studies on the prevalence of depression after a TIA in the acute and sub-acute time periods.

Firstly I found that the prevalence of depression after a TIA or minor stroke, whilst less than after a stroke, was still substantial affecting 1-in-5 at one month and 1-in-6 at twelve months. This was similar to other studies with a pooled prevalence rate of depression acutely of 1-in-5. Secondly, risk factors for post-event depression included pre-morbid depression and reporting often feeling sad at time of the TIA or minor stroke. Though similar acutely, by

one year the prevalence rates of depression after a TIA compared with a minor stroke diverged with a lower rate found after a TIA.

For future research, I aim to assess the prevalence rate of depression beyond the first year using the five-year follow-up geriatric depression scores that are currently being collected in OxVasc. Further work includes assessment of the anti-depressant prescription rates and their potential impact upon depression prevalence after a TIA. In my analysis the pre-morbid diagnosis of depression was retrospective, based on a combination of primary care coding and patient recollection and as such was subject to a combination of attendance and recall bias. Using data from longitudinal studies of aging, where psychological data may have been collected both before and after a stroke may remove the recall and coding biases.

9.3 Anxiety after a TIA or minor stroke

Similar to depression, anxiety affects 1-in-3 patients in the first year after a stroke. However, little is known about the prevalence and risk factors for anxiety after TIA or the relationship of anxiety with depression in these patients. Therefore I completed a meta-analysis of prevalence rates of anxiety after a TIA and assessed the prevalence and risk factors for symptoms of anxiety and depression after a TIA and minor stroke.

Firstly I found that, though restricted by a limited number of eligible studies, 1-in-10 patients had an anxiety disorder in the first six months after a TIA. However, self-reported symptoms of anxiety or depression were higher affecting nearly 1-in-3 patients in the first month after a TIA or minor stroke and nearly 1-in-4 at twelve months. Again, whilst rates were similar at one month after a TIA compared with a minor stroke they diverged by twelve months with lower rates after a TIA. Secondly, risk factors for anxiety or depression included a premorbid history of anxiety or depression, reporting often feeling sad at baseline and for the TIA subjects alone, female sex and younger age. The different longitudinal trends and risk factors suggests some differences in the mechanism behind anxiety and depression

disorders in patients after a TIA patients compared with a stroke which is a hypothesis that requires further exploration.

For further research, I aim to assess the longer-term prevalence rate of anxiety and depression symptoms (up to ten years). As OxVasc has also performed serial cognitive assessments on patients after a TIA and minor stroke I also intend to assess the interrelationship of anxiety and depression symptoms with cognitive performance. Further work should look at the diagnosis and sub-typing of anxiety disorders, both separately and in combination with depression, after a TIA.

9.4 Imaging predictors of anxiety and depression after a TIA or minor stroke

Imaging markers such as moderate-to-severe white matter disease and lesion location have been associated with post-stroke depression. Therefore, they could aid clinicians to identify patients who are at higher risk of subsequent depression and facilitate proactive counselling and heightened surveillance. However, the association of imaging markers with depression or anxiety disorders after a TIA has not been defined. Therefore, I assessed the relationship between white matter disease and acute lesions and subsequent anxiety and depression symptoms.

I was able to show that moderate-to-severe white matter disease, after adjustment for age and sex, remained associated with depression in the first year after a TIA when diagnosed using a validated assessment tool. However, the presence of an acute lesion on baseline brain imaging was not associated with subsequent anxiety and depression symptoms within the first year.

For further research I aim to further stratify the severity of white matter disease and assess whether there is a step-wise increase in the risk of subsequent depression with each increase in severity. I further aim to assess whether both subcortical and periventricular white matter disease were similarly associated with subsequent depression. Additionally, I aim to assess whether, if not the presence, but the location of the acute lesion instead was

predictive of post TIA depression or anxiety disorders. Using both the imaging markers and susceptibility factors (identified in chapter 3 and 4) I will then aim to develop and validate a risk prediction model for post TIA depression and anxiety. Further work should investigate any potential relationship between depression and other markers of small vessel disease such as microbleeds and periventricular spaces.

9.5 Mortality associated with anxiety and depression after a TIA or minor stroke

Post-stroke depression is associated with increased all-cause mortality and potentially with an increased risk of recurrent vascular events. However, the relationship between post-TIA depression and subsequent risk of recurrence or death has not been described. Therefore, I assessed the association between the 1-month and 12-month symptoms of anxiety and depression with subsequent risk of recurrent acute vascular event and death.

I was able to show that anxiety and depression symptoms within the first year were not associated with subsequent (up to 10-years) risk of recurrent stroke or of recurrent acute vascular event. However, the symptoms were associated with increased mortality, a relationship that was particularly marked in males.

For further research I aim to explore whether there are potential ameliorators of any relationship between depression / anxiety and subsequent risk of recurrent events, such as prescription of antidepressant medication or the intensive follow-up schedule in OxVasc. Additionally, I aim to explore the relationship between anxiety and depression and mortality in greater depth by describing the mortality causes. The lack of association between the symptoms and recurrent events perhaps suggests that the increased mortality is not attributable to vascular causes of death. Furthermore, the relationship may be in part confounded by the fact that anxiety and depression symptoms can be prodromal features of many dementia syndromes accounting for the increased mortality. Further work should also investigate the impact of treatment compliance and life-style modifications upon the risk of subsequent mortality. Finally as depression and anxiety disorders can engender

different life-style choices and health-seeking behaviours I aim to describe their subsequent risks of recurrence or mortality separately.

9.6 Pre-stroke dementia prevalence, time-trend and associated factors

A previous review found that one-in-ten patients who have their first stroke have pre-stroke dementia. However, previously there has been only limited description of the impact of methodological factors, such as method of diagnosis of dementia and the population studied. Furthermore, little was known about the independent associations of pre-stroke dementia. Therefore, I completed a systematic review and meta-analysis of studies on pre-stroke dementia and collated the results with the data from a longitudinal population-based study.

Firstly, as stated in the previous review, I found that overall one-in-ten patients who have their first stroke have pre-stroke dementia. Secondly, the prevalence was higher in studies that used an informant-based structured interview compared with studies that used a non-structured interview or records / coding. Thirdly, I found that the independent associations with pre-stroke dementia included increasing age, female sex, cortical atrophy, medial temporal lobe atrophy, prior stroke, silent strokes, diabetes and increasing severity of stroke.

For further research firstly I aim to describe the prevalence rate of pre-stroke dementia in intracerebral haemorrhages compared with ischaemic stroke. Secondly, I aim to assess the impact of stroke and transient ischaemic attack on patients who have pre-stroke dementia with regards to their subsequent cognitive state, risk of recurrent event and mortality. Thirdly, I aim to delineate the subtypes of pre-stroke dementia in the OxVasc population which will enable both a more detailed associated factor analysis and a description of any potential time-trend in prevalence rates of vascular and mixed dementias. Further work should address whether there is a potential impact of the new diagnostic criteria (DSM-5) upon the reported prevalence rates of pre-stroke dementia.

9.7 Post-stroke dementia prevalence, time-trend and associated factors

A previous review found that one-in-ten patients develop dementia shortly after their first stroke and more than a third after a recurrent stroke. However, since then numerous large studies on post-stroke dementia prevalence have been published and the potential impact of the significant improvements to stroke care have not been described. Therefore, I completed a systematic review and meta-analysis on studies of post-stroke dementia and collated the results with the data from a longitudinal population-based study.

Firstly, I found that the pooled prevalence of post-stroke dementia was lowest, affecting one in every ten patient, in population-based studies of first stroke where pre-stroke dementia had been excluded. The pooled prevalence was highest, affecting four in every ten patients, in hospital-based studies of recurrent stroke where pre-stroke dementia had been included. Secondly, over the past two decades the pooled prevalence of new-onset dementia in the first year after a stroke has halved from 20% to 8%. Thirdly, independent associations with post-stroke dementia reflect those associated with the stroke itself (severity, recurrence) and with those associated with neurodegenerative processes (age, low education, prior cognitive impairment).

For further research I aim to describe the prevalence rate and risk factors for post-stroke dementia beyond the first year. A more detailed analysis of the factors accountable for the potential time-trend is required as it may be compounded by factors such as the recent heightened awareness of dementia. In this study the time-trend analysis was limited by only a small number of studies reporting the prevalence rate of post-stroke dementia within the same population at different time points. As OxVasc continues to collect cognitive data on all patients I aim to use this to describe the time-trend in the prevalence rate from 2002 onwards. Given the study is upon the same population using the same methods over the years this should minimise heterogeneity and allow for an assessment of any potential associations of the trend. Confirmation of the findings through analysis of other large-scale population and hospital-based studies should also be completed.

9.8 Impediments to telephone cognitive assessments

Telephone forms of cognitive assessments are increasingly being used in longitudinal studies due to their convenience and cost-effectiveness. However, there is little literature on the possible difficulties and limitations of using these tools. Therefore, I completed a systematic review in order to assess the feasibility, reliability and reporting of potential impediments of telephone cognitive assessments. Additionally I assessed the prevalence and impact of potential impediments reported during a study of older adults who had completed two brief telephone cognitive assessments.

Firstly, I found that the majority of studies that used a telephone-based cognitive assessment did not report on any potential impediments that they had encountered. Secondly, when a study did report a potential impediment, it was most frequently related to impaired hearing. Thirdly, mild hearing impairments were not associated with lower scores on brief telephone cognitive assessments though were associated with an increased time to complete the tests.

For further research using data obtained from a longitudinal population-based study I aim to describe the prevalence and impact of potential impediments to telephone cognitive assessments in a post-stroke and post-TIA population. Assessment of the potential limitations by completion of both telephone and face-to-face brief screening assessments should be completed on an unselected, rather than volunteer based, population.

9.9 Impact of time-of-day and season on telephone cognitive assessments

Previous studies have suggested that cognitive performance exhibits both diurnal and seasonal variation. However, it is uncertain whether any such effects would influence the outcome of brief cognitive screening assessments or be sufficiently large to necessitate same time-of-day or same time-of-year testing in studies involving serial assessments. Therefore I determined whether the time-of-day or the season affected the results of telephone cognitive testing in older individuals who were at risk of stroke.

Firstly, I was able to show that the time-of-day did not affect the results of a brief telephone cognitive assessment. Secondly, I demonstrated that individuals may obtain lower scores when tested during the Winter and Spring seasons compared with during the Summer and Autumn.

For further research once TIME-COG has been unblinded I aim to repeat the analysis taking into account any impact from the timing of antihypertensive medication. Whilst not possible within this study protocol, in future the impact of the time-of-day should be assessed in a general older population within the same subject by serial assessments in the morning versus the afternoon. I also aim to assess the impact of season using cognitive assessments performed after a stroke as part of the longitudinal population-based study. This will also allow for adjustment for potential mood disorders associated with seasonal change.

9.10 Conclusion

This thesis has provided data regarding the cognitive and psychological outcomes of both TIA and strokes. Additionally it has sought to present data on the potential limitations that may be encountered during telephone-based cognitive screening. The findings of this thesis are of particular relevance to clinicians counselling patients after a TIA or stroke as to their future psychological and cognitive risks and should provide heightened insight as to the potential consequence of these conditions.

Appendix I: Ascertainment form for TIA and Stroke in The Oxford Vascular Study

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SUSPECTED TIA & STROKE

OREC A:05/Q1604/70 Year 16-

SUBJECT ID NO:

Patient identification label
(check address is current)

Was patient interviewed		**Y**	**N**
If NO why not?	Please tick		
1	Refused interview		
2	Aphasic		
3	Too unwell/ multiple medical problems		
4	Dementia (need to record AMTS)		
5	Late ascertainment from notes only		
6	Ascertainment after death		
7	Diagnosis uncertain		
9	Unknown		
10	Doesn't speak English		
11	Other: specify		
Was relative interviewed		**Y**	**N**

Patient contact details	
Telephone	(day)
Telephone (evening)	
Mobile	
Email address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone	(day)
Telephone (evening)	
Mobile phone no	
Email address	

AVIC ID			
Research Bloods	**Taken**	**Not taken**	**Incomplete set taken**
If not taken, why?	**Refused**	**Hard to bleed**	**No clinical need for venepuncture**
To be taken/completed at one month?	**Yes**	**No**	**Other plan: write below**

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SUSPECTED TIA & STROKE

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Consultant surname	

Circle consultant's specialism:

1 Physician	5 Vascular surgeon
2 Physician with stroke interest	6 Cardiologist
3 Neurologist	7 Neurosurgeon
4 General surgeon	9 Other

Name Examiner

GP DETAILS					
Location		01 Beaumont Street 02 KEY (Kidlington)	03 East Oxford 04 Berinsfield 05 Malthouse 07 Wantage	08 Marcham Road 09 Stert Street 99 Other (please provide)	Other:
Surname					
First name or Initials					

Summary Diagnosis		Specify:

S= Stroke	TNA = Transient neurological attack	O= other OCAs
T= TIA	MA = Migraine Aura	Z= Other (specify)
A= Amaurosis fugax	BL = BPPV/Labyrinthitis	
R= Retinal artery Occlusion	PS = Partial seizure	

Is this the first ever in a lifetime (incident) stroke? *	**Y**	**N**	**U**
Is this the first ever in a lifetime (incident) TIA? *	**Y**	**N**	**U**

* Please tick as appropriate

Date of notification event (DD-MM-YY)	

Location of interview	1 JRH inpatient 3 Community hosp 4 Outpatients 5 Home 6 Other (specify) 7 Not interviewed			Specify:
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up 4 Other (specify) 6 No follow-up 7 Home visits			Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify) 5 Health authority search 6 Death 9 Other (specify)			Specify:

HISTORY OF NOTIFICATION EVENT	Please tick if:	All fields unknown on page 3+4

1.1 **Narrative history & examination**

Did patient have PRANS events? (PRevious, medical Attention Not Sought)		Y	N	U
If yes, how many?		Date most recent	OXCODE for PRANS event:	
		U	2	

Describe all PRANS events in chronological order:

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SUSPECTED TIA & STROKE

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Did patient have previous suspected TIA or stroke for which they sought medical attention, but which was not diagnosed at the time?	**Y**	**N**	**U**

If yes, how many?		**Date most recent**	**OXCODE for this event:**

Details:

Notification event (The event that led to first seeking medical attention)			
Date DD-MM-YY Please indicate accuracy		**Time** 24 hr clock Please indicate accuracy	
	Accurate/ Last Seen Well/ Estimated	:	**Accurate/ Last Seen Well/ Estimated/ Unknown**

Onset during sleep?	**Y**	**N**	**U**
If Yes, time awake 24 hour clock	:		
Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
If Yes, Date/Time for initial admission	DD/MM/YY	24hr clock	
Reason for initial admission	**elective**	**emergency**	**Other, specify**
Managing team following notification event	**stroke**	**medical**	**other**
Ascertainment by OXVASC	DD/MM/YY	24hr clock	

If <u>not</u> occurring during hospital admission, location of event	1 Home 2 Work 3 Leisure (non-sport) 4 Sport 8 Other (specify) 9 Unknown		Specify:

HISTORY OF NOTIFICATION EVENT continued:

What was thought to be wrong?	**Patient himself:**			
	Other person:			
Was patient able to call for help? According to interviewer's judgement	**Y**	**N**	**U**	
Why was the patient not able to call for help? (Please choose)	**1. Found collapsed 2. Aphasic/Dysphasic 3. Confused but not aphasic 4. Other, Specify**			

Was the patient alone?	**Y**	**N, with whom:**	**U**
Who called for help?	**patient**	**other, specify:**	**U**
If the patient who was able to did not call for help, why?			**U**

Who did you/ informant 1st call for help?	1= Medical 2=Non-Medical 9= Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
1st call for ANY help non-medical or medical			Please give date/time for any 1st call *	
				: U
1st call for MEDICAL help GP/ A&E / 999/ NHS direct			Please give date/time for 1st medical call	
				: U

* This could be the same date and time as the first call for medical help (please provide anyway)

Outcome of first call for medical assistance (flow)
Please summarise the flow **e.g. 999→A&E→admitted; Called GP→GP appointment→NHS clinic→OXVASC clinic**

Have you **recently stopped taking** (circle) aspirin / clopidogrel / anticoagulation?	**Y**	**N**	**U**	Date DD-MM-YY	Reason
After the onset of symptoms, did you take aspirin before taking medical advice?	**Y**	**N**	**U**	Date DD-MM-YY	Time 24 hr clock

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SUSPECTED TIA & STROKE

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CALLS FOR MEDICAL ATTENTION

			Date DD-MM-YY	Time 24 hr clock	Aspirin				Brain Scan Y/N	Outcome D= discharged R= referred A= admitted G= for GP review
GP by telephone	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
GP in person	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
Telephoned 999	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
If relevant: ambulance sent out	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
Ambulance arrival with patient				:	**given**	**already on**	**N**	**U**		
Ambulance arrival in hospital				:	**given**	**already on**	**N**	**U**		
Went to A&E in person	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
Telephoned NHS direct / 111	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
Went to Oxford Eye Hospital	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
Went to CAU (Community Assessment Unit)	**Y**	**N**		:	**given**	**already on**	**N**	**U**		
Other (Specify)				:	**given**	**already on**	**N**	**U**		

				Date DD-MM-YY	Time 24 hr clock
Seen in A&E but not admitted?	**Y**	**N**	**U**		:
Admitted to hospital? (If admitted from A&E, give time seen in A&E as time of admission)	**Y**	**N**	**U**		: U

Managing team	**ASU**	**Med**	**Neuro**	**Other**

Ascertainment by OXVASC staff		: U

HISTORY OF NOTIFICATION EVENT continued

Was patient seen as an outpatient?	**Y**	**N**	**U**
	Date DD-MM-YY		**Time** 24 hr clock
If GP referred subject to OXVASC clinic: **Notification by GP to OXVASC**	U		: U
If referred by A&E/med/ambulance to OXVASC clinic **Referral from A&E /medical team/ ambulance**	U		: U
If seen first in NHS TIA clinic, **Assessment** by NHS clinic	U		: U
Ascertainment by OXVASC staff	U		: U

Was there a further event between notification event and assessment?	Y	N	U

Event	**History of events between notification event and assessment**		
2		**Event date*:** U	**Time** : U
3		**Event date*:** U	**Time** : U

Use extra piece of paper for event 4 onwards. * DD-MM-YY 24 Hr clock

ANY PREVIOUS ACUTE VASCULAR EVENT (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						**Cerebral**						**Aortic or Peripheral**		
	NSTEMI			**STEMI**			**TIA**			**CVA**					
Prior acute events?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Date of most recent			U			U			U			U			U
Any not known to OXVASC?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
If unknown-to-OXVASC event, reason: 1: before 01/04/2002 2: with non-OXVASC GP 3: Missed by OXVASC															

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SUSPECTED TIA & STROKE

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MEDICAL HISTORY **PRIOR** TO NOTIFICATION EVENT

Please tick if:	**All No**	**All U**

	Y/N/U											
Angina												
Hypertension		**Treated?**					**Y**		**N**		**U**	
Diabetes Mellitus		**Treatment**										
		Diet			**Tablets**				**Insulin**			
		Y	**N**	**U**	**Y**	**N**	**U**		**Y**	**N**	**U**	
Valvular heart disease		**Nature:**										U
Intermittent Claudication												
Peripheral vascular intervention		**Site:**		1 Arm 2 Leg 3 Bowel 4 Carotid		5 Abdo aneurysm 6 Thoracic aneurysm 7 Other 8 Uncertain						
		Type:	**Angiogram**			**Angioplasty**			**Bypass**			**Amputation**
			Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Atrial fibrillation (diagnosed **before** this TIA/stroke)		1 Current 2 Previous 9 Unknown										
		OUTCOME 1=Cardioversion 2=Paroxysmal 3=Persistent 4=Permanent 9=Unknown										
Pacemaker		**Type pacemaker**										
Hyper lipidaemia		**Treatment**										
		Diet			**Statin**				**Other**			
		Y	**N**	**U**	**Y**	**N**	**U**		**Y**	**N**	**U**	
Cardiac failure		**Treated** (loop diuretic)**?**							**Y**	**N**	**U**	
Migraine		**With Aura?**			**Prolonged aura (>1hr)**				**Aura type**			
		Y	**N**	**U**	**Y**	**N**	**U**					
		How long since the last episode?			**Days**	**Weeks**	**Months**		**Years**		**More than 10 years**	

MEDICAL HISTORY **PRIOR** TO NOTIFICATION EVENT - CONTINUED

Please tick if:	**All No**	**All U**	
	Y/N/U choose		
Epilepsy			

Cardiac intervention		**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**		
			Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Carotid: Endarterectomy		**Side**		
		Left	**Right**	**Both**

Carotid: Stent		**Side**		
		Left	**Right**	**Both**

Diagnosed dementia? (check notes)		**Type:**		**1: Alzheimer's** **2: Vascular** **3: Mixed** **4: Lewy body**	**5: Other** **9: Dementia of unknown type**

Ever referred to a memory clinic? (check notes)		**Which area clinic or consultant?**	

Depression diagnosed? (by a clinician, not self-diagnosed)		**Age first diagnosed**		**Age at most recent treated episode**	

COAD		

GI HISTORY	**Peptic ulcer disease**			**GI bleed**			**Persistent dyspepsia**			**Persistent diarrhoea**		
	Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Previous venous thromboses		
End stage renal failure/ dialysis		

Cancer (excluding localised non-melanoma skin cancer)		**Type(s)**		**Number**	

Any other past medical history		**Details:** enter U if unknown

Allergies	Please list all. If no allergies or unknown please enter No or Unknown.

Have you ever been on OCP?	**Y**	**N**	**U**	**Years:**
Have you ever been on HRT?	**Y**	**N**	**U**	**Years:**
Are you currently on OCP or HRT?	**Y**	**N**	**U**	**Include details on medication page**

MEDICATION AT THE TIME OF THE NOTIFICATION EVENT

Was subject taking medication <u>at the time</u> of the notification event? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other ASK: *hormonal contraception? HRT? Nicotine replacement?*					
Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter “No other”.				

MEDICATION AT DISCHARGE OR DEATH (inpatients)
PRESCRIPTION GIVEN AT ASCERTAINMENT CLINIC (clinic patients)

Was subject's medication <u>changed</u> following the notification event? If YES provide details below				Y	N	U
Drug Category	**Change** **0**: Unchanged **1**: new drug added **2**: stopped **3**: up dose **4**: down dose **5**: other **9**: unknown	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet						
Anticoagulant	If considering a NOAC prescription, get a *measured* weight.					
BP lowering						
Lipid lowering						
Other						
Other additional medication + dose/unit		If all lines above have been used and subject is not taking other medication please enter "No other".				

BIRTH HISTORY

Were you born premature?	**Y**	**N**	**U**	**Gestation if known**
Were there complications at your birth?	**Y**	**N**	**U**	**Details**

FAMILY HISTORY

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest →

		Mum	Dad	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
	Age 1st*														
MI	**Y/N/U**														
	Age 1st*														
Diabetes	**Y/N/U**														
	Age 1st*														
Dementia	**Y/N/U**														
	Age 1st*														

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U
Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12 youngest	**A**	**D**	**U**	**M**	**F**	U	U

Total number of subject's children	Number of sons	Number of daughters	Any information about children

SMOKING TOBACCO

Have you ever smoked?	**Y**	**N**	**U**
Are you a lifetime non-smoker?	**Y**	**N**	**U**
Smoking oddities (pipes etc)			U
Are you an ex-smoker?	**Y**	**N**	**U**
If so how long ago did you stop? (< 1 month = current smoker)	**Years**		**Months**
<u>If you have stopped</u>: How many years did you smoke?	# Years:		U
Do you currently smoke?	**Y**	**N**	**U**
How many do you smoke per day?	Number:		U
<u>If you are still smoking</u>: How many years have you smoked?	# Years:		U

E-CIGARETTES/ VAPING

Have you ever used e-cigs/vapers?	**Y**		**N**		**U**
Are you currently using e-cigs/vapers?	**Y** At least daily		**N** Or less than daily		**U**
How much liquid is used daily (mls)?	**<1**	**1-2**	**>2-5**	**>5**	
Preferred type of vaping	Cigarette-like	Shisha-like	Pipe-like		
Steam effect	**Y**		**N**		**U**
Nicotine concentration	zero	low	medium	high	**U**
Tobacco taste	**Y**		**N**		**U**

Premorbid modified Rankin

Do you have any symptoms?	**Y**	**N**	**U**
Are you able to look after yourself and carry out normal activities?	**Y**	**N**	**U**
Does anyone else help pay the bills, do the shopping, cleaning etc?	**Y**	**N**	**U**
Do you need someone to help you walk?	**Y**	**N**	**U**
Do you need help to wash yourself?	**Y**	**N**	**U**
Do you need to be lifted in and out of bed?	**Y**	**N**	**U**

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death 7 = Estimated 0, 1 or 2 8 = Estimated 3, 4 or 5	Key differences between scores: ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**
1= Interview 2 = Medical notes 3 = GP notes 4 = Other (please specify)	***Other:***	**Source**

OXFORD VASCULAR STUDY 1August2017

SUSPECTED TIA & STROKE

OREC A:05/Q1604/70 Year 16-

PREMORBID BARTHEL

1. The index should be used as a record of what a patient does, ***not*** a record of what a patient can do. It considers ability not technique, over the last month.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
4. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent.

	Key	Score
Feeding	0 = Unable 1 = Needs help cutting, spreading butter, etc, or requires modified diet 2 = Independent	
Bathing	0 = Dependent 1 = Independent (or in shower)	
Grooming	0 = Needs help with personal care 1 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 = Dependent 1 = Needs help but can do about half unaided 2 = Independent (including buttons, zips, laces, etc.)	
Bowels	0 = Incontinent (or needs to be given enemas) 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Bladder	0 = Incontinent, or catheterised and unable to manage alone 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Toilet use	0 = Dependent 1 = Needs some help, but can do something alone 2 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 = Unable, no sitting balance 1 = Major help (one or two people, physical), can sit 2 = Minor help (verbal or physical) e.g. asst of 1 person 3 = Independent	
Mobility (on level surfaces)	0 = Immobile 1 = Wheelchair independent, including corners, > 50 metres 2 = Walks with help of one person (verbal or physical) > 50 metres 3 = Independent (but may use any aid; for example, stick) > 50 metres	
Stairs	0 = Unable 1 = Needs help (verbal, physical, carrying aid) 2 = Independent	
	BARTHEL SCORE	
	Source of information 1 = Interview, 2 = Estimated from Medical notes 3 = Estimated from GP notes 4 = other (please specify below)	
Notes:		

OXFORD VASCULAR STUDY 1August2017

SUSPECTED TIA & STROKE

OREC A:05/Q1604/70 **Year 16-**

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND				
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing 5 Care home 8 Other (specify) 9 Not known		**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**SPOUSE or:**	
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility		
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer 4 Community services (specify) 5 No assistance needed 6 Friend or neighbour 9 Not known		**4-Specify:**
Marital status		1 Married 2 Widow 3 Single 4 Separated 5 Partner 9 Not known		
Age left school				
Education		1 Basic 2 Further 3 Higher 9 Not known		
Age left full-time education				
Employment status		1 Working FT 2 Working PT 3 Caring for home 4 Unemployed 5 Unable to work 6 Retired 7 Student 9 Not known		
Age of retirement				
Most recent occupation (spouse's occupation if not employed)		U		
Socioeconomic class		1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**		
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known		
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known		
Alcohol units per week		*Use table below to calculate weekly alcohol units; only the total units is required data.*		
If less than one alcohol unit per week:		**Units per: (circle)**	**Month**	**Year**

(Sparkling) wine and Champagne			
	ml	10%-units	14% - units
M glass	175	1.75	2.5
L glass	250	2.5	3.5
Bottle		7.5	10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)		
	ml	Units
Small	25	1
Large	35	1.3
Double	50	2
L double	70	2.8

Lager, Beer and Cider			
	ml	4% - units	9%-units
Bottle	330	1.3	3
Can	440	1.8	4
Pint	568	2.3	5.1

275 ml bottle alcopops
1.4 units
50 ml glass Sherry/ Port
1 Unit

IF USUAL LIVING ARRANGEMENT IS A CARE HOME - turn to next page.

Do you live alone?
Yes ☐ No ☐ If **No**, who do you live with?.....

Does anyone give you any kind of help because of long-term physical or mental ill-health / disability, or problems related to old age?

Yes ☐ No ☐ (If **No**: turn to next page. If Yes, continue below.)

Types of help include: (choose the number for the highest-dependency help received)
1=Personal care, e.g. dressing, bathing, showering, eating, getting in/out of bed, using the toilet
2=Practical household help, e.g. preparing meals, gardening, transportation, shopping, household chores
3=Other e.g. Help with paperwork, such as filling out forms, settling financial or legal matters

Who provides help?	Care provided by the person(s) who lives with you	Not living-in care, e.g. relative, friend, neighbour, charitable organisation (Specify……)	Professional/paid help (Specify care giving agency if known……)
Type of help:	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3 Was help two-handed? Yes ☐ No ☐
How often do you receive this help? (Total for personal, practical and other)		☐ daily ☐ weekly ☐ monthly ☐ Less often	☐ daily ☐ weekly ☐ monthly ☐ Less often
How many times/hours do you receive this help?		If daily: ____ times per day If weekly: ____ hours per week If monthly: ____ hours per month If less often: ____ hours per year	If daily: ____ times per day If weekly: ____ hours per week If monthly: ____ hours per month If less often: ____ hours per year

Do you receive Attendance Allowance/ Disability Living Allowance? No ☐ Yes, lower rate ☐ Yes, higher rate ☐

Do you attend a day centre or luncheon club? No ☐ Yes ☐ Number of days per week____

Do you have respite care? No ☐ Yes ☐ Number of weeks per year ____

Notes:

SLEEP				
What is the likelihood of you dozing in the following <u>three</u> situations:				
1) Sitting and reading				0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon				
3) Sitting and talking to someone				
On average, how many hours of sleep do you get per night?			U	
Do you snore?	Y	N	U	
Do you snore loudly (louder than talking or loud enough to be heard through a closed door)?	Y	N	U	
Have you been told that you stop breathing at night?	Y	N	U	
People tell me that I snore				1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8 = I don't know 9 = Unknown C=Already on CPAP for Sleep Apnoea
People tell me that I gasp, choke or snort while I am sleeping				

NUTRITION			
How is your appetite?		1= Good 2= Normal	3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U		
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week	3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U		
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed	4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week	4= 1 /day 5= 2-4 /day 6= > 4 /day 9= Unknown

OXFORD VASCULAR STUDY 1August2017

SUSPECTED TIA & STROKE

OREC A:05/Q1604/70 Year 16-

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	**Y**	**N**	**U**	
DRIVING	Do you drive?	**Y**	**N**	**U**	
HANDEDNESS		**Left**	**Right**	**Both**	**Unknown**
MEMORY	Do you have problems with memory?	**Y**	**N**	**U**	
FALLS	Have you had any falls in the past year?	**None**	**One**	**More than one**	**Unknown**
	Have you ever been referred to a falls clinic?	**Y**	**N**	**U**	
Clinical impression of frailty					1= Frail 2= Normal 9= Unknown

AMTS		
Age	**0**	**1**
Time (nearest hour)	**0**	**1**
Give address for later recall: ask patient to repeat it to check they have heard correctly. "42, West Street".		
Year	**0**	**1**
Name of place	**0**	**1**
Recognition of 2 persons (eg doctor, nurse)	**0**	**1**
Date and month of birth	**0**	**1**
Date of 1st World War (either 1914 or 1918)	**0**	**1**
Name of present Monarch	**0**	**1**
Count 20-1 backwards	**0**	**1**
Recall full street address	**0**	**1**
	0= Fail 1= Pass	

If AMTS not done, why not?		
1 Sensory impairment: 1a Poor vision 1b Deaf	2 Aphasic 3 Refused 4 Severe dementia	5 Language barrier 6 Too Unwell 7 Other: Specify

GENERAL EXAMINATION			
	cm*	**inches***	
Collar size			U
Waist measurement			U
Hip measurement			U
Height			U
	kg*	**stone***	
Weight *			U

*Data entry instructions: Please take care not to enter inches in cm box, and vice versa. If entering feet/inches or stone/ pounds, do not leave the inches or pounds box blank; fill in with zero if relevant, so that the BMI calculation will happen.

If considering prescribing a NOAC, measured weight is needed.

If not done, please put down the reason and if possible an estimated BMI:

Reason for not done	
Estimated BMI	

For all patients: 1st HEART RATE and BLOOD PRESSURE post event				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	:	U
Blood pressure 1st BP post event		**Sys**	**Dias**	U
Heart rate 1st HR post event				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE at admission				
Temp on admission		ºC		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects:
HEART RATE, RHYTHM and BLOOD PRESSURE
at assessment (for inpatients record last two BPs from epr)

Blood Pressure:	**Side**			**Cuff size**				**Systolic**	**Diastolic**	**HR**
Sitting or lying	**L**	**R**	**U**	**S**	**M**	**L**	**U**			
Sitting or lying	**L**	**R**	**U**	**S**	**M**	**L**	**U**			
Standing	**L**	**R**	**U**	**S**	**M**	**L**	**U**			

Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Any pre-existing neurological disability?		Y	N	U

OXFORD VASCULAR STUDY 1August2017

SUSPECTED TIA & STROKE

OREC A:05/Q1604/70 Year 16-

Normal exam | All Unknown

SYMPTOMS AT ONSET

	Weakness		Sensory		Eyes/vision			Other	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemianopia**			**Dysphasia**	
Arm					**Monocular**			**Dysarthria**	
Hand					**Diplopia**			**Vertigo**	
Leg								**Dizziness without Vertigo**	
Confusion	1: None 2: Usual for them 3: Worse than usual 4: New 9: Unknown							**Unsteadiness**	
								Headache	

FINDINGS ON EXAMINATION

Glasgow Coma Scale			
Eyes	**/4**	1 – No eye opening 2 – Eye opening in response to pain	3- Eye opening in response to speech 4- Spontaneous eye opening
Motor	**/6**	1 – No response to pain 2 – Extensor posturing to pain 3 - Flexor response to pain	4 – Withdrawal to pain 5 - Localizing response to pain 6 – Obeys commands
verbal	**/5**	1 – No speech 2 – Incomprehensible speech 3 – Inappropriate speech	4 – Confused conversation 5 – Oriented

	Weakness		Sensory		Eyes/ vision		Other	
	Right	Left	Right	Left	Right	Left		
	Please fill in: Y / N / U				Y / N / U			Y / N / U
Face							**Dysphasia**	
Arm							**Dysarthria**	
Hand							**Ataxia**	
Leg							**Neglect**	
							Swallowing problem	

NIH STROKE SCALE *- AT TIME OF ASSESSMENT* For instructions see separate sheet				Source:		**1:EXAMINED 2:ESTIMATED FROM NOTES 3:NOT DONE**	
LOC		LOC questions		LOC commands		Best gaze	
Best visual		Facial Palsy		Left arm		Right arm	
Left leg		Right leg		Limb ataxia		Sensory	
Language		Dysarthria		Neglect		**TOTAL**	

NIH STROKE SCALE *- worst score in first 24 hours* For instructions see separate sheet				Source:		**1:EXAMINED 2:ESTIMATED FROM NOTES 3:NOT DONE**	
LOC		LOC questions		LOC commands		Best gaze	
Best visual		Facial Palsy		Left arm		Right arm	
Left leg		Right leg		Limb ataxia		Sensory	
Language		Dysarthria		Neglect		**TOTAL**	

ABCD^2 score: for all <u>transient</u> neurological attacks including TIA/TNA/stroke mimics

A (Age)	1 point for age ≥60 years	
B (Blood pressure)	1 point for ≥ 140/90 mmHg at the acute evaluation	
C (Clinical features)	2 points for unilateral weakness 1 for speech disturbance without weakness	
D (Symptom Duration)	2 points for ≥60 minutes 1 point for 10-59 minutes	
D (Diabetes)	1 point	
Total		

Symptom duration:		
Hours	Minutes	Seconds

For digits 1-9 see Z:\Oxvasc\ OXVASC file SD and codes \coding_for_events_ interventions_investigations

11 digit OXCODE for notification event										

"Syndromes" coding definitions (last two digits) (For detailed definitions see Z:\Oxvasc\OXVASC file SD and codes\OXCODE DEFINITIONS)	
01. Isolated Vertigo (IV)	12. Classical migraine (different to usual)
02. "Vertigo Plus " (VP)	13. Ischaemic Migraine (IM)
03. Isolated Double Vision (IDV)	14. Transient Confusion (TC)
04. Microvascular Cranial Nerve Lesions (CN)	15. Vascular Cognitive Impairment (VCI)
05. Other Binocular Visual Disturbance (BVD)	16. Low Flow Phenomena (LF)
06. Retinal Migraine (RM)	17. Hemisensory symptoms (HS)
07. Atypical Amaurosis fugax (AAF)	18. Unexplained Coma Death (UCD)
08. Transient Total Paralysis (TTP)	19. Non-Stroke Cerebrovascular Burden (B)
09. Transient Speech Arrest (TSA)	20. Other
10. Isolated slurred speech (ISS)	21. Probable/definite TIA or stroke
11. Classical Migraine (no migraine history)	22. Stroke without ictus

For inpatient strokes:

Date of discharge	
Discharge destination: 1. Home 2. Community Hospital 3. OCE 4. Care home 5. Relative's home 6. Death 7. Other (specify)	
Functional status at discharge	

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

DATE DD/MM/YYYY**:**

CATEGORY:

Please check previous correspondence and circle one
For Afx please circle TIA

Possible	TIA	STROKE	OTHER:
Probable			SAH ICH
Definite			

Follow up form completed / entered by Name:

Signature:

CHANGES TO DEMOGRAPHICS (PLEASE ADD TO DATABASE)

Name?	**Y**	**N**	
Address?	**Y**	**N**	
Telephone number?	**Y**	**N**	
GP name?	**Y**	**N**	
GP surgery?	**Y**	**N**	
Can provide control?	**Y**	**N**	
Signed consent for this event?	**Y**	**N**	

SOCIAL HISTORY

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)		
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home 6 In intermediate care e.g. community hospital, OCE	7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	Other:
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

Currently smoking tobacco?	Y	N	U
Currently smoking e-cigarettes?	Y	N	U
Are you driving?	Y	N	U
Are you in paid employment?	Y	N	U

OBJECTIVE ASSESSMENT

Time BP taken	**Side**		**Cuff size**			**Systolic**	**Diastolic**	**HR**
At start of FU	**L**	**R**	**S**	**M**	**L**			

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

Cardiac rhythm on palpation	**4 = Regular**	**5 = Irregular**
If irregular and untreated please recommend ECG in out patients		

RECURRENT EVENTS SINCE ASCERTAINMENT If 'Yes' please complete recurrent event form and enter event on spreadsheet				
Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			**1**	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			**1**	
			2	
			3	
Stroke (>24h)			**1**	
			2	
Acute PVD event embolus, aneurysm			**1**	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

OTHER EVENTS SINCE ASCERTAINMENT					
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**	
Admissions					
Admissions?			**1**		
			2		
Procedures?			**1**		
			2		
Memory					
Hospital admission during which you were confused or muddled?			**1**		
			2		
Referred to a memory clinic? (check notes)				**Which area clinic or consultant?**	
Diagnosed dementia? (check notes)		Type:		1: Alzheimer's 2: Vascular 3: Mixed 4: Lewy body	5: Other 6: MCI 9: Dementia of unknown type
		Source:		1: GP 2: Memory clinic 3: Other physician	4: Unknown 5: Other (please specify)
AF					
New AF?		Type:		1 = Paroxysmal 2 = Persistent 3 = Permanent 4 = Unknown	
		Mode:		1 = ECG 2 = Prolonged monitoring 3 = Unknown	

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

OTHER EVENTS SINCE ASCERTAINMENT				
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**
New diagnosis				
Cancer?				
Major diseases e.g. Parkinson's, #, Surgery?			1	
			2	
			3	
Further information				
Seizures?				
Clinically diagnosed depression?				
Symptoms from current treatment				
Bleeding requiring medical attention?				
Persistent diarrhoea?				
Low magnesium?				
Pneumonia?				
Other				
Falls				
Any falls?			1	
			2	
			3	
Syncope?				
Light-headedness or dizziness?				
Referral to falls clinic?				

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

MOCA TESTING

Perform the test in the following order:

1. Naming (animals)
2. Visuospatial/executive
   - Clock
   - Cube
   - Trail test

Then follow the order shown on the sheet

Record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet on the following page. Similarly, please record start and finish time for the MMSE at the end of the follow-up.	
Problems with cognitive testing Please record any problems with testing at the end of the MMSE using the boxes provided	

For further information, please see the information sheet (and please refer to this each time you perform the MoCA to ensure consistency of administration).

When conducting the assessment face to face, ask subject to answer <u>all</u> MOCA questions (max score:30).

When conducting the assessment over the phone, ask all MOCA items not requiring a visual stimulus (max score: 22). For tapping at the letter A, ask patient to tap on the side of the phone with a pen or pencil. In the database, select “telephone MOCA” from the drop-down box.

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

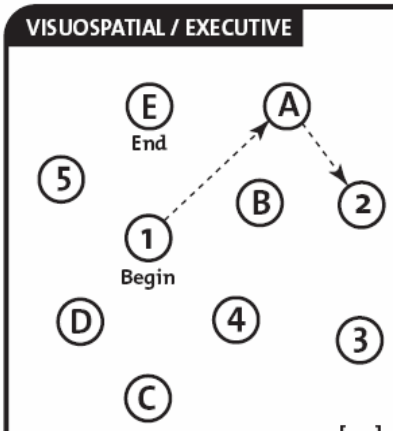
Please complete ALL fields

MOCA	Full test*	Short test*	Not done
	START TIME:		

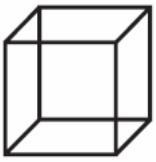
Age finished school:
Any further/higher education: Y / N
Any diploma/degree: Y / N

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

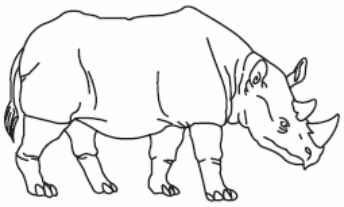
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

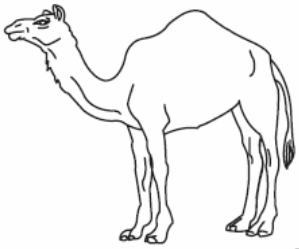
NAMING



[ ]



[ ]



[ ] __/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

PHONE

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt __/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

PHONE

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

PHONE

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

PHONE

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

FINISH TIME:	

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

Is subject taking medication? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od/bd/tds/ qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant *(If new, check if for AF)*					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					
Other additional medication + dose/unit, or information on compliance	If all lines above have been used and subject is not taking other medication please enter "No other".				
Blood pressure medication changes	Name of drug changed		Name of drug changed		
	Date of change		Date of change		
	Who made change?		Who made change?		
	Why change made?		Why change made?		

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

RANKIN SCORE

Do you have ***any*** symptoms?	Y	N	U
Are you able to look after yourself and carry out normal activities?	Y	N	U
Does anyone else help pay the bills, do the shopping, cleaning etc? check that this is different since the event	Y	N	U
Do you need someone to help you walk?	Y	N	U
Do you need help to wash yourself?	Y	N	U
Do you need to be lifted in and out of bed?	Y	N	U

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death 7 = Estimated 0, 1 or 2 8 = Estimated 3, 4 or 5	Key differences between scores: ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**
1= Interview 2 = Medical notes 3 = GP notes 4 = Other (please specify)	***Other:***	**Source**

If there is significant *non-stroke* disability, enter reason in "other comments" box on database.

SIMPLE QUESTIONS

Please ask the patient:

Do you need help with every day activities?										Y	N	U
Following your vascular event	1	3	6	12	18	24	36	48	60	months ago		
Have you been left with any problems?										Y	N	U
Have you made a full recovery?										Y	N	U

Other comments

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

BARTHEL

1. The index should be used as a record of what a patient does, ***not*** a record of what a patient can do. It considers ability not technique, over the last 24-48 hours.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
4. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent.

	Key	Score
Feeding	0 = Unable 1 = Needs help cutting, spreading butter, etc, or requires modified diet 2 = Independent	
Bathing	0 = Dependent 1 = Independent (or in shower)	
Grooming	0 = Needs help with personal care 1 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 = Dependent 1 = Needs help but can do about half unaided 2 = Independent (including buttons, zips, laces, etc.)	
Bowels	0 = Incontinent (or needs to be given enemas) 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Bladder	0 = Incontinent, or catheterised and unable to manage alone 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Toilet use	0 = Dependent 1 = Needs some help, but can do something alone 2 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 = Unable, no sitting balance 1 = Major help (one or two people, physical), can sit 2 = Minor help (verbal or physical) e.g. asst of 1 person 3 = Independent	
Mobility (on level surfaces)	0 = Immobile 1 = Wheelchair independent, including corners, > 50 metres 2 = Walks with help of one person (verbal or physical) > 50 metres 3 = Independent (but may use any aid; for example, stick) > 50 metres	
Stairs	0 = Unable 1 = Needs help (verbal, physical, carrying aid) 2 = Independent	

BARTHEL SCORE	
Source of information **1 = Interview, 2 = Estimated from Medical notes 3 = Estimated from GP notes 4 = other (please specify below)**	
Notes:	

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

RIVERMEAD MOBILITY INDEX

The patient is asked the following 15 questions and observed (for item 5). Score 1 if the answer is Yes, and 0 for the answer No.

1. Score 1 if they complete the task independently using an aid e.g. climb stairs with 1 stick
2. Score 0 if equipment does the task for them e.g. stairlift, helping hand
3. Help is defined as the assistance of a person.

	QUESTION	COMMENT	N = 0 Y = 1	
1	Do you turn over from your back to your side without help?		N	Y
2	From lying in bed do you get up to sit on the edge of the bed?		N	Y
3	Do you sit on the edge of the bed without holding on for 10 seconds?		N	Y
4	Do you stand up (from any chair) in less then 15 sec & stand there for 15 sec (using hands & with aid if necessary)?		N	Y
5	Observe standing for 10 sec without any aid or support.		N	Y
6	Do you manage to move, e.g. from bed to chair and back, without any help?		N	Y
7	Do you walk 10 metres, with an aid or furniture if necessary but with no stand-by help?		N	Y
8	Do you manage a flight of stairs without help?		N	Y
9	Do you walk around outside, on pavements without help?		N	Y
10	Do you walk 10m inside with no calliper, splint or aid and no stand-by help?		N	Y
11	If you drop something on the floor, do you manage to walk 5 m, pick it up and walk back?		N	Y
12	Do you walk around outside over uneven ground (grass, gravel, dirt, snow etc) without help?		N	Y
13	Do you get in/out of the bath or shower unsupervised and wash yourself?		N	Y
14	Do you manage to go up and down four steps with no rail, but with using an aid if necessary?		N	Y
15	Do you run 10m without limping in 4 seconds? (fast walk is acceptable)		N	Y
		TOTAL		/15

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

YOUR OWN HEALTH STATE TODAY

By placing a TICK in ONE box in each group below, please indicate which statement best describes your own health state today.

DO NOT TICK MORE THAN ONE BOX IN EACH GROUP

MOBILITY	
I have no problems in walking about	
Or: I have some problems in walking about	
Or: I am confined to bed	

SELF-CARE	
I have no problems with self-care	
Or: I have some problems washing or dressing myself	
Or: I am unable to wash or dress myself	

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	
Or: I have some problems with performing my usual activities	
Or: I am unable to perform my usual activities	

PAIN / DISCOMFORT	
I have no pain or discomfort	
Or: I have moderate pain or discomfort	
Or: I have extreme pain or discomfort	

ANXIETY / DEPRESSION	
I am not anxious or depressed	
Or: I am moderately anxious or depressed	
Or: I am extremely anxious or depressed	

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

Please could you indicate on this scale, in your opinion, how good or bad your health is today. Please do this by drawing a line from the box on the left to whichever point on the scale indicates your health state. The best state you can imagine is 100, the worst state is 0.

Best imaginable health state



Your own health state today ▶

Worst imaginable health state

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

Instructions: Circle the answer that best describes how you felt over the **past week**

1	Are you basically satisfied with your life?	Yes	No
2	Have you dropped many of your activities and interests?	Yes	No
3	Do you feel that your life is empty?	Yes	No
4	Do you often get bored?	Yes	No
5	Are you in good spirits most of the time?	Yes	No
6	Are you afraid that something bad is going to happen to you?	Yes	No
7	Do you feel happy most of the time?	Yes	No
8	Do you often feel helpless?	Yes	No
9	Do you prefer to stay at home, rather than going out and doing new things?	Yes	No
10	Do you feel that you have more problems with memory than most?	Yes	No
11	Do you feel it's wonderful to be alive?	Yes	No
12	Do you feel pretty worthless the way you are now?	Yes	No
13	Do you feel full of energy?	Yes	No
14	Do you feel that your situation is hopeless?	Yes	No
15	Do you think that most people are better off than you?	Yes	No
	Total	/15	

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

Symbol digit coding task. Look at the key to see which number goes with each symbol. Complete the practice section (up to thick line); interviewer will correct if necessary.
Then complete as many as you can, as accurately as you can, in **90 seconds**.

								
1	2	3	4	5	6	7	8	9

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

MMSE: MINI MENTAL STATE EXAMINATION

START TIME*:*

ORIENTATION TO TIME, What is the…

NOTE: IGNORE the items shown in smaller type (these have already been assessed in the MoCA) and only ask the highlighted questions

	Response		
Year?		0	1
Season?		0	1
Month of the year?		0	1
Day of the week?		0	1
Date?		0	1
	TOTAL		

ORIENTATION TO PLACE*, Where are we now, what is the…

	Response		
County?		0	1
City/town/village		0	1
Street (suburb)		0	1
House name/ no (building name)		0	1
Room of house (ward number/level)		0	1
	TOTAL		

***** Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are …APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but only score on the first trial]

	Response		
APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

**Now keep those words in mind. I am going to ask you to say them again in a few minutes. ***Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION

NOTE: Perform the WORLD task on all subjects
DO NOT USE THIS SCORE IN THE TOTAL MMSE SCORE, INSTEAD USE THE SERIAL 7S SCORE FROM THE MOCA.

Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling.

D		L		R		O		W		Score 1 each	

RECALL

What were those three words I asked you to remember? *[Do not offer any hints]*

APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

NAMING*			
What is this? [point to pencil/ pen]		**0**	**1**
What is this? [watch]		**0**	**1**
	TOTAL		
* Alternative common objects (e.g.eyeglasses, chair, keys may be substituted and noted			

REPETITION			
Now I am going to ask you to repeat what I say. Ready? "NO IFs ANDs OR BUTs." Now you say that. [repeat up to 5 times, but score only on the first trial]			
NO IFs ANDs OR BUTs		0	1
	TOTAL		

COMPREHENSION			
Listen carefully because I am going to ask you to do something. Take this paper in your right hand *[pause]*, **fold it in half** *[pause]***, and put it on the floor (or table).**			
Take in right hand		0	1
Fold in half		0	1
Put on floor/table		0	1
	TOTAL		

READING			
Please read this and do what it says. [Show the examinee the words on the stimulus form]			
Close your eyes		0	1
	TOTAL		

WRITING		
Please write a sentence. [If examinee does not respond, say: **Write about the weather.**] Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.	0	1

DRAWING		
Please copy this design. [Display the intersecting pentagons on the stimulus form]. Score 1 point if the drawing consists of two 5-sided figures that intersect to from a 4-sided figure.	0	1
FINISH TIME:		
NB Using serial 7s score and NOT WORLD TOTAL/30		

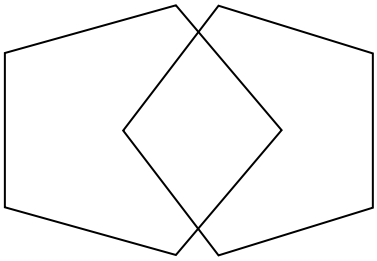
Any problem with testing? ie the MMSE/MoCA **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment a) Poor vision b) Deaf c) Both 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor 6 Co-existent neurological dis.	7 First language not English 8 Other - specify 9 Only MoCA done, not MMSE 10 Only MMSE done, not MoCA 11 Fatigued 12 Incomplete at request of patient/family IL Illiteracy C Known cognitive impairment
If not done, why not? ie if the MMSE/MoCA was **not** done, what was the reason?		1 Sensory impairment a) Poor vision b) Deaf c) Both 2 Aphasic 3 Refused cognitive testing 4 Severe dementia	5 Illiterate 6 Language barrier 7 Unwell 8 Telephone/email FU 9 Other , specify 10 MoCa and MMSE both done 11 Fatigued

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

CLOSE YOUR EYES



Time BP taken	Side		Cuff size			Systolic	Diastolic	HR
At end of FU	L	R	S	M	L			
Standing if required	L	R	S	M	L			

SUBJECT ID NO:

MONTH 1 – CLINIC PATHWAY

Please complete ALL fields

OUTSTANDING INVESTIGATIONS

Blood Pressure:

2 BP readings taken	**Y**	**N**	**Target over 130/80mmHg?**	**Y**	**N**
If so why?					
24 hour BP needed?	**Y**	**N**	**Fitted and downloaded?**	**Y**	**N**
Conventional monitor needed?	**Y**	**N**	**Loan form entered onto database?**	**Y**	**N**

Bloods:

Clinical Bloods taken?	**Y**	**N**
Green bottle: **Lipids Profile, Creatinine Kinase, LFTs, U&Es (incl Urea), Magnesium and Calcium** Gold bottle: **B12 and Folate if MMSE <24; Other? (please specify)**		
If not taken, why?		
Any research bloods taken at this appointment?	**Y**	**N**

Other investigations:

Echo done?	**Y**	**N**	**If no why?**
TCD done?	**Y**	**N**	**If no why?**
R Test done?	**Y**	**N**	**If no why?**
X ray meeting form completed	**Y**	**N**	**If no why?**
Other investigations required	**Y**	**N**	**Please specify**

IQCODE:

Completed and entered?	YES	NO
Issued with prepaid envelope?	YES	NO
If not done, please give the reason		

Appendix III: Six-month follow-up form for TIA and Stroke in The Oxford Vascular Study

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

DATE DD/MM/YYYY:

CATEGORY:

Please check previous correspondence and circle one

Possible	TIA	STROKE	OTHER:
Probable			SAH ICH
Definite			

For Afx please circle TIA

Follow up form completed / entered by Name:

Signature:

CHANGES TO DEMOGRAPHICS (PLEASE ADD TO DATABASE)

Name?	**Y**	**N**	
Address?	**Y**	**N**	
Telephone number?	**Y**	**N**	
GP name?	**Y**	**N**	
GP surgery?	**Y**	**N**	
Can provide control?	**Y**	**N**	

SOCIAL HISTORY

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)		
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home	6 In intermediate care e.g. community hospital, OCE 7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	Other:
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

Currently smoking tobacco?	Y	N	U
Currently smoking e-cigarettes?	Y	N	U
Are you driving?	Y	N	U
Are you in paid employment?	Y	N	U

OBJECTIVE ASSESSMENT

Time BP taken	**Side**		**Cuff size**			**Systolic**	**Diastolic**	**HR**
At start of FU	**L**	**R**	**S**	**M**	**L**			

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

Cardiac rhythm on palpation	**4 = Regular**	**5 = Irregular**
If irregular and untreated please recommend ECG at GP practice		

RECURRENT VASCULAR EVENTS SINCE LAST FOLLOW-UP

If 'Yes' please complete recurrent event form and enter event on spreadsheet

Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			**1**	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			**1**	
			2	
			3	
Stroke (>24h)			**1**	
			2	
Acute PVD event embolus, aneurysm			**1**	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

OTHER EVENTS SINCE LAST FOLLOW UP					
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**	
Admissions					
Admissions?			**1**		
			2		
Procedures?			**1**		
			2		
Memory					
Hospital admission during which you were confused or muddled?			**1**		
			2		
Referred to a memory clinic? (check notes)				**Which area clinic or consultant?**	
Diagnosed dementia? (check notes)		Type:		1: Alzheimer's 2: Vascular 3: Mixed 4: Lewy body	5: Other 6: MCI 9: Dementia of unknown type
		Source:		1: GP 2: Memory clinic 3: Other physician	4: Unknown 5: Other (please specify)
AF					
New AF?		Type:		1 = Paroxysmal 2 = Persistent 3 = Permanent 4 = Unknown	
		Mode:		1 = ECG 2 = Prolonged monitoring 3 = Unknown	

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

OTHER EVENTS SINCE LAST FOLLOW UP				
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**
New diagnosis				
Cancer?				
Major diseases e.g. Parkinson's, #, Surgery?			1	
			2	
			3	
Further information				
Seizures?				
Clinically diagnosed depression?				
Symptoms from current treatment				
Bleeding requiring medical attention?				
Persistent diarrhoea?				
Low magnesium?				
Pneumonia?				
Other				
Falls				
Any falls?			1	
			2	
			3	
Syncope?				
Light-headedness or dizziness?				
Referral to falls clinic?				

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

MOCA TESTING

Perform the test in the following order:

1. Naming (animals)
2. Visuospatial/executive
   - Clock
   - Cube
   - Trail test

Then follow the order shown on the sheet

Record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet on the following page. Similarly, please record start and finish time for the MMSE at the end of the follow-up.	
Problems with cognitive testing Please record any problems with testing at the end of the MMSE using the boxes provided	

For further information, please see the information sheet (and please refer to this each time you perform the MoCA to ensure consistency of administration).

When conducting the assessment face to face, ask subject to answer <u>all</u> MOCA questions (max score:30).

When conducting the assessment over the phone, ask all MOCA items not requiring a visual stimulus (max score: 22). For tapping at the letter A, ask patient to tap on the side of the phone with a pen or pencil. In the database, select “telephone MOCA” from the drop-down box.

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

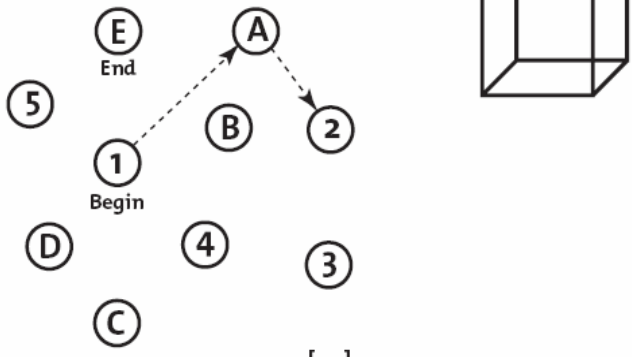
MOCA	Full test*	Short test*	Not done

START TIME:

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Age finished school:
Any further/higher education: Y / N
Any diploma/degree: Y / N

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

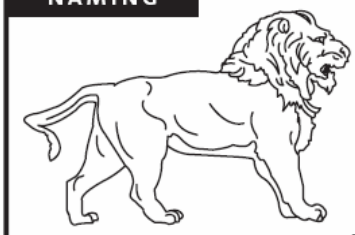
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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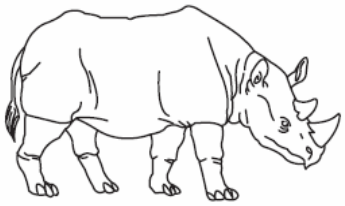

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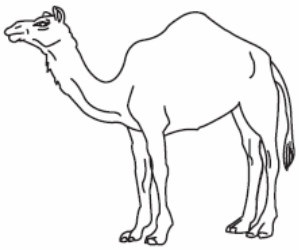

[ ]

__/3

PHONE

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

PHONE

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

PHONE

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

PHONE

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

FINISH TIME:

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

Is subject taking medication? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od/bd/tds/ qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant *(If new, check if for AF)*					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					
Other additional medication + dose/unit, or information on compliance	If all lines above have been used and subject is not taking other medication please enter "No other".				
Blood pressure medication changes	Name of drug changed		Name of drug changed		
	Date of change		Date of change		
	Who made change?		Who made change?		
	Why change made?		Why change made?		

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

IF USUAL LIVING ARRANGEMENT IS A CARE HOME - turn to next page.

Do you live alone?

Yes ☐ No ☐ If **No**, who do you live with?.....

Does anyone give you any kind of help because of long-term physical or mental ill-health / disability, or problems related to old age?

Yes ☐ No ☐ (If **No**: turn to next page. If Yes, continue below.)

Types of help include: (choose the number for the highest-dependency help received)
1=Personal care, e.g. dressing, bathing, showering, eating, getting in/out of bed, using the toilet
2=Practical household help, e.g. preparing meals, gardening, transportation, shopping, household chores
3=Other e.g. Help with paperwork, such as filling out forms, settling financial or legal matters

Who provides help?	Care provided by the person(s) who lives with you	Not living-in care, e.g. relative, friend, neighbour, charitable organisation (Specify……)	Professional/paid help (Specify care giving agency if known……)
Type of help:	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3 Was help two-handed? Yes ☐ No ☐
How often do you receive this help? (Total for personal, practical and other)		☐ daily____ times per day ☐ weekly____ hours per week ☐ monthly____ hours per month ☐ Less often____ hours per year	☐ daily____ times per day ☐ weekly____ hours per week ☐ monthly____ hours per month ☐ Less often____ hours per year

Do you receive Attendance Allowance/ Disability Living Allowance? No ☐ Yes, lower rate ☐ Yes, higher rate ☐

Do you attend a day centre or luncheon club? No ☐ Yes ☐ Number of days per week____

Do you have respite care? No ☐ Yes ☐ Number of weeks per year ____

Notes:

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

RANKIN SCORE

Do you have ***any*** symptoms?	Y	N	U
Are you able to look after yourself and carry out normal activities?	Y	N	U
Does anyone else help pay the bills, do the shopping, cleaning etc? check that this is different since the event	Y	N	U
Do you need someone to help you walk?	Y	N	U
Do you need help to wash yourself?	Y	N	U
Do you need to be lifted in and out of bed?	Y	N	U

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death 7 = Estimated 0, 1 or 2 8 = Estimated 3, 4 or 5	Key differences between scores: ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**
1= Interview 2 = Medical notes 3 = GP notes 4 = Other (please specify)	***Other:***	**Source**

If there is significant *non-stroke* disability, enter reason in "other comments" box on database.

SIMPLE QUESTIONS

Please ask the patient:

Do you need help with every day activities?										Y	N	U
Following your vascular event	1	3	6	12	18	24	36	48	60	months ago		
Have you been left with any problems?										Y	N	U
Have you made a full recovery?										Y	N	U

Other comments

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

BARTHEL

1. The index should be used as a record of what a patient does, ***not*** a record of what a patient can do. It considers ability not technique, over the last 24-48 hours.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
4. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent.

	Key	Score
Feeding	0 = Unable 1 = Needs help cutting, spreading butter, etc, or requires modified diet 2 = Independent	
Bathing	0 = Dependent 1 = Independent (or in shower)	
Grooming	0 = Needs help with personal care 1 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 = Dependent 1 = Needs help but can do about half unaided 2 = Independent (including buttons, zips, laces, etc.)	
Bowels	0 = Incontinent (or needs to be given enemas) 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Bladder	0 = Incontinent, or catheterised and unable to manage alone 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Toilet use	0 = Dependent 1 = Needs some help, but can do something alone 2 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 = Unable, no sitting balance 1 = Major help (one or two people, physical), can sit 2 = Minor help (verbal or physical) e.g. asst of 1 person 3 = Independent	
Mobility (on level surfaces)	0 = Immobile 1 = Wheelchair independent, including corners, > 50 metres 2 = Walks with help of one person (verbal or physical) > 50 metres 3 = Independent (but may use any aid; for example, stick) > 50 metres	
Stairs	0 = Unable 1 = Needs help (verbal, physical, carrying aid) 2 = Independent	

BARTHEL SCORE	
Source of information **1 = Interview, 2 = Estimated from Medical notes 3 = Estimated from GP notes 4 = other (please specify below)**	
Notes:	

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

RIVERMEAD MOBILITY INDEX

The patient is asked the following 15 questions and observed (for item 5).
Score 1 if the answer is Yes, and 0 for the answer No.

1. Score 1 if they complete the task independently using an aid e.g. climb stairs with 1 stick
2. Score 0 if equipment does the task for them e.g. stairlift, helping hand
3. Help is defined as the assistance of a person.

	QUESTION	COMMENT	N = 0 Y = 1	
1	Do you turn over from your back to your side without help?		N	Y
2	From lying in bed do you get up to sit on the edge of the bed?		N	Y
3	Do you sit on the edge of the bed without holding on for 10 seconds?		N	Y
4	Do you stand up (from any chair) in less then 15 sec & stand there for 15 sec (using hands & with aid if necessary)?		N	Y
5	Observe standing for 10 sec without any aid or support.		N	Y
6	Do you manage to move, e.g. from bed to chair and back, without any help?		N	Y
7	Do you walk 10 metres, with an aid or furniture if necessary but with no stand-by help?		N	Y
8	Do you manage a flight of stairs without help?		N	Y
9	Do you walk around outside, on pavements without help?		N	Y
10	Do you walk 10m inside with no calliper, splint or aid and no stand-by help?		N	Y
11	If you drop something on the floor, do you manage to walk 5 m, pick it up and walk back?		N	Y
12	Do you walk around outside over uneven ground (grass, gravel, dirt, snow etc) without help?		N	Y
13	Do you get in/out of the bath or shower unsupervised and wash yourself?		N	Y
14	Do you manage to go up and down four steps with no rail, but with using an aid if necessary?		N	Y
15	Do you run 10m without limping in 4 seconds? (fast walk is acceptable)		N	Y
		TOTAL		/15

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

YOUR OWN HEALTH STATE TODAY

By placing a TICK in ONE box in each group below, please indicate which statement best describes your own health state today.

DO NOT TICK MORE THAN ONE BOX IN EACH GROUP

MOBILITY	
I have no problems in walking about	
Or: I have some problems in walking about	
Or: I am confined to bed	

SELF-CARE	
I have no problems with self-care	
Or: I have some problems washing or dressing myself	
Or: I am unable to wash or dress myself	

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	
Or: I have some problems with performing my usual activities	
Or: I am unable to perform my usual activities	

PAIN / DISCOMFORT	
I have no pain or discomfort	
Or: I have moderate pain or discomfort	
Or: I have extreme pain or discomfort	

ANXIETY / DEPRESSION	
I am not anxious or depressed	
Or: I am moderately anxious or depressed	
Or: I am extremely anxious or depressed	

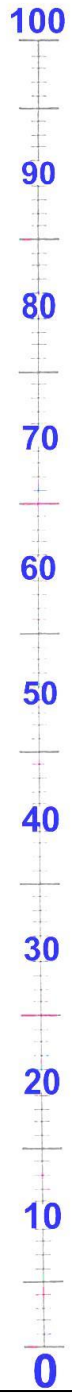
SUBJECT ID NO:

MONTH 6

Please complete ALL fields

Please could you indicate on this scale, in your opinion, how good or bad your health is today. Please do this by drawing a line from the box on the left to whichever point on the scale indicates your health state. The best state you can imagine is 100, the worst state is 0.

Best imaginable health state



Your own health state today ▶

Worst imaginable health state

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

FATIGUE QUESTIONNAIRE

To be completed if Barthel ≥18/20 and MMSE ≥24/30

Please answer all the questions simply by underlining or circling the answer that you think most nearly applies to you.

We would like to know whether or not you have been having any problems with feeling tired, weak or lacking in energy in the last month. If you have been feeling tired for a long time we want you to compare yourself to how you felt when last well.

1	Do you have problems with tiredness?	Less than usual	No more than usual	More than usual	Much more than usual
2	Do you need to rest more?	Less than usual	No more than usual	More than usual	Much more than usual
3	Do you feel sleepy or drowsy?	Less than usual	No more than usual	More than usual	Much more than usual
4	Do you have problems starting things?	Less than usual	No more than usual	More than usual	Much more than usual
5	Do you lack energy?	Less than usual	No more than usual	More than usual	Much more than usual
6	Do you have less strength in your muscles?	Better than usual	No more than usual	More than usual	Much more than usual
7	Do you feel weak?	Less than usual	No more than usual	More than usual	Much more than usual
8	Do you have difficulty concentrating?	Less than usual	No more than usual	More than usual	Much more than usual
9	Do you make slips of the tongue when speaking?	Less than usual	No more than usual	More than usual	Much more than usual
10	Do you find it more difficult to find the correct word?	Less than usual	No more than usual	More than usual	Much more than usual
11	How is your memory?	Better than usual	No worse than usual	Worse than usual	Much worse than usual

Why do you think you are feeling tired? (Please try to give one reason).

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

MMSE: MINI MENTAL STATE EXAMINATION

START TIME*:*

ORIENTATION TO TIME, What is the…

NOTE: IGNORE the items shown in smaller type (these have already been assessed in the MoCA) and only ask the highlighted questions

	Response		
Year?		0	1
Season?		0	1
Month of the year?		0	1
Day of the week?		0	1
Date?		0	1
	TOTAL		

ORIENTATION TO PLACE*, Where are we now, what is the…

	Response		
County?		0	1
City/town/village		0	1
Street (suburb)		0	1
House name/ no (building name)		0	1
Room of house (ward number/level)		0	1
	TOTAL		

***** Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are …APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but only score on the first trial]

	Response		
APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

**Now keep those words in mind. I am going to ask you to say them again in a few minutes. ***Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION

NOTE: Perform the WORLD task on all subjects
DO NOT USE THIS SCORE IN THE TOTAL MMSE SCORE, INSTEAD USE THE SERIAL 7S SCORE FROM THE MOCA.

Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling.

D		L		R		O		W		Score 1 each	

RECALL

What were those three words I asked you to remember? *[Do not offer any hints]*

APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

NAMING*			
What is this? [point to pencil/ pen]		**0**	**1**
What is this? [watch]		**0**	**1**
	TOTAL		
* Alternative common objects (e.g.eyeglasses, chair, keys may be substituted and noted			
REPETITION			
Now I am going to ask you to repeat what I say. Ready? "NO IFs ANDs OR BUTs." Now you say that. [repeat up to 5 times, but score only on the first trial]			
NO IFs ANDs OR BUTs		0	1
	TOTAL		
COMPREHENSION			
Listen carefully because I am going to ask you to do something. Take this paper in your right hand *[pause]*, **fold it in half** *[pause]***, and put it on the floor (or table).**			
Take in right hand		0	1
Fold in half		0	1
Put on floor/table		0	1
	TOTAL		
READING			
Please read this and do what it says. [Show the examinee the words on the stimulus form]			
Close your eyes		0	1
	TOTAL		
WRITING			
Please write a sentence. [If examinee does not respond, say: **Write about the weather.**] Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.		0	1
DRAWING			
Please copy this design. [Display the intersecting pentagons on the stimulus form]. Score 1 point if the drawing consists of two 5-sided figures that intersect to from a 4-sided figure.		0	1
	FINISH TIME:		
NB Using serial 7s score and NOT WORLD	TOTAL/30		

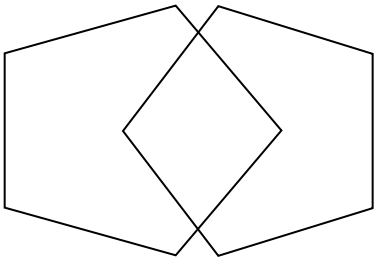
Any problem with testing? ie the MMSE/MoCA **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment a) Poor vision b) Deaf c) Both 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor 6 Co-existent neurological dis.	7 First language not English 8 Other - specify 9 Only MoCA done, not MMSE 10 Only MMSE done, not MoCA 11 Fatigued 12 Incomplete at request of patient/family IL Illiteracy C Known cognitive impairment
If not done, why not? ie if the MMSE/MoCA was **not** done, what was the reason?		1 Sensory impairment a) Poor vision b) Deaf c) Both 2 Aphasic 3 Refused cognitive testing 4 Severe dementia	5 Illiterate 6 Language barrier 7 Unwell 8 Telephone/email FU 9 Other , specify 10 MoCa and MMSE both done 11 Fatigued

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

CLOSE YOUR EYES



Time BP taken	Side		Cuff size			Systolic	Diastolic	HR
At end of FU	L	R	S	M	L			
Standing if required	L	R	S	M	L			

SUBJECT ID NO:

MONTH 6

Please complete ALL fields

If undecided at 3 month follow up, asked about brain donation?	Y	N	If consented, copy to patient, notes and add to GP letter. Send original form
1 Consented 2 Refused 3 Undecided, please ask at next FU			

OUTSTANDING INVESTIGATIONS

Blood Pressure:

2 BP readings taken	**Y**	**N**	**Target over 130/80mmHg?**	**Y**	**N**
If so why?					
Using conventional home BP monitor?	**Y**	**N**	**Conventional readings collected / new sheet issued?**	**Y**	**N**

Other investigations required	**Y**	**N**	**Please specify**

1 mn IQCODE FORM received and entered?	YES	NO

Appendix IV: Twelve-month and Five-year follow-up form for TIA and Stroke in The Oxford Vascular Study

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

DATE DD/MM/YYYY**:**

CATEGORY:

Please check previous correspondence and circle <u>one</u>

Possible	TIA	STROKE	OTHER:
Probable			SAH ICH
Definite			

For Afx please circle TIA

Follow up form completed / entered by Name:

Signature:

CHANGES TO DEMOGRAPHICS (PLEASE ADD TO DATABASE)

Name?	**Y**	**N**	
Address?	**Y**	**N**	
Telephone number?	**Y**	**N**	
GP name?	**Y**	**N**	
GP surgery?	**Y**	**N**	
Can provide control?	**Y**	**N**	

SOCIAL HISTORY

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)		
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home	6 In intermediate care e.g. community hospital, OCE 7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	<u>Other:</u>
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	<u>Other:</u>

Currently smoking tobacco?	Y	N	U
Currently smoking e-cigarettes?	Y	N	U
Are you driving?	Y	N	U
Are you in paid employment?	Y	N	U

OBJECTIVE ASSESSMENT

Time BP taken	**Side**		**Cuff size**			**Systolic**	**Diastolic**	**HR**
At start of FU	**L**	**R**	**S**	**M**	**L**			

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

Cardiac rhythm on palpation	**4 = Regular**	**5 = Irregular**
If irregular and untreated please recommend	**ECG in OP if seen in clinic**	**ECG at GP practice if HV**

RECURRENT VASCULAR EVENTS SINCE LAST FOLLOW-UP If 'Yes' please complete recurrent event form and enter event on spreadsheet				
Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			**1**	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			**1**	
			2	
			3	
Stroke (>24h)			**1**	
			2	
Acute PVD event embolus, aneurysm			**1**	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

OTHER EVENTS SINCE LAST FOLLOW-UP					
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**	
Admissions					
Admissions			**1**		
			2		
Procedures			**1**		
			2		
Memory					
Hospital admission during which you were confused or muddled			**1**		
			2		
More forgetful in past 12 months to the extent that it's affected daily life?					
Referred to a memory clinic? (check notes)				**Which area clinic or consultant?**	
Diagnosed dementia? (check notes)		Type:		1: Alzheimer's 2: Vascular 3: Mixed 4: Lewy body	5: Other 6: MCI 9: Dementia of unknown type
		Source:		1: GP 2: Memory clinic 3: Other physician	4: Unknown 5: Other (please specify)
AF					
New AF?		Type:		1 = Paroxysmal 2 = Persistent 3 = Permanent 4 = Unknown	
		Mode:		1 = ECG 2 = Prolonged monitoring 3 = Unknown	
Repeat R Test required?		**Notes:**			
5 year clinic patients only: AVIC MRI					
AVIC ID					
Willing to have a repeat AVIC MRI in future for research purposes?		**Y**	**N**	**If Y, we may contact them at a later date**	

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

OTHER EVENTS SINCE LAST FOLLOW-UP				
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**
New diagnosis				
Cancer?				
Major diseases e.g. Parkinson's, #, Surgery?			1	
			2	
			3	
Further information				
Seizures?				
Clinically diagnosed depression?				
Symptoms from current treatment				
Bleeding requiring medical attention?				
Persistent diarrhoea?				
Low magnesium?				
Pneumonia?				
Other				
Falls				
Any falls?			1	
			2	
			3	
Syncope?				
Light-headedness or dizziness?				
Referral to falls clinic?				

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

MOCA TESTING

Perform the test in the following order:

1. Naming (animals)
2. Visuospatial/executive
   - Clock
   - Cube
   - Trail test

Then follow the order shown on the sheet

Record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet on the following page. Similarly, please record start and finish time for the MMSE at the end of the follow-up.	
Problems with cognitive testing Please record any problems with testing at the end of the MMSE using the boxes provided	

For further information, please see the information sheet (and please refer to this each time you perform the MoCA to ensure consistency of administration).

When conducting the assessment face to face, ask subject to answer <u>all</u> MOCA questions (max score:30).

When conducting the assessment over the phone, ask all MOCA items not requiring a visual stimulus (max score: 22). For tapping at the letter A, ask patient to tap on the side of the phone with a pen or pencil. In the database, select “telephone MOCA” from the drop-down box.

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

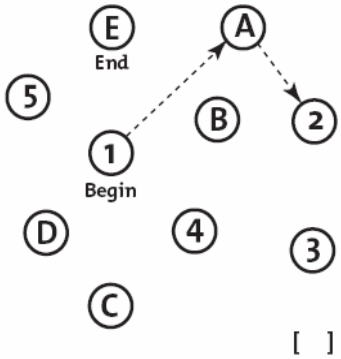
MOCA	Full test*	Short test*	Not done

START TIME:

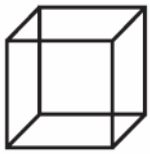
Age finished school:
Any further/higher education: Y / N
Any diploma/degree: Y / N

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

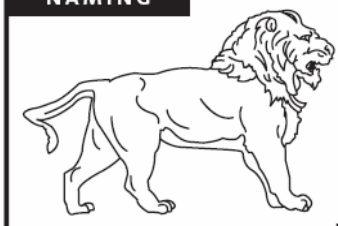
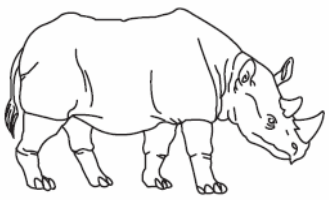
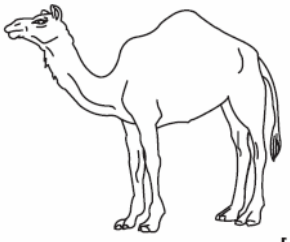


[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING

[ ] [ ] [ ] __/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

FINISH TIME:

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

Is subject taking medication? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od/bd/tds/ qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant *(If new, check if for AF)*					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					
Other additional medication + dose/unit, or information on compliance	If all lines above have been used and subject is not taking other medication please enter "No other".				
Blood pressure medication changes	Name of drug changed		Name of drug changed		
	Date of change		Date of change		
	Who made change?		Who made change?		
	Why change made?		Why change made?		

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

IF USUAL LIVING ARRANGEMENT IS A CARE HOME - turn to next page.

Do you live alone?

Yes ☐ No ☐ If **No**, who do you live with?.....

Does anyone give you any kind of help because of long-term physical or mental ill-health / disability, or problems related to old age?

Yes ☐ No ☐ (If **No**: turn to next page. If Yes, continue below.)

Types of help include: (choose the number for the highest-dependency help received)
1=Personal care, e.g. dressing, bathing, showering, eating, getting in/out of bed, using the toilet
2=Practical household help, e.g. preparing meals, gardening, transportation, shopping, household chores
3=Other e.g. Help with paperwork, such as filling out forms, settling financial or legal matters

Who provides help?	Care provided by the person(s) who lives with you	Not living-in care, e.g. relative, friend, neighbour, charitable organisation (Specify……)	Professional/paid help (Specify care giving agency if known……)
Type of help:	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3 Was help two-handed? Yes ☐ No ☐
How often do you receive this help? (Total for personal, practical and other)		☐ daily____ times per day ☐ weekly____ hours per week ☐ monthly____ hours per month ☐ Less often____ hours per year	☐ daily____ times per day ☐ weekly____ hours per week ☐ monthly____ hours per month ☐ Less often____ hours per year

Do you receive Attendance Allowance/ Disability Living Allowance? No ☐ Yes, lower rate ☐ Yes, higher rate ☐

Do you attend a day centre or luncheon club? No ☐ Yes ☐ Number of days per week____

Do you have respite care? No ☐ Yes ☐ Number of weeks per year ____

Notes:

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

RANKIN SCORE

Do you have ***any*** symptoms?	Y	N	U
Are you able to look after yourself and carry out normal activities?	Y	N	U
Does anyone else help pay the bills, do the shopping, cleaning etc? check that this is different since the event	Y	N	U
Do you need someone to help you walk?	Y	N	U
Do you need help to wash yourself?	Y	N	U
Do you need to be lifted in and out of bed?	Y	N	U

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death 7 = Estimated 0, 1 or 2 8 = Estimated 3, 4 or 5	Key differences between scores: ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**
1= Interview 2 = Medical notes 3 = GP notes 4 = Other (please specify)	***Other:***	**Source**

If there is significant *non-stroke* disability, enter reason in "other comments" box on database.

Please ask the patient:

Do you need help with every day activities?									Y	N	U
Following your vascular event	1	3	6	12	18	24	36	48	60	months ago	
Have you been left with any problems?									Y	N	U
Have you made a full recovery?									Y	N	U

Other comments

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

BARTHEL

1. The index should be used as a record of what a patient <u>does</u>, ***not*** a record of what a patient can do. It considers ability not technique, over the last 24-48 hours.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
4. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent.

	Key	Score
Feeding	0 = Unable 1 = Needs help cutting, spreading butter, etc, or requires modified diet 2 = Independent	
Bathing	0 = Dependent 1 = Independent (or in shower)	
Grooming	0 = Needs help with personal care 1 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 = Dependent 1 = Needs help but can do about half unaided 2 = Independent (including buttons, zips, laces, etc.)	
Bowels	0 = Incontinent (or needs to be given enemas) 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Bladder	0 = Incontinent, or catheterised and unable to manage alone 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Toilet use	0 = Dependent 1 = Needs some help, but can do something alone 2 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 = Unable, no sitting balance 1 = Major help (one or two people, physical), can sit 2 = Minor help (verbal or physical) e.g. asst of 1 person 3 = Independent	
Mobility (on level surfaces)	0 = Immobile 1 = Wheelchair independent, including corners, > 50 metres 2 = Walks with help of one person (verbal or physical) > 50 metres 3 = Independent (but may use any aid; for example, stick) > 50 metres	
Stairs	0 = Unable 1 = Needs help (verbal, physical, carrying aid) 2 = Independent	

BARTHEL SCORE	
Source of information **1 = Interview, 2 = Estimated from Medical notes 3 = Estimated from GP notes 4 = other (please specify below)**	
Notes:	

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

RIVERMEAD MOBILITY INDEX

The patient is asked the following 15 questions and observed (for item 5). Score 1 if the answer is Yes, and 0 for the answer No.

1. Score 1 if they complete the task independently using an aid e.g. climb stairs with 1 stick
2. Score 0 if equipment does the task for them e.g. stairlift, helping hand
3. Help is defined as the assistance of a person.

	QUESTION	COMMENT	N = 0 Y = 1	
1	Do you turn over from your back to your side without help?		N	Y
2	From lying in bed do you get up to sit on the edge of the bed?		N	Y
3	Do you sit on the edge of the bed without holding on for 10 seconds?		N	Y
4	Do you stand up (from any chair) in less then 15 sec & stand there for 15 sec (using hands & with aid if necessary)?		N	Y
5	Observe standing for 10 sec without any aid or support.		N	Y
6	Do you manage to move, e.g. from bed to chair and back, without any help?		N	Y
7	Do you walk 10 metres, with an aid or furniture if necessary but with no stand-by help?		N	Y
8	Do you manage a flight of stairs without help?		N	Y
9	Do you walk around outside, on pavements without help?		N	Y
10	Do you walk 10m inside with no calliper, splint or aid and no stand-by help?		N	Y
11	If you drop something on the floor, do you manage to walk 5 m, pick it up and walk back?		N	Y
12	Do you walk around outside over uneven ground (grass, gravel, dirt, snow etc) without help?		N	Y
13	Do you get in/out of the bath or shower unsupervised and wash yourself?		N	Y
14	Do you manage to go up and down four steps with no rail, but with using an aid if necessary?		N	Y
15	Do you run 10m without limping in 4 seconds? (fast walk is acceptable)		N	Y
		TOTAL		/15

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

YOUR OWN HEALTH STATE TODAY

By placing a TICK in ONE box in each group below, please indicate which statement best describes your own health state today.

DO NOT TICK MORE THAN ONE BOX IN EACH GROUP

MOBILITY	
I have no problems in walking about	
Or: I have some problems in walking about	
Or: I am confined to bed	

SELF-CARE	
I have no problems with self-care	
Or: I have some problems washing or dressing myself	
Or: I am unable to wash or dress myself	

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	
Or: I have some problems with performing my usual activities	
Or: I am unable to perform my usual activities	

PAIN / DISCOMFORT	
I have no pain or discomfort	
Or: I have moderate pain or discomfort	
Or: I have extreme pain or discomfort	

ANXIETY / DEPRESSION	
I am not anxious or depressed	
Or: I am moderately anxious or depressed	
Or: I am extremely anxious or depressed	

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

Please could you indicate on this scale, in your opinion, how good or bad your health is today. Please do this by drawing a line from the box on the left to whichever point on the scale indicates your health state. The best state you can imagine is 100, the worst state is 0.

Best imaginable health state



Your own health state today ►

Worst imaginable health state

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

Instructions: Circle the answer that best describes how you felt over the **past week**

1	Are you basically satisfied with your life?	Yes	No
2	Have you dropped many of your activities and interests?	Yes	No
3	Do you feel that your life is empty?	Yes	No
4	Do you often get bored?	Yes	No
5	Are you in good spirits most of the time?	Yes	No
6	Are you afraid that something bad is going to happen to you?	Yes	No
7	Do you feel happy most of the time?	Yes	No
8	Do you often feel helpless?	Yes	No
9	Do you prefer to stay at home, rather than going out and doing new things?	Yes	No
10	Do you feel that you have more problems with memory than most?	Yes	No
11	Do you feel it's wonderful to be alive?	Yes	No
12	Do you feel pretty worthless the way you are now?	Yes	No
13	Do you feel full of energy?	Yes	No
14	Do you feel that your situation is hopeless?	Yes	No
15	Do you think that most people are better off than you?	Yes	No
	Total	/15	

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

NOTTINGHAM EXTENDED ADL INDEX

Please answer all the questions by placing a TICK in the box under the answer that you think most nearly applies to you.

Where appropriate use relative/carer input as well as self-reported answers.

DO YOU?	Not at all (0)	With help (1)	On your own with difficulty (2)	On your own easily (3)
Walk around outside?				
Climb stairs?				
Get in and out of a car?				
Walk over uneven ground?				
Cross roads?				
Travel on public transport?				
Manage to feed yourself?				
Manage to make yourself a hot drink?				
Take hot drinks from one room to another?				
Do the washing up?				
Make yourself a hot snack?				
Manage your own money when you are out?				
Wash small items of clothing?				
Do your own housework?				
Do your own shopping?				
Do a full clothes wash?				
Read newspapers or books?				
Use the telephone?				
Write letters?				
Go out socially?				
Manage your own garden?				
Drive a car?				
Total / 66				

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

MMSE: MINI MENTAL STATE EXAMINATION

START TIME:

ORIENTATION TO TIME, What is the…

NOTE: IGNORE the items shown in smaller type (these have already been assessed in the MoCA) and only ask the highlighted questions

	Response		
Year?		0	1
Season?		0	1
Month of the year?		0	1
Day of the week?		0	1
Date?		0	1
	TOTAL		

ORIENTATION TO PLACE*, Where are we now, what is the…

	Response		
County?		0	1
City/town/village		0	1
Street (suburb)		0	1
House name/ no (building name)		0	1
Room of house (ward number/level)		0	1
	TOTAL		

***** Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are …APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but only score on the first trial]

	Response		
APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

**Now keep those words in mind. I am going to ask you to say them again in a few minutes. ***Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION

NOTE: Perform the WORLD task on all subjects
DO NOT USE THIS SCORE IN THE TOTAL MMSE SCORE, INSTEAD USE THE SERIAL 7S SCORE FROM THE MOCA.

Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling.

D		L		R		O		W		Score 1 each	

RECALL

What were those three words I asked you to remember? *[Do not offer any hints]*

APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

NAMING*			
What is this? [point to pencil/ pen]		**0**	**1**
What is this? [watch]		**0**	**1**
	TOTAL		

* Alternative common objects (e.g.eyeglasses, chair, keys may be substituted and noted

REPETITION			
Now I am going to ask you to repeat what I say. Ready? "NO IFs ANDs OR BUTs." Now you say that. [repeat up to 5 times, but score only on the first trial]			
NO IFs ANDs OR BUTs		0	1
	TOTAL		

COMPREHENSION			
Listen carefully because I am going to ask you to do something. Take this paper in your right hand *[pause]*, **fold it in half** *[pause]***, and put it on the floor (or table).**			
Take in right hand		0	1
Fold in half		0	1
Put on floor/table		0	1
	TOTAL		

READING			
Please read this and do what it says. [Show the examinee the words on the stimulus form]			
Close your eyes		0	1
	TOTAL		

WRITING		
Please write a sentence. [If examinee does not respond, say: **Write about the weather.**] Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.	0	1

DRAWING		
Please copy this design. [Display the intersecting pentagons on the stimulus form]. Score 1 point if the drawing consists of two 5-sided figures that intersect to from a 4-sided figure.	0	1

FINISH TIME:	
NB Using serial 7s score and NOT WORLD TOTAL/30	

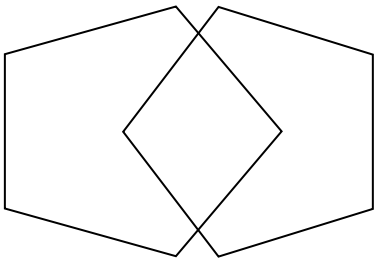
Any problem with testing? ie the MMSE/MoCA **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment a) Poor vision b) Deaf c) Both 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor 6 Co-existent neurological dis.	7 First language not English 8 Other - specify 9 Only MoCA done, not MMSE 10 Only MMSE done, not MoCA 11 Fatigued 12 Incomplete at request of patient/family IL Illiteracy C Known cognitive impairment
If not done, why not? ie if the MMSE/MoCA was **not** done, what was the reason?		1 Sensory impairment a) Poor vision b) Deaf c) Both 2 Aphasic 3 Refused cognitive testing 4 Severe dementia	5 Illiterate 6 Language barrier 7 Unwell 8 Telephone/email FU 9 Other , specify 10 MoCa and MMSE both done 11 Fatigued

SUBJECT ID NO:

MONTH 12 / 60 **Please circle one**

Please complete ALL fields

CLOSE YOUR EYES



Time BP taken	Side		Cuff size			Systolic	Diastolic	HR
At end of FU	L	R	S	M	L			
Standing if required	L	R	S	M	L			

SUBJECT ID NO:

MONTH 12 / 60 Please circle one

Please complete ALL fields

If undecided at last follow up, asked about brain donation?	Y	N	If consented, copy to patient, notes and add to GP letter. Send original form
1 Consented 2 Refused 3 Undecided at 12 months, please ask at next FU			

OUTSTANDING INVESTIGATIONS

Blood Pressure:

2 BP readings taken	**Y**	**N**	**Target over 130/80mmHg?**	**Y**	**N**
If so why?					
24 hour BP needed?	**Y**	**N**	**Fitted and downloaded?**	**Y**	**N**
Using conventional home BP monitor?	**Y**	**N**	**Conventional readings collected / new sheet issued?**	**Y**	**N**

Bloods:

Clinical Bloods taken?	**Y**	**N**
Lavender: FBC **Green: TSH, Lipids Profile, LFTs, U&Es (incl Urea); Calcium and Magnesium at 1 year** **Grey: Glucose at 1 year** **Other (please specify)**		
If not taken, why?		
Any research bloods taken at this appointment?	**Y**	**N**
2 Blues, 1 Yellow, 1 Green. No. Purples needed:	**1**	**2**

Other investigations:

R Test needed?	**Y**	**N**	**Fitted and downloaded?**	**Y**	**N**
Other investigations required	**Y**	**N**	**Please specify**		

IQCODE (60 months only)

Completed and entered?	YES	NO
Issued with prepaid envelope?	YES	NO
If not done, please give the reason		

GP Printout:

GP problem list collected	YES	NO	**Source**	EPR	EMIS
GP medication list collected	YES	NO	**Source**	EPR	EMIS
If not done, why?					

The Stroke Prevention Research Unit
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PI: Professor Peter Rothwell

OREC A: 05/Q1604/70
Version 7 8th January 2019

Information sheet: Outpatient participants

Study title: The Oxford Vascular Study (OXVASC)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The purpose of this study is to find out how common vascular disease (e.g. heart attacks, strokes, transient ischaemic attacks (TIA or mini-stroke) and other circulatory problems) is in Oxfordshire, the causes of vascular disease and how it affects people's lives. This has never been done before for different types of vascular disease at the same time and in the same population. We hope the study will provide us with useful information on the best way of providing services and treatment for those who suffer from these common problems. We hope we can build up a detailed picture of the way that people recover and the subsequent changes in health and memory over several years.

Why have I been chosen?
You have been chosen because you are registered with one of the nine GP practices in Oxfordshire which are collaborating in the study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to read and be asked to sign a consent form. You will be given a copy of the information sheet and signed consent form to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
If you decide to take part you would agree to an interview and a clinical examination by the researcher. It would also involve taking an extra sample of blood in clinic. If you are being seen following a possible TIA or stroke, you will require scans of your brain (magnetic resonance imaging–MRI or Computerised Tomography-CT), blood vessels and heart (with

a non-invasive ultrasound probe, similar to those used in pregnant women before birth) as part of your standard clinical care, but will take a little longer than standard in order to collect additional information. We would like to use these standard scans as well as some additional images for research. We will also assess your heart rate and your blood pressure with a continuous blood pressure monitor on the finger and ask you to perform mental arithmetic aloud and hold your breath for 30 seconds. When these tests are completed, a measurement of pulse waves in your arm, upper thigh and neck will assess the stiffness of your arteries. These extra measurements will take approximately 20 minutes.

Additionally, you may be invited to have an additional brain scan for research purposes only using a specialist research MRI scanner that operates at a high magnetic field (over twice the magnetic field of standard hospital scanners). This 7 Tesla scanner is located at the University's FMRIB Centre at the John Radcliffe Hospital. MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). However, because they use a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part. For example, if you suffer from claustrophobia, you could not be scanned. Normally, MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body. While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. We do not test for pregnancy as routine so if you think you may be pregnant you should not take part in this study. As some of the scans are noisy, we would give you earplugs, head padding or headphones to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your ears. In preparation for your scan and for your comfort and safety we may ask you to change into pocketless and metal free "pyjama-style" top and trousers, which are available in a range of sizes. You may keep your underwear and socks on, but we would ask ladies to remove underwired bras. If you have a suitable sports type bra you may wear this instead. Metal jewellery, including body piercing, must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan we can provide makeup removal wipes but you are advised to bring your own makeup to reapply. Lockers are provided to secure your personal belongings and clothing.

It is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a doctor's appointment. Scans are not routinely looked at by a doctor; rather our scans are intended for research purposes only. Occasionally, a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about you is kept strictly confidential.

What do I have to do?
This is an observational study and taking part in the study will not affect your current or future care. No new drugs or other treatments will be tested.

What are the possible disadvantages and risks to taking part?
You will be required to give a blood sample which will cause mild discomfort. Where possible this will be taken at the same time as those collected in the course of your normal medical care. Some people scanned in MRI scanners, especially 7T-MRI scanners, may experience a mild dizzy sensation as they are moved into the scanner. This is normal and

the sensation starts to go away as soon as you are in the scanner. There are no additional risks involved in this part of the study.

What are the possible benefits of taking part?
We hope the information we get from this study may help us to treat future patients with vascular disease better.

What if something goes wrong?
The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Professor Peter Rothwell, Tel no: 01865 231603, email: peter.rothwell@ndcn.ox.ac.uk or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrg@admin.ox.ac.uk

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

Responsible members of the University of Oxford and Oxford University Hospitals NHS Foundation Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

What will happen to my data?
Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly. We will be using information from you, your medical records and NHS Digital using the minimum personally-identifiable information possible. We will store research data and any research documents with personal information, such as consent forms, securely at the University of Oxford. The study team will use your name, NHS number, home address, and contact details to contact you about the research study e.g. to arrange follow up visits, to make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. They will keep identifiable information about you from this study for five years after the study has finished.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at *http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/]*

What will happen to the results of the research study?
It is likely that the results of this study will be published in medical journals after completion of the research. If you decide to take part in the study you will not be identified in any report.

Who is organising and funding the research?

This research is being organised by Professor Rothwell at The Stroke Prevention Research Unit, University of Oxford in collaboration with the Department of Primary Health Care, the Department of Cardiology and your participating General Practice. The study is funded by the Wellcome Trust and the NIHR Biomedical Research Centre, Oxford.

Who has reviewed the study?
The Oxfordshire Research Ethics Committee A has approved the study.

Where can I find independent information about taking part in research?
You can contact local branches of the NHS Patient Advisory Liaison Service (PALS). Here is their website: http://www.pals.nhs.uk/

Contact for Further Information
If you would like any further information please ask the researcher who is discussing this information sheet with you or by contacting the Oxford Vascular Study Office on 01865 231601 or go to www.stroke.ox.ac.uk

Thank you for reading this.

Stroke Prevention Research Unit
Department of Clinical Neurology
Level 6, West Wing
John Radcliffe Hospital
Oxford

OREC A: 05/Q1604/70 Version 7: 8th January 2019

Consent form: Outpatient participants
Study title: The Oxford Vascular Study (OXVASC)

	Please initial the relevant box	**Initials**
1.	I confirm that I have read and understand the information sheet dated 18th February 2015 for the above study and have had the opportunity to ask questions.	☐
2.	I agree to take part in the above study.	☐
3.	I understand that sections of any of my medical and GP notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that the information held and maintained by NHS Digital / NHS Central Register may be used to provide information about my health status.	☐
4.	I understand future research using the blood samples I give may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for me personally.	☐
5.	I agree for data collected in this study to be given to researchers, including those working outside of the EU, to be used in other research studies. I give permission for data from this study to be used in publications. I understand that any shared and published data will be fully anonymised so that I cannot be identified.	☐
6.	I understand that I may be invited to undertake a research-only 7 Tesla MRI scan. If invited I agree to this scan, and understand that it would not be diagnostically interpretable.	☐
7.	I agree to take part in the follow up study that involves being interviewed in clinic, at home or by telephone at 1 month, 3 months, 6 months, 12 months, 5 years and 10 years, and when I am in hospital with other medical problems.	☐
8.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐

Name of Patient	Date	Signature
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Oxford University Hospitals NHS
NHS Foundation Trust

Stroke Prevention Research Unit
Department of Clinical Neurology
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John Radcliffe Hospital
Oxford

OREC A: 05/Q1604/70 **Version 2: 8th January 2019**

Assent form

Study title: The Oxford Vascular Study (OXVASC)

	Please initial the relevant box	**Initials**
1.	I confirm that I have read and understand the information sheet dated 18th February 2015 for the above study and have had an opportunity to ask questions.	
2.	I agree for my relative to take part in the above study.	
3.	I understand that sections of any of my relative's medical and GP notes may be looked at by responsible individuals where it is relevant to them taking part in research. I give permission for these individuals to have access to my relative's records. I understand that the information held and maintained by NHS Digital / NHS Central Register may be used to provide information about my relatives health status.	
4.	I understand future research using the blood sample my relative gives may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for my relative personally.	
5.	I agree for my relative's data collected in this study to be given to researchers, including those working outside of the EU, to be used in other research studies. I give permission for my relative's data from this study to be used in publications. I understand that any shared and published data will be fully anonymised so that my relative cannot be identified.	
6.	If my relative has been seen following a stroke or TIA, I agree to them taking part in the follow up study that involves being seen in clinic, at home or by telephone at 1 month, 6 months, 12 months, 5 years and 10 years, and when they are in hospital with other medical problems.	
7.	I understand that the participation of my relative is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	

_____
Name of Patient

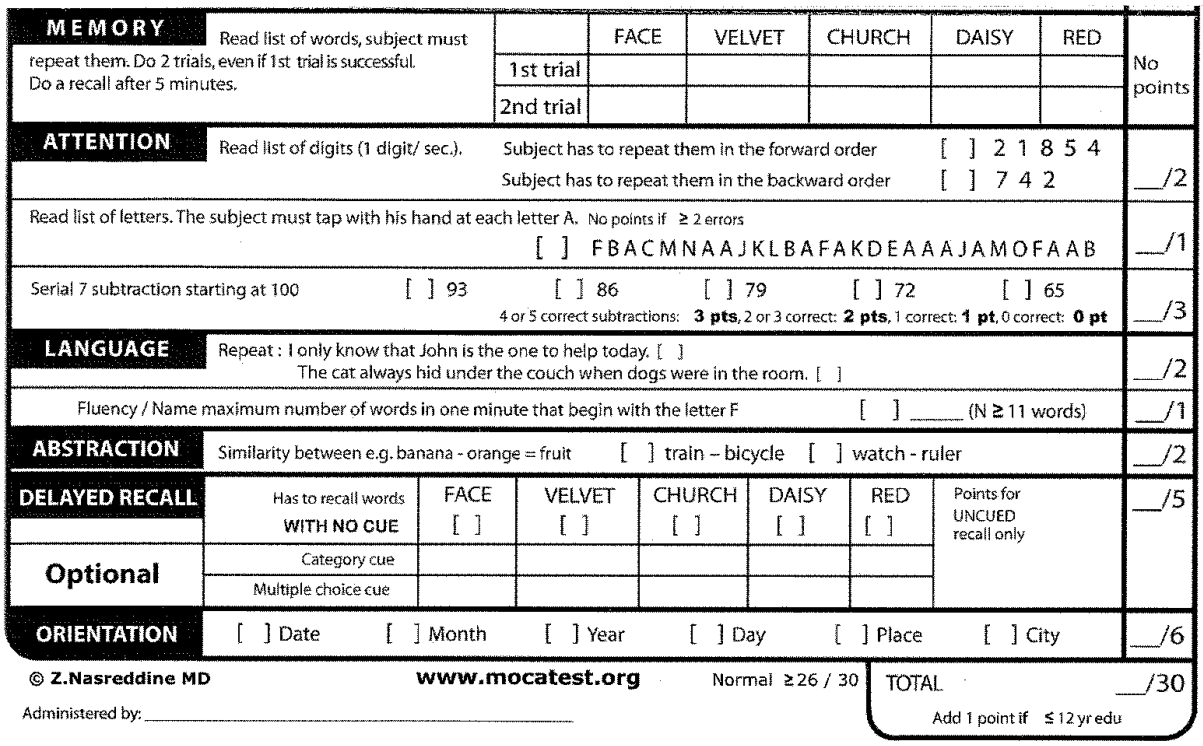
Name of Next of Kin	Date	Signature
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix VIII: Telephone Montreal Cognitive Assessment

IDNO: **NAME:** **DATE:**
TEL NO: **AGE:**
STREET: **TOWN/CITY:**

HEIGHT:



MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
	1st trial						
	2nd trial						
ATTENTION Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order [ ] 2 1 8 5 4						
	Subject has to repeat them in the backward order [ ] 7 4 2						/2
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B							/1
Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**							/3
LANGUAGE Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]							/2
Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)							/1
ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler							/2
DELAYED RECALL	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only /5
Optional	Category cue						
	Multiple choice cue						
ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City							/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30 TOTAL /30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start time: **Finish time:**	

Appendix IX: Telephone Interview for Cognitive Status

Time at start: ……..

Orientation

What is today's date?	Day	1/0
	Date	1/0
	Month	1/0
	Year	1/0
	Season	1/0
What is your age? ……		1/0
What is your telephone number? (Code & Number) ……		1/0

Registration & Free Recall

I am going to read you out a list of words.	Cabin	1/0
Please listen carefully and try to remember them.	Pipe	1/0
When I am done, tell me as many as you can in	Elephant	1/0
any order. Ready?	Chest	1/0
	Silk	1/0
Now tell me all the words you can remember	Theatre	1/0
	Watch	1/0
	Whip	1/0
	Pillow	1/0
	Giant	1/0

Attention/Calculation

Please take 7 away from 100. Now	93	1/0
continue to take 7 away from what you have	86	1/0
left over until I ask you to stop	79	1/0
	72	1/0
	65	1/0
Please count backwards from 20 to 1	No mistakes	1/0

Remote & Recent Memory

What do people use to cut paper?	Scissors	1/0
What is the prickly green plant found in the desert?	Cactus	1/0
Who is the reigning monarch now?	E, QE, QE2	1/0
Who is PM now?	Surname	1/0
What is opposite of east?	West	1/0

Language/repetition

Please say this 'Methodist Episcopal'	Exactly right	1/0

Delayed recall

Please repeat the 10 words I read earlier

Cabin	1/0
Pipe	1/0
Elephant	1/0
Chest	1/0
Silk	1/0
Theatre	1/0
Watch	1/0
Whip	1/0
Pillow	1/0
Giant	1/0

Time on completion: ……

Total TICS-M score …….. / 39

Completed Y/N ☐

Reason Not: ☐

1 = Participant incapable
2 = Terminated at participants request
3 = Other……..

Appendix X: Information sheet for TIME participants

Principal Investigator: Professor Tom MacDonald

Contact for queries:
If you have any queries about this study, you can contact: Professor Tom MacDonald. Dr Isla Mackenzie (Doctor), Evelyn Findlay (Study Co-ordinator) or one of the other study doctors or nurses at the Medicines Monitoring Unit (MEMO), University of Dundee on 01382 383119 or Freephone 0800 9173509(answering machine out of office hours).
Email:- info@timestudy.co.uk

Study title: **Treatment In Morning versus Evening (TIME)Study**

We invite you to participate in a research project. We believe it to be of potential importance. However, before you decide whether or not you wish to participate, we need to be sure that you understand firstly why we are doing it, and secondly what it would involve if you agree. We are therefore providing you with the following information. Read it carefully and be sure to ask any questions you have, and, if you want, discuss it with outsiders. We will do our best to explain and to provide any further information you may ask now or later. You do not have to make an immediate decision.

Why are we doing this study?
Patients traditionally take their blood pressure lowering tablets in the morning and blood pressure is traditionally measured at some time during the working day. Most of the current evidence that shows the benefits to patients of reducing their blood pressure comes from studies where tablets were taken in the morning and BP was measured in the daytime.

In recent years, special monitors that can measure blood pressure throughout the day and the night have been developed. Results from studies using these monitors have suggested that night time blood pressure might be a better measurement of the benefits of blood pressure lowering. In addition, tablets taken at night lower night-time blood pressure more than tablets taken in the morning. The big question is, would night time dosing be better (or worse) than morning dosing in preventing the bad things associated with high blood pressure (such as strokes and heart attacks)?

The present study will try to answer this question. To do this we are asking patients who take medicines for high blood pressure to take part in a study that will compare morning dosing (some time between 6am and 10am) with night-time dosing (some time between 8pm and midnight).

Why are we doing this study in this way?
To be able to answer this question we will need to study a lot of people. The reason for this is that heart attacks and stroke events are uncommon. To be able to know with confidence that morning and night-time dosing are different (or the same) at preventing these events, a lot of people have to be studied over a number of years. For practical (and cost) reasons such a study cannot really be done in the conventional way where patients see a clinician regularly for a large number of study visits. For this reason we are doing this study by email and a secure website so there are no study visits at all. However, this means that only those patients who have internet access at home and a valid email address that we can use to

regularly contact them, can participate. If you do not have this in your home then I am afraid that you cannot participate.

Who else cannot take part in this research?
The following people will not be able to participate:

Those who currently take blood pressure lowering tablets both in the morning and at night.
Those who work night shifts.
Those participating in another clinical trial or who have done in the last 3 months.

What do I do if I am interested in taking part in this study?
If you have email facilities and you would like to participate in this study you can register your interest by going to https://www.timestudy.co.uk Note that this is a secure website like the banks use.

After you register your interest you will be sent an email with a web-link to confirm your email address.

Consent

We will want to be sure that you understand all of the things that the study needs to be successful and we will need you to explicitly consent to each of these. This is so that we have a positive record that you agree to each of these things.

For this reason, you will be asked to tick boxes agreeing to each of the things required to make the study a success. These are explained below:

What will I have to do if I do take part?
The way this trial works is that people who sign up to it will be followed over time to see if they have to go to hospital with a heart attack or stroke or if, unfortunately, they pass away due to a cardiovascular problem. This follow up is possible because the NHS keeps central records of all hospital admissions and the General Registers Office (Scotland), the Office for National Statistics (England), and the Government in Wales keep a record of all causes of death. We can only get these data about you with your explicit consent, so to take part in this trial you have to agree that these agencies can let us know that one of these things has happened to you.

To do this, we have to share some of your personal data (name, date of birth, address/postcode, NHS/CHI number and possibly GP address) with the relevant NHS or Government agency. These are:

- Health and Social Care Information Centre (HSCIC) and Office for National Statistics (ONS) in England,
- The NHS National Services Scotland and the General Register Office in Scotland,
- The NHS Shared Services Partnership in Wales
- The NHS Health and social Care in Northern Ireland(HSC).

These agencies will look at your electronic medical records, and then let us know about any hospitalisations, occurrences of cancer, or death. Please note that, apart from these agencies, your information will not be shared with anyone not involved with the TIME Study or your NHS care. If you want more information then please contact a member of the study team.

(Note: that if a stroke or heart attack does happen to you, you can report it to us yourself on the web-site. This is particularly useful where this event occurs outside of the UK as we will only be able to track events in the UK).

Since we will study large numbers of patients over a number of years it is (unfortunately) inevitable that some people will die and some will become unwell in other ways that make it difficult for them to keep in contact with us. We can never predict who this will happen to. In order to be able to be certain about what happened to these patients we are asking all participants to let medical researchers look at their electronic or paper health records. It would also be helpful if you were able to provide the contact details of a close relative or friend that we could contact if we were unable to contact you for any reason. Finally, we would like to be able to contact your family doctors to help find out what has happened to you.

We wish to keep in periodic contact with you. We will do this by sending you emails, initially at 1 month and subsequently 3 or 6 monthly intervals. These emails will contain web-links to enable the vast majority of people to quickly answer our questions. For example, the email may ask:

Are you still taking your medicines in the morning / at night? If you are still taking your treatment at this time and there have been no changes to your prescribed treatment and there is nothing you want to tell us then please click this link (example link https//www.timestudy.co.uk/Ab1433296553).

This is all you have to do if there is no change to your information. You will then get taken to a web page thanking you for your response.

If you wish to tell us that something has changed then you will be asked to click another link: (example link https//www.timestudy.co.uk/Axyzt433865). This will take you to the website page where you can enter the information you want to tell us. You will then get shown a web page thanking you for your response.

Details about you collected at baseline
You will be asked to fill in contact details about yourself. This is to allow us to be able to contact you by telephone or letter if, for some reason, your email stops working.

We would also like details of an alternative person we could contact should you stop replying to us for any reason. This could be a close family member for example. Finally, we will need your agreement to be able to contact your family doctor to find out about your health if required.

We need to know about your own history of high blood pressure, your drug treatment, a family history, whether you have other significant medical conditions etc. This sounds like a lot but nearly all of it is tick boxes or picking from a list of options. You should not worry if you cannot remember precise details as most people cannot. You can always go back later and edit your data if you wish.

Randomisation
When you have done this, you will then be allocated to take your treatment in the morning or at night. This will be allocated to you at random by a computer and cannot then be changed so if you would be unhappy to take your medicines at night then you should not participate. You will also be unable to participate if you take twice daily medication for blood pressure or if you work night shifts.

When we do not know which way of treating patients is best, we need to make a comparison. An important part of making a fair comparison is 'randomisation'. Most large trials are randomised. The decision about which treatment you receive is random – based on chance. This is done by a computer programme, not the patient or the doctor. This is called randomisation. Randomisation ensures that the two groups of people in the trial are as similar as possible. This means that the results are more reliable and it is the best way of ensuring that the results of the trial are not biased by the way treatments are allocated.

Are there any possible problems that could arise if I participate?
Part of the reason for doing the study is to see if there are any downsides to taking tablets in the morning compared with at night time. Some of the possible issues that we speculate might arise are mainly to do with evening dosing. We would like to know if these are problems or not.

Diuretic therapy (with thiazide-type diuretics) and evening dosing
Diuretic tablets (sometimes known as 'water tablets' i.e. bendroflumethiazide) could theoretically increase urine volume at night and lead to early wakening to visit the toilet. In practice, when people have been on these tablets for a long time the effect on urine volume is small or absent. However, we recognise that this might still be a problem. For those people taking this sort of tablet we would like patients to try taking this tablet in the evening but if they find it a problem they could take it earlier (6pm). If this still does not resolve the problem then they could take it at 4pm and so on in 2 hour increments until it is no longer a problem. We would like patients to tell us about this as we need to know if this really is an issue or not.

Diuretic therapy (with loop-type diuretics) and evening dosing
A few patients will be taking so-called loop diuretics like frusemide or bumetanide. These tablets typically cause a prompt increase in urine volume that lasts a few hours. Patients taking these tablets will be aware of how long this effect lasts in them. We would like patients taking these drugs who are randomly allocated evening dosing to take these tablets at 6pm in the first instance. If this results in difficulties then patients should revert to taking this tablet in the morning. Again, these practical issues are part of the reason for doing the research and we want to collect these data.

Evening dosing and nocturnal dizziness or morning dizziness
Some patients, often older men, get up at night to visit the toilet or for other reasons. We want to know if taking medicines in the evening causes increased symptoms of dizziness or light headedness when they get up at night or first thing in the morning. We would like to know if such symptoms are an issue.

Other Commonly asked Questions

What if I sign up but then change my mind?
As with all research you are free at any time to withdraw without giving a reason. Your medical care and legal rights will not be affected by this. With this particular trial this can be done by going to the website to register your withdrawal. You can withdraw partially or completely. Partial withdrawal means that you no longer want to take treatment at the allocated time but that you do not mind being followed up by the study team. Full withdrawal means that you do not wish to be followed up any more.

Who will see my personal data?
As well as the agencies already named, clinical staff running the study may see your personal health records but they will treat these in strict confidence. Your study files that undergo statistical analysis by non-clinical staff will be anonymised. Publications will never

contain any personal or identifiable details about you. Nowadays all studies are monitored and audited by the study sponsor (University of Dundee-NHS Tayside) or by external government agencies such as the Medicines and Healthcare products Regulatory Agency (MHRA). Monitors and auditors work under conditions of strict confidentiality. Your data will be kept in a secure location at the University of Dundee-NHS Tayside for 5 years after the study has completed in line with European Guidelines.

What if there is a problem?
If you have a concern about any aspect of this study you should ask to speak with the study doctor who will do their best to answer your questions [tel. 01382 383119]. If you remain unhappy and wish to complain formally you can do this through the Complaints Procedure of your GP's practice. Details can be obtained from the practice.

In the event that something goes wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against either the University of Dundee or your GP practice.

Can I get further information?
The study website contains much more information including details of those involved with the research and frequently asked questions. We also have a telephone help-line for issues not covered by the website – 0800 917 3509

Who will approve this trial?
The East of Scotland Research Ethics Service (EoSRES), which has the responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of medical ethics. EoSRES will evaluate and monitor ethical issues as the trial proceeds. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from NHS Tayside, whose role it is to check that research is properly conducted and the interests of those taking part are adequately protected.

The trial has undergone scientific scrutiny by doctors and scientists belonging to the British Hypertension Society. The trial has now completed a successful pilot phase and the roll-out has now been funded by the British Heart Foundation.

Will my doctor know if I am participating?
We are unable to inform all GPs of their patient participation in the study, but advise patients to update their GP at their next visit.

What if I am taking part in another study?
If you are taking part in another study that is a clinical trial you cannot participate in this one as well. If you are unsure about this, please contact us to check. If you have recently completed another clinical trial you must wait 3 months from the end of that study before signing up to this one.

Will the results of this study be made public?
Yes we will publish the results of this study as soon as they are available. We will also email the results to all participants.

Thank you for taking the time to read this Information Sheet and for considering taking part in this study.

Cognitive Function Sub-study
Patient Information Sheet

Principal Investigator: Professor Tom MacDonald

Contact for queries:
If you have any queries about this sub-study, you can contact: Professor Peter Rothwell (Cognitive Substudy Lead); Mrs Sarah Welch (Research Nurse); Mrs Sharon Christie (Research Nurse) Nuffield Department of Clinical Neurosciences, University of Oxford on 01865 231603 or Freephone 0800 9173509(answering machine out of office hours).
Email:- info@timestudy.co.uk

Study title: **TIME - Cognitive Function Sub-study**

Thank you for participating in the TIME (Time in Morning versus Evening) Study. We would like to extend a further invitation to participate in another project that is running alongside the TIME study. If you do not wish to participate in this additional project you can still take part in TIME.

We believe that this sub-study will be of potential benefit to the population. However, before you decide whether or not you wish to participate, we need to be sure that you understand firstly why we are doing it, and secondly what it would involve if you agree. We are therefore providing you with the following information. Read it carefully and be sure to ask any questions you have, and, if you want, discuss it with outsiders. We will do our best to explain and to provide any further information you may ask now or later. You do not have to make an immediate decision.

Why are we doing this sub-study?
We know that many people aged 70 or over with high blood pressure experience difficulties from time to time with thinking, knowing and remembering. This is known as cognitive impairment or decline. Most of the current evidence about cognitive impairment does not show any benefit in reducing high blood pressure. However, it is possible that taking blood pressure medications at night or the morning may have an effect on cognitive impairment.

It is may be that taking blood pressure medication in the evening may slow cognitive decline by better controlling blood pressure during the night and reducing too-low blood pressure episodes during the afternoon. There is also a possibility that taking blood pressure medication at night could drop some people's night time blood pressure too much and worsen cognitive decline.

The TIME Cognitive Testing Sub-study will try to answer whether evening dosing of blood pressure medication affects cognitive impairment compared to morning dosing. To do this we are asking patients over 70yrs old, who are taking part in the TIME study, to also take part in a smaller study that will assess cognitive function.

Why are we doing this sub-study in this way?
In order to detect changes in cognitive functioning over time we need to follow-up a group of around 600 people with repeated telephone assessments. Previous experience has shown this telephone testing approach to be effective in measuring changes in cognitive function over time.

Who cannot take part in this research?
Patients taking in part in TIME but who are below 70 years of age of will not be able to take part.

What do I do if I am interested in taking part in this sub-study?
You can choose to take part in this sub-study by clicking on the appropriate link at the end on the TIME study enrolment process, if you are aged 70 years or over.

Consent
We will want to be sure that you understand all of the things that the study needs to be successful and we will need you to explicitly consent to each of these. This is so that we have a positive record that you agree to each of these things.

For this reason, you will be asked to tick boxes agreeing to each of the things required to make the study a success. These are explained below:

What will I have to do if I do take part?
If you sign up to this sub-study, you will be contacted shortly after by a specially trained research nurse who will explain the telephone assessment process to you. The sub-study is being undertaken by the Centre for Prevention of Stroke and Dementia part of the University of Oxford who have a team of nurses experienced in doing these tests by phone.

The nurse will arrange to conduct a telephone assessment that involves completing two questionnaires. Previous experience has shown this to take between 15 and 30 minutes.

6 months after your initial telephone assessment, the nurse will contact you again to repeat the same tests. This will be done again after another 6 months and then annually until the end of the TIME study. This process will be independent of the TIME study online follow-ups.

Details about you collected at baseline
We do not need to collect any additional information from you aside from the information collected for the TIME study.

Randomisation
You will be randomised to take your medication in the morning or evening as part of the TIME study. You do not need to make any other changes for this Cognitive Testing sub-study.

Are there any possible problems that could arise if I participate?
The telephone tests that we will be using in the study have been well tested in previous studies and have not been found to cause any problems. We do not anticipate you having any problems arising from the Cognitive Function testing sub-study.

Other Commonly asked Questions

What if I sign up but then change my mind?
As with all research you are free at any time to withdraw without giving a reason. With this cognitive function sub-study this can be done by going to the website to register your withdrawal or by informing the research nurse who conducts your telephone consultation.

Who will see my personal data?
Research staff running the study will treat all data in strict confidence. Your study files that undergo statistical analysis by non-clinical staff will be anonymised. Publications will never contain any personal or identifiable details about you. Nowadays all studies are monitored and audited by the study sponsor (University of Dundee) or by external government agencies. Monitors and auditors work under conditions of strict confidentiality.

Can I get further information?
The study website will contain much more information including details of those involved with the research and frequently asked questions. We also have a telephone help-line for issues not covered by the website – 0800 917 3509

Who will approve this trial?
The Tayside Committee on Medical Research Ethics, which has the responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of medical ethics. The Edinburgh Independent Ethics Committee for Medical Research will evaluate and monitor ethical issues as the TIME trial proceeds.

The TIME study has undergone scientific scrutiny by doctors and scientists belonging to the British Hypertension Society. The trial completed a successful pilot phase and the study is being funded by the British Heart Foundation.

Will my doctor know if I am participating?
We are unable to inform all GPs of their patient participation in this substudy, but it is probably good practice that you update your GP at your next visit.

What if I am taking part in another study?
If you are taking part in another study that is a clinical trial you cannot participate in the TIME study as well. The TIME Cognitive Function testing study is part of the TIME study and you will be able to participate.

Will the results of this study be made public?
Yes we will publish the results of this study as soon as they are available. We will also email the results to all participants.

Thank you for taking the time to read this Information Sheet and for considering taking part in this study.

TIME - Cognitive Function Sub-study

Principal Investigator: Professor Tom MacDonald
Contact for queries:
If you have any queries about this study, you can contact: Professor Tom MacDonald, Dr Amy Rogers (Doctor), Wendy Saywood (Project Manager) or one of the other study doctors or nurses at the Medicines Monitoring Unit (MEMO), University of Dundee on 01382 383119 or Freephone 0800 9173509(answering machine out of office hours).
Email:- info@ timestudy.co.uk

Study title: **Treatment In Morning vs Evening (TIME) Study - Cognitive Function Sub-study**

Informed Consent Form

Please select yes or no (radio buttons)

I confirm that I have read and understood the information sheet for the above sub-study. I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily.
Yes ○ No ○

I understand that a research nurse will contact me by telephone Yes ○ No ○

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If I withdraw I understand that the sponsor will retain the data collected up to the point I withdraw Yes ○
No ○

I agree to take part in the TIME Cognitive Function Sub-study Yes ○ No ○

Please enter your name to confirm that you have read the information sheet and answered the questions above. By entering the following information this will be equivalent to your signature on this consent form.

Forename: _____ **Surname:** _____

I have read, answered and understood all of the above questions ☐

A dated version of this completed form will be emailed to you as a portable document file (PDF)

Submit

Appendix XIII: Search strategy for systematic review of psychological distress after a TIA

EMBASE
1. depression/
2. anxiety/
3. exp depression/
4. exp anxiety/
5. exp distress syndrome/
6. exp posttraumatic stress disorder/
7. (transient isch?emi$ attack$ or tia$1).tw.
8. Conference*.pt.
9. (exp animals/ or nonhuman/) not human/
10. 1 or 2 or 3 or 4 or 5 or 6
11. 10 and 7
12. 11 not 8 not 9

MEDLINE
1. exp Depression/
2. Depression/
3. anxiety/
4. exp anxiety/
5. Stress Disorders, Post-Traumatic/
6. exp Psychological Distress/
7. exp Stress Disorders, Post-Traumatic/
8. Ischemic Attack, Transient/
9. (transient isch?emi$ attack$ or tia$1).tw.
10. exp animals/ not humans.sh.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7
12. 8 or 9
13. 11 and 12
14. 13 not 10

PsychInfo
1. exp "Long-term Depression (Neuronal)"/ or exp Endogenous Depression/ or exp "Depression (Emotion)"/ or exp Major Depression/ or exp Reactive Depression/ or exp Recurrent Depression/ or exp Late Life Depression/
2. exp Health Anxiety/ or exp Anxiety Disorders/ or exp Anxiety/ or exp Generalized Anxiety Disorder/ or exp Anxiety Management/
3. exp Mental Health/ or exp Emotional Trauma/ or exp Posttraumatic Stress Disorder/ or exp Distress/
4. exp Psychological Stress/ or exp Distress/
5. (transient isch?emi$ attack$ or tia$1).tw.
6. 1 or 2 or 3 or 4
7. 5 and 6
8. limit 7 to human

Appendix XIV: Baseline characteristics and multivariate regression for the risk of depression at (a) 1-month and (b) 12-months after a TIA / minor stroke in subjects who did not have a history of premorbid depression

(a) 1-month:

Baseline characteristic	All	Depression at 1 month	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	162 (46.0)	24 (51.1)	138 (45.2)	1.26 (0.68-2.34)	0.457	1.25 (0.67-2.34)	0.480	-	-
Mean age at event (s.d)	70.2 (14.0)	70.8 (17.1)	70.2 (13.4)	1.00 (0.98-1.03)	0.779	1.00 (0.98-1.03)	0.876	-	-
[$]ABCD2 ≥ 4 (%)*	124 (55.1)	14 (48.3)	110 (56.4)	0.72 (0.33-1.58)	0.412	0.64 (0.28-1.47)	0.289	-	-
[$]Symptoms > 1 hour (%)*	91 (40.4)	11 (37.9)	80 (40.8)	0.89 (0.40-1.98)	0.768	0.90 (0.40-2.01)	0.795	-	-
[$]Isolated speech symptoms (%)	54 (23.9)	7 (24.1)	47 (23.9)	1.02 (0.41-2.53)	0.974	0.98 (0.39-2.47)	0.971	-	-
[$]Weakness symptoms (%)	64 (28.3)	8 (27.6)	56 (28.4)	0.96 (0.40-2.29)	0.925	0.96 (0.40-2.29)	0.920	-	-
[%]Mean NIHSS (s.d)	1.2 (1.2)	1.5 (1.1)	1.1 (1.2)	1.35 (0.91-2.01)	0.135	1.37 (0.91-2.05)	0.132	-	-
Smoking – current/prior (%)	168 (47.7)	25 (53.2)	143 (46.9)	1.29 (0.70-2.38)	0.421	1.46 (0.76-2.83)	0.260	-	-
Hypertension	196 (55.7)	26 (55.3)	170 (55.7)	0.98 (0.53-1.82)	0.957	0.94 (0.49-1.82)	0.864	-	-
Hyperlipidaemia	118 (33.5)	13 (27.7)	105 (34.4)	0.73 (0.37-1.44)	0.362	0.73 (0.37-1.46)	0.377	-	-
Atrial fibrillation	43 (12.2)	9 (19.1)	34 (11.1)	1.89 (0.84-4.24)	0.124	1.96 (0.84-4.57)	0.120	-	-
Diabetes mellitus	53 (15.1)	9 (19.1)	44 (14.4)	1.41 (0.64-3.11)	0.401	1.29 (0.69-2.43)	0.423	-	-
Peripheral vascular disease	17 (4.8)	3 (6.4)	14 (4.6)	1.42 (0.39-5.13)	0.595	1.45 (0.39-5.32)	0.578	-	-
IHD / angina	45 (12.8)	7 (14.9)	38 (12.5)	1.23 (0.51-2.94)	0.642	1.28 (0.52-3.15)	0.591	-	-
Past history of TIA / stroke	3 (0.9)	0	3 (1.0)	0	0.999	0	0.999	-	-
Low education (%)	178 (50.6)	24 (51.1)	154 (50.5)	1.02 (0.55-1.89)	0.942	1.03 (0.55-1.93)	0.924	-	-
Socio-economic deprivation (%)	46 (13.1)	10 (21.3)	36 (11.8)	2.02 (0.93-4.41)	0.078	2.08 (0.94-4.60)	0.070	-	-

Baseline characteristics of 357 subjects, without a history of premorbid or baseline depression, with a TIA / minor stroke stratified by their subsequent 1-month presence or absence of depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 1-month also included. (Missing data = 2 ABCD2 scores, 1 TIA symptom duration, 3 NIHSS.) [$]For TIA subjects only. [%]For minor stroke patients only.

(b) 12-months:

Baseline characteristic	All	Depression at 12 months	No Depression	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	134 (45.6)	12 (37.5)	122 (46.6)	0.69 (0.32-1.47)	0.333	0.67 (0.31-1.44)	0.308	0.63 (0.27-1.49)	0.294
Mean age at event (s.d)	70.2 (13.5)	76.4 (18.4)	70.1 (12.8)	1.01 (0.98-1.03)	0.724	1.01 (0.98-1.04)	0.634	1.01 (0.98-1.05)	0.397
[$]ABCD2 ≥ 4 (%)	107 (56.3)	12 (75.0)	95 (54.6)	2.50 (0.77-8.04)	0.126	2.95 (0.85-10.25)	0.088	-	-
[$]Symptoms > 1 hour (%)	82 (43.2)	8 (50.0)	74 (42.5)	1.35 (0.49-3.77)	0.565	1.34 (0.48-3.74)	0.581	-	-
[$]Isolated speech symptoms (%)	44 (23.2)	3 (18.8)	41 (23.6)	0.75 (0.20-2.76)	0.663	0.75 (0.20-2.79)	0.672	-	-
[$]Weakness symptoms (%)	55 (28.9)	8 (50.0)	47 (27.0)	2.70 (0.96-7.61)	0.060	2.81 (0.98-8.02)	0.054	-	-
[%]Mean NIHSS (s.d)	1.3 (1.2)	1.7 (1.5)	1.2 (1.2)	1.33 (0.87-2.02)	0.186	1.32 (0.86-2.04)	0.208	-	-
Smoking – current/prior (%)	141 (48.0)	18 (56.3)	123 (46.9)	1.45 (0.69-3.04)	0.322	1.32 (0.60-2.88)	0.490	-	-
Hypertension	161 (54.8)	21 (65.6)	140 (53.4)	1.66 (0.77-3.59)	0.194	1.72 (0.77-3.85)	0.190	-	-
Hyperlipidaemia	97 (33.0)	9 (28.1)	88 (33.6)	0.77 (0.34-1.74)	0.536	0.72 (0.32-1.64)	0.436	-	-
Atrial fibrillation	30 (10.2)	5 (15.6)	25 (9.5)	1.76 (0.62-4.96)	0.289	1.64 (0.56-4.80)	0.368	-	-
Diabetes mellitus	40 (13.6)	4 (12.5)	36 (13.7)	0.90 (0.30-2.71)	0.847	0.84 (0.28-2.57)	0.762	-	-
Peripheral vascular disease	12 (4.1)	0	12 (4.6)	0	0.999	0	0.999	-	-
IHD / angina	37 (12.6)	5 (15.6)	32 (12.2)	1.33 (0.48-3.70)	0.584	1.20 (0.42-3.44)	0.739	-	-
Past history of TIA / stroke	3 (1.0)	1 (3.1)	2 (0.8)	4.19 (0.37-47.60)	0.247	4.51 (0.37-51.13)	0.242	-	-
Low education (%)	143 (48.6)	18 (56.3)	125 (47.7)	1.41 (0.67-2.95)	0.363	1.36 (0.65-2.87)	0.418	-	-
Socio-economic deprivation (%)	39 (13.3)	8 (25.0)	31 (11.8)	2.48 (1.03-6.01)	**0.044**	2.66 (1.08-6.56)	**0.034**	2.15 (0.77-5.96)	0.142
Depression at 1 month	35 (11.9)	16 (50.0)	19 (7.3)	12.79 (5.55-29.49)	**<0.001**	13.00 (6.00-30.19)	**<0.001**	12.32 (5.26-28.83)	**<0.001**
Recurrent event between 1-12months	15 (5.1)	2 (6.3)	13 (5.0)	1.01 (0.40-2.60)	0.976	1.23 (0.26-5.77)	0.789	-	-

Baseline characteristics of 294 TIA / minor stroke subjects, without a history of premorbid or baseline depression, stratified by their subsequent 12-month presence or absence of depression. Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 12-months also included. [$]For TIA subjects only. [%]For minor stroke patients only.

Appendix XV: Reasons for exclusions after full text review in systematic review of psychological distress after a TIA

Reason for exclusion	Number of studies
For depression systematic review (Chapter 2)	
TIA data not presented separately to stroke data	21
No depression data	11
Editorial / Letters to the Editor	5
Review articles	5
No prevalence rates	2
Association of TIA with pre-morbid psychological distress	3
Stroke, not TIA, population	3
Excluded TIA participants	2
Unable to access text	2
Total	54
For anxiety, PTSD, and comorbid anxiety / depression systematic review (Chapter 3)	
TIA data not presented separately to stroke data	21
No anxiety, PTSD or comorbid anxiety / depression data	15
Editorial / Letters to the Editor	5
Review articles	5
No prevalence rates	2
Association of TIA with pre-morbid psychological distress	3
Stroke, not TIA, population	3
Excluded TIA participants	2
Unable to access text	2
Total	58

Appendix XVI: Susceptibility to bias in systematic review of psychological distress after a TIA

	Study design	TIA Case Definition	Method for selecting study participants	Design-specific source of bias	Participation rate (included/ eligible)	Attrition rate	Missing data management	Premorbid outcome measure reported	Validated method for measuring outcome & cut-off stated	Assessment method	Same measure/ method used at all time points
Broomfield NM et al, 2014	Cross-sectional	Retrospective primary care coding (time based)	N/A	N/A	35%	N/A	Reasons given & comparison completed.	No	Yes	Face to face	N/A
Carnes-Vendrell A, et al 2019	Prospective cohort	Stroke neurologist examination (time based)	Consecutive admissions to single centre	5% excluded due to MCI/ dementia	*Overall 63%	15%	No information provided	Yes	Cut-off values not stated	Face to face	Yes
El Husseini N et al, 2012	Prospective cohort	Physician evaluation (time based)	From multi-centre registry (AVAIL)	Secondary analysis	Not stated	16%	Reasons given & comparison completed.	No	Yes	Telephone	Yes
Hickie I et al, 2003	Cohort	Retrospective hospital coding (time based)	Recruited from prior cohort		84.2%	N/A		Yes	Yes	Face to face	N/A
Luijendijk HJ et al, 2011	Cross-sectional	Retrospective self-reporting + hospital record / brain imaging reviews by Neurologist (time based)	Embedded in longitudinal cohort study (Rotterdam Study)		Not stated	N/A		Participants with pre-morbid depressive symptoms excluded	Yes	Face to face and assessment of medical records	N/A
Maaijwee NA et al, 2016	Prospective cohort	Neurologist examination (time based)	Consecutive admissions/ referrals to a single centre	Aged 18 – 50 only	*Overall 71%	N/A	Reasons given and comparison completed	Yes	Yes	Face to face / self-administered if unable to attend	N/A
Naess H et al, 2012	Prospective cohort	Neurologist examination (imaging and time based)	Consecutive admissions to a single centre		54%	N/A	Comparison completed but reasons not provided.	*For overall cohort	Yes	Postal questionnaire	N/A
Rao R et al, 2001	Cohort	Not stated	Letter invitations to consecutive patients on a waiting list	Only participants with >70% carotid artery stenosis included.	Not stated	N/A		Yes	Cut-off values partly stated	Face to face	N/A

				Excluded if 'too frail/ cognitively impaired'							
Sackley CM et al, 2019	Prospective cohort	Stroke physician or Neurological examination (imaging and time based)	Consecutive referrals to TIA clinics (multi-centre)		Not stated	*Overall 24%	No information provided	No	Cut-off values not stated	Postal questionnaire	N/A
Sanner Beauchamp JE et al, 2020	Retrospective cohort	Not stated	Identified through electronic health records	Only those attending outpatient clinic included	67.8%	N/A	Reasons given, but no comparison completed	No	Yes	Face to face	N/A
Snaphaan L et al, 2009	Prospective cohort	Neurologist examination (time based)	Consecutive admissions to a single centre	Only participants able to visit the hospital were included.	Not stated	N/A		Participants with pre-morbid depression symptoms excluded	Yes	Face to face	N/A
Tanislav C et al, 2015	Cohort	Neurologist examination (time based)	Referrals or admissions to stroke /TIA units (multi-centre study)	Aged 18 – 55 only	Not stated	*Overall 60%	Comparison completed but reasons not provided.	No	Yes	Face to face	N/A
Kiphuth IC et al, 2014** Utz KS et al, 2019**	Prospective cohort	Neurologist review (time and imaging based)	Consecutive admissions to a single centre		51%	7.4%	Reasons given and comparison completed	No	Yes	Postal questionnaire	Yes
van Rooij FG et al, 2017	Prospective cohort	Neurologist examination (time based)	Consecutive referrals to a single centre	Included non classical TIA participants also	Not stated	25%	Reasons given and comparison completed	No	Yes	Face to face	Yes
Wong A et al, 2016	Cohort	Neurologist examination (time and imaging based)	Sample of consecutive admissions to a single centre that had been recruited to	Cross-sectional at 3-6 months post event	51% of those in parent study participated in sub-study	N/A	Comparison completed but reasons not provided.	No	Validated in assessing neuropsychiatric manifestations of dementia	Face to face	N/A

			parent study (STRIDE)								
Wu KY et al, 2010	Cross-sectional	Self-reported	Sampling of a nationwide survey	Aged 65 years and older	Overall 82%	N/A		No	Yes	Face to face	N/A
Wilson D et al, 2010	Cohort	Stroke senior physician diagnosis (time based)	Outpatient referrals (single-centre)		Not stated	N/A		No	Yes	Face to face	N/A
Turner A et al, 2016	Cohort	Not stated	Outpatient follow up clinic (single centre) attendees	Only participants able to visit the hospital were included	Not stated	10%	No information provided	Yes	Yes	Baseline: Face to face Follow up: telephone	Different methods of assessment
Von Weitzel-Mudersbach P et al, 2011	Cohort	Not stated			Not stated	Not stated		No	Cut-off values not stated		
Chun HY et al, 2018	Prospective cohort	Stroke consultant examination (time based)	Consecutive admissions to single centre		Not stated	13%	Reasons given & comparison completed.	*For overall cohort	Yes	Telephone	N/A
Kapoor A et al, 2019	Prospective cohort	Neurologist examination (imaging & time based)	Consecutive referrals to single centre	Yes	Not stated	N/A	No information provided	No	Yes	Face to face	N/A
Rizos T et al, 2016	Cohort	Not stated	Consecutive admissions to a single centre		Not stated	16%	No information provided	No	No		
Turner GM et al, 2016	Retrospective cohort	Method of diagnosis not stated (time based)	Primary care coding (The Health Improvement Network database)	Excluded if baseline psychological impairment	Coding data only so N/A	N/A		Yes	Coding data only so individual methods not known/not standardised	GP consultation	N/A
Thayabaranathan T et al, 2018	Prospective cohort	Stroke physician examination (TIA definition not stated)	Identified through a (complete) stroke registry of admissions (multi-centre)		Overall 71%	N/A	Comparison completed but reasons not provided.	Odds ratio for outcome based on premorbid presence of outcome provided but not prevalence data	Yes	Postal questionnaire with telephone follow up if failed to answer	N/A

[5]Winward C et al, 2009	Prospective cohort	Neurologist examination (time based)	Population based with near complete ascertainment of all acute vascular events		Not stated	Not stated		No	Yes	Face to face	

Red: high risk, orange: unclear/insufficient information provided, green: low risk). * Data for TIA participants alone not stated, overall data (for combined TIA/stroke participants) available. N/A = not applicable. Susceptibility to bias for included studies to assess the prevalence (in a general population) of depression, anxiety, PTSD or psychological distress after a TIA (black: high risk, dark grey: unclear/insufficient information provided, light grey: low risk). * Data for TIA participants alone not stated, overall data (for combined TIA/stroke participants) available. **Utz et al 2019 and Kiphurth et al 2014 report on the same study population but at different time points and providing different outcome data – for the purposes of the susceptibility to bias assessment they have been considered as one study. N/A = not applicable.

Appendix XVII: Baseline characteristics of the patients that did not complete follow-up in the study of symptoms of anxiety and / or depression after a TIA or minor stroke

	Completed at least 1 month of follow up	Did not complete 1 month of follow-up	p value†	Completed 12 months of follow-up	Completed 1 but not 12 months of follow-up	p value‡
Overall, n (%) of total eligible	2137 (77.9)	607 (22.1)	n/a	1822 (85.3)	315 (14.7)	n/a
TIA alone	1162 (80.7)	278 (19.3)	n/a	1010 (86.9)	152 (13.1)	n/a
Minor stroke alone	975 (74.8)	329 (25.2)	n/a	812 (83.3)	163 (16.7)	n/a
Age at event, mean (s.d)	71.1 (13.2)	75.6 (13.3)	**<0.001**	70.6 (12.9)	74.3 (14.3)	**<0.001**
TIA alone	71.3 (13.0)	76.6 (13.5)	**<0.001**	70.9 (12.6)	74.1 (15.0)	**0.005**
Minor stroke alone	71.0 (13.4)	74.7 (13.2)	**<0.001**	70.3 (13.3)	74.5 (13.6)	**<0.001**
Female sex, n (%)	1031 (48.2)	322 (53.0)	**0.037**	872 (47.9)	159 (50.5)	0.394
TIA alone	586 (50.4)	154 (55.4)	0.134	501 (49.6)	85 (55.9)	0.148
Minor stroke alone	445 (45.6)	168 (51.1)	0.084	371 (45.7)	74 (45.4)	0.944
Pre-morbid anxiety/depr, n (%)*	558 (26.3)	167 (28.6)	0.267	472 (26.0)	86 (27.7)	0.530
TIA alone	306 (26.5)	75 (28.1)	0.595	262 (26.0)	44 (29.5)	0.366
Minor stroke alone	252 (26.0)	92 (29.0)	0.295	210 (26.0)	42 (26.1)	0.979
SED, mean IMD (s.d)*	10.8 (7.2)	11.1 (7.3)	0.397	10.6 (7.1)	11.8 (7.8)	**0.006**
TIA alone	10.6 (6.9)	11.2 (7.3)	0.197	10.4 (6.7)	11.8 (8.2)	0.052
Minor stroke alone	11.0 (7.5)	11.0 (7.3)	0.913	10.8 (7.5)	11.8 (7.5)	0.127
Hypertension, n (%)*	1230 (57.6)	377 (62.9)	**0.020**	1034 (56.8)	196 (62.2)	0.073
TIA alone	643 (55.3)	173 (63.4)	**0.015**	549 (54.4)	94 (61.8)	0.087
Minor stroke alone	587 (60.2)	204 (62.6)	0.442	485 (59.7)	102 (62.6)	0.490
Hyperlipidaemia, n (%)*	710 (33.2)	194 (32.4)	0.713	607 (33.3)	64 (20.3)	**<0.001**
TIA alone	388 (33.4)	94 (34.4)	0.753	344 (34.1)	44 (28.9)	0.205
Minor stroke alone	322 (33.0)	100 (30.7)	0.443	263 (32.4)	59 (36.2)	0.347
Atrial fibrillation, n (%)*	311 (14.6)	123 (20.5)	**<0.001**	247 (13.6)	64 (20.3)	**0.002**
TIA alone	160 (13.8)	57 (20.9)	**0.003**	134 (13.3)	26 (17.1)	0.206
Minor stroke alone	151 (15.5)	66 (30.7)	**<0.001**	113 (13.9)	38 (23.3)	**0.003**
Previous TIA / stroke, n (%)*	264 (12.4)	118 (19.7)	**<0.001**	219 (12.0)	45 (14.3)	0.252
TIA alone	142 (12.2)	61 (22.3)	**<0.001**	122 (12.1)	20 (13.2)	0.700
Minor stroke alone	122 (12.5)	57 (17.5)	**0.023**	97 (11.9)	25 (15.3)	0.231
Diabetes mellitus, n (%)*	299 (14.0)	101 (16.9)	0.076	238 (13.1)	61 (19.4)	**0.003**
TIA alone	148 (12.7)	48 (17.6)	**0.034**	118 (11.7)	30 (19.7)	**0.006**
Minor stroke alone	151 (15.5)	53 (16.3)	0.731	120 (14.8)	31 (19.0)	0.177
Peripheral vascular disease, n (%)*	143 (6.7)	55 (9.2)	**0.037**	93 (5.1)	20 (6.3)	0.379
TIA alone	51 (4.4)	27 (9.9)	**<0.001**	41 (4.1)	10 (6.6)	0.163
Minor stroke alone	92 (6.4)	28 (8.6)	0.177	52 (6.4)	10 (6.1)	0.886
IHD/ angina, n (%)*	367 (17.2)	140 (23.4)	**0.006**	299 (16.4)	68 (21.6)	**0.024**
TIA alone	183 (15.7)	62 (22.7)	**0.006**	152 (15.0)	31 (20.4)	0.088
Minor stroke alone	184 (18.9)	78 (23.9)	**0.052**	147 (18.1)	37 (22.7)	0.171
Current / prior smoking, n (%)*	1198 (56.1)	341 (58.3)	0.342	1010 (55.4)	188 (59.7)	0.156
TIA alone	622 (53.5)	146 (55.5)	0.557	526 (52.1)	96 (63.2)	**0.011**
Minor stroke alone	576 (59.1)	177/322	0.196	484 (59.6)	92 (56.4)	0.449
Education <12 years, n (%)*	1305 (61.9)	292 (65.8)	0.123	1101 (61.1)	204 (66.9)	0.054
TIA alone	673 (58.7)	129 (65.2)	0.085	585 (58.5)	88 (59.9)	0.748
Minor stroke alone	632 (65.8)	163 (66.3)	0.883	516 (64.3)	116 (73.4)	**0.028**
TIA (ABCD2 score≥4), n (%)*	661 (57.1)	177 (68.3)	**<0.001**	567 (63.5)	94 (63.5)	0.094
Minor stroke (NIHSS) mean, s.d*	1.4 (1.3)	1.6 (1.4)	**0.013**	1.4 (1.3)	1.5 (1.3)	0.342
Recurrent event by 12m, n (%)	n/a	n/a	n/a	149 (8.2)	37 (11.7)	**0.042**
TIA alone	n/a	n/a	n/a	85 (8.4)	17 (11.2)	0.255
Minor stroke alone	n/a	n/a	n/a	64 (7.9)	20 (12.3)	0.068
A/D symptoms at 1 month, n (%)	n/a	n/a	n/a	543 (29.8)	96 (30.5)	0.802
TIA alone	n/a	n/a	n/a	290 (28.7)	44 (28.9)	0.960
Minor stroke alone	n/a	n/a	n/a	253 (31.2)	52 (31.9)	0.861

p value for difference between completing †1 month of follow up and no follow-up and ‡all follow up and only 1 month of follow-up. *Missing data overall: 36 x pre-morbid anxiety/depr (depression), 2 x socio-economic deprivation status, 22 x smoking history, 193 x education level, 24 x ABCD2 scores, 2 x NIHSS scores, 8 x vascular history/risk factors (hypertension, hyperlipidaemia, previous TIA/stroke, diabetes mellitus, peripheral vascular disease, IHD/angina).. A/D = anxiety / depression

Appendix XVIII: Baseline characteristics of minor stroke or TIA patients (without a history of pre-morbid anxiety or depression or reporting often feeling low at time of event) stratified by their subsequent (a) 1-month (n=1277) and (b) 12-month (n=1104) presence or absence of moderate to extreme symptoms of anxiety and/or depression.

(a) 1-month:

Baseline characteristic	All	Anxiety / depression symptoms at 1 month	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	536 (42.0)	116 (46.8)	420 (40.8)	1.27 (0.96-1.68)	0.088	1.31 (0.98-1.73)	0.064	1.32 (1.00-1.75)	0.053
Mean age at event (s.d)	71.7 (12.7)	71.1 (13.7)	71.9 (12.3)	1.00 (0.99-10.1)	0.406	0.99 (0.98-1.01)	0.271	0.99 (0.98-1.00)	0.166
$ABCD2 ≥ 4 (%)*	413 (58.7)	81 (60.4)	332 (58.2)	1.08 (0.73-1.58)	0.705	1.18 (0.79-1.77)	0.425	-	-
$Symptoms > 1 hour (%)*	258 (40.7)	57 (42.5)	228 (40.2)	1.01 (0.75-1.61)	0.622	1.11 (0.76-1.63)	0.582	-	-
$Isolated speech symptoms (%)	189 (26.5)	42 (31.3)	144 (25.4)	1.34 (0.89-2.03)	0.158	1.37 (0.90-2.07)	0.140	-	-
$Weakness symptoms (%)	235 (33.5)	39 (29.1)	196 (34.5)	0.78 (0.52-1.18)	0.234	0.79 (0.53-1.20)	0.274	-	-
%Mean NIHSS (s.d)	1.5 (1.3)	1.7 (1.3)	1.5 (1.3)	1.13 (0.97-1.32)	0.114	1.14 (0.98-1.33)	0.100	-	-
Smoking – current/prior (%)	701 (54.9)	137 (55.2)	564 (54.8)	1.02 (0.77-1.35)	0.902	1.11 (0.83-1.48)	0.502	-	-
Hypertension	734 (57.5)	138 (55.6)	596 (57.9)	0.91 (0.69-1.21)	0.515	0.94 (0.70-1.25)	0.665	-	-
Hyperlipidaemia	408 (31.9)	72 (29.0)	336 (32.7)	0.84 (0.62-1.14)	0.273	0.88 (0.64-1.19)	0.396	-	-
Atrial fibrillation	194 (15.2)	40 (16.1)	154 (15.0)	1.09 (0.75-1.60)	0.647	1.13 (0.77-1.67)	0.523	-	-
Diabetes mellitus	173 (13.5)	26 (10.5)	147 (14.3)	0.70 (0.45-1.09)	0.118	0.72 (0.46-1.12)	0.145	-	-
Peripheral vascular disease	76 (6.0)	13 (5.2)	63 (6.1)	0.85 (0.46-1.57)	0.599	0.88 (0.48-1.63)	0.687	-	-
IHD / angina	208 (16.3)	36 (14.5)	172 (16.7)	0.85 (0.57-1.25)	0.400	0.91 (0.61-1.36)	0.646	-	-
Past history of TIA / stroke	145 (11.4)	36 (14.5)	109 (10.6)	1.43 (0.96-2.15)	0.082	1.52 (1.00-2.29)	**0.048**	1.52 (1.00-2.29)	**0.048**
Low education (%)	750 (59.5)	152 (61.3)	598 (59.0)	1.10 (0.83-1.46)	0.516	1.13 (0.85-1.51)	0.398	-	-
Socio-economic deprivation (%)	138 (10.8)	32 (12.9)	106 (10.3)	1.29 (0.85-1.97)	0.237	1.29 (0.84-1.96)	0.244	-	-

Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 1 also included. (*1 month missing data: 4 ABCD2 scores, 3 symptom duration, 2 speech/weakness symptoms, 16 education histories.) $For TIA subjects only. %For minor stroke patients only.

(b) 12-months:

Baseline characteristic	All	Anxiety / depression symptoms at 12 months	No symptoms	Crude OR (95% CI)	p value	Age/sex adj OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Female (%)	462 (41.8)	77 (48.7)	385 (40.7)	1.39 (0.99-1.94)	0.059	1.33 (0.94-1.87)	0.103	1.34 (0.93-1.93)	0.122
Mean age at event (s.d)	71.2 (12.4)	72.8 (12.9)	70.9 (12.3)	1.01 (1.00-1.03)	0.078	1.01 (1.00-1.03)	0.134	1.01 (0.99-1.02)	0.444
[$]ABCD2 ≥ 4 (%)	357 (58.0)	50 (61.7)	307 (57.4)	1.20 (0.74-1.94)	0.461	1.06 (0.64-1.75)	0.817	-	-
[$]Symptoms > 1 hour (%)	251 (40.7)	37 (45.1)	214 (40.0)	1.23 (0.77-1.97)	0.380	1.21 (0.76-1.94)	0.425	-	-
[$]Isolated speech symptoms (%)*	162 (26.3)	18 (22.2)	144 (26.9)	0.78 (0.44-1.36)	0.372	0.72 (0.41-1.26)	0.251	-	-
[$]Weakness symptoms (%)*	199 (32.3)	34 (42.0)	165 (30.8)	1.62 (1.01-2.62)	**0.047**	1.59 (0.98-2.57)	0.060	-	-
[%]Mean NIHSS (s.d)	1.5 (1.3)	1.8 (1.4)	1.4 (1.3)	1.24 (1.03-1.49)	**0.020**	1.25 (1.04-1.51)	**0.018**	[%]1.22 (1.00-1.48)	**0.046**
Smoking – current/prior (%)	600 (54.3)	84 (53.2)	516 (54.5)	0.95 (0.68-1.33)	0.747	1.05 (0.73-1.49)	0.804	-	-
Hypertension	624 (56.5)	90 (57.0)	534 (56.4)	1.02 (0.73-1.44)	0.904	0.95 (0.67-1.35)	0.757	-	-
Hyperlipidaemia	355 (32.2)	50 (31.6)	305 (32.2)	0.97 (0.68-1.40)	0.882	0.97 (0.67-1.39)	0.851	-	-
Atrial fibrillation	155 (14.0)	27 (17.1)	128 (13.5)	1.32 (0.84-2.07)	0.235	1.27 (0.80-2.01)	0.316	-	-
Diabetes mellitus	143 (13.0)	20 (12.7)	123 (13.0)	0.97 (0.59-1.61)	0.905	0.99 (0.60-1.65)	0.972	-	-
Peripheral vascular disease	65 (5.9)	10 (6.3)	55 (5.8)	1.10 (0.55-2.20)	0.799	1.08 (0.54-2.17)	0.832	-	-
IHD / angina	176 (15.9)	36 (22.8)	140 (14.8)	1.70 (1.12-2.57)	**0.012**	1.71 (1.11-2.62)	**0.014**	1.13 (2.81-1.78)	**0.013**
Past history of TIA / stroke	126 (11.4)	29 (18.4)	97 (10.3)	1.97 (1.25-3.10)	**0.003**	1.90 (1.20-3.01)	**0.006**	1.65 (1.01-2.71)	**0.047**
Low education (%)*	642 (58.7)	99 (63.1)	543 (58.0)	1.24 (0.87-1.75)	0.235	1.20 (0.84-1.71)	0.309	-	-
Socio-economic deprivation (%)	119 (10.8)	22 (13.9)	97 (10.3)	1.42 (0.86-2.33)	0.170	1.42 (0.86-2.34)	0.165	-	-
Anxiety/depression symptoms at 1 month	212 (19.2)	75 (47.5)	137 (14.5)	5.34 (3.72-7.66)	**<0.001**	5.30 (3.69-7.62)	**<0.001**	5.35 (3.70-7.71)	**<0.001**
Recurrent event between 1-12months	77 (7.0)	14 (8.9)	63 (6.7)	1.36 (0.74-2.50)	0.316	1.35 (0.74-2.48)	0.334	-	-

Crude odds ratio, age/sex adjusted odds ratio and multivariate regression analysis for the risk of depression at 12 months also included. [$]For TIA subjects only. [%]For minor stroke patients only. (*12 month missing data: 1 ABCD2 score, 1 speech / weakness symptom 11 education histories).

Appendix XIX: Search strategy for systematic review of pre-stroke and post-stroke dementia

EMBASE
1. cerebrovascular accident/
2. exp brain ischemia/
3. exp brain infarction/
4. brain hemorrhage/
5. (stroke or poststroke or post-stroke or cva$ or apoplex$ or transient isch?emi$ attack$ or tia$1).tw.
6. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or anterior circulation or posterior circulation or basal ganglai) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
7. ((lacunar or cortical) adj5 infarct$).tw.
8. ((brain$ or cereb$ or cerebell$ or intracerebral or intracran$ or parenchymal or infratentorial or supratentorial or basal ganli$ or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ of hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
9. ((brain or intracranial or basal ganglia or lenticulostriate) adj5 (vascular adj5 (disease$ or disorder or accident or insult or event))).tw.
10. ((isch?emic or apoplectic) adj5 (event or events or insult or attack$)).tw.
11. dementia/ or alzheimer disease/ or diffuse lewy body disease/ or diffuse neurofibrillary tangles with calcification/ or frontotemporal dementia/ or hiv associated dementia/ or huntington chorea/ or multiinfarct dementia/ or pick presenile dementia/ or presenile dementia/ or prion disease/ or senile dementia/
12. (dementia or lewy$ bod$ or binswanger$ or alzheimer$).tw.
13. (exp animals/ or nonhuman/) not human/
14. Conference*.pt.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
16. 11 or 12
17. 15 and 16
18. 17 not 13 not 14
19. limit 18 to yr="2009 -Current"

MEDLINE
1. cerebrovascular disorders/
2. exp basal ganglia cerebrovascular disease/
3. exp brain ischemia/
4. stroke/
5. exp brain infarction/
6. exp intracranial hemorrhages/
7. (stroke or poststroke or post-stroke or cva$ or apoplex$ or transient isch?emi$ attack$ or tia$1).tw.
8. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
9. ((lacunar or cortical) adj5 infarct$).tw.
10. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
11. ((brain or intracranial or basal ganglia or lenticulostriate) adj5 (vascular adj5 (disease$ or disorder or accident or insult or event))).tw.
12. ((isch?emic or apoplectic) adj5 (event or events or insult or attack$)).tw.

13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. dementia/ or aids dementia complex/ or alzheimer disease/ or aphasia, primary progressive/ or primary progressive nonfluent aphasia/ or creutzfeldt-jakob syndrome/ or dementia, vascular/ or dementia, multi-infarct/ or diffuse neurofibrillary tangles with calcification/ or frontotemporal lobar degeneration/ or frontotemporal dementia/ or "pick disease of the brain"/
15. exp lewy bodies/
16. dement$.tw.
17. alzheimer$.tw.
18. lewy$ bod$.tw.
19. binswanger$.tw.
20. 14 or 15 or 16 or 17 or 18 or 19
21. 13 and 20
22. limit 21 to yr="2009 -Current"
23. exp animals/ not humans.sh.
24. 22 not 23

PSYCHINFO
1. cerebrovascular accident/
2. exp cerebral ischemia/
3. cerebral hemorrhage/
4. stroke/
5. (stroke or poststroke or post-stroke or cva$ or apoplex$ or transient isch?emi$ attack$ or tia$1).tw.
6. ((brain$ or cereb$ or cerebell$ or intracerebral or intracran$ or parenchymal or infratentorial or supratentorial or basal ganli$ or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ of hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
7. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlu$)).tw.
8. ((lacunar or cortical) adj5 infarct$).tw.
9. ((isch?emic or apoplectic) adj5 (event or events or insult or attack$)).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. dementia/ or aids dementia complex/ or dementia with lewy bodies/ or presenile dementia/ or pseudodementia/ or semantic dementia/ or senile dementia/ or vascular dementia/ or alzheimer's disease/ or creutzfeldt jakob syndrome/ or picks disease/
12. dement$.tw.
13. alzheimer$.tw.
14. lewy$ bod$.tw.
15. binswanger$.tw.
16. 11 or 12 or 13 or 14 or 15
17. 10 and 16
18. limit 17 to human
19. limit 18 to yr="2009 -Current"

Top 4 journals with most eligible articles from electronic search:
Stroke
Journal of Neurology, Neurosurgery & Psychiatry
Journal of Stroke & Cerebrovascular Diseases
Neurology

Appendix XX: Definition of severity of stroke according to the different functional scales

	Mild	Moderate	Severe	Reference
Barthel Index (20 points)	10-20	3-9	0-2	Govan L et al, 2009[1]
Barthel Index (100 points)	91-99	61-90	0-60	Shah S et al, 1989[2]
Modified Rankin Scale	0-3	4	5	Govan L et al, 2009[1]
Scandinavian Stroke Scale	43-58	26-42	0-25	Govan L et al, 2009[1]
National Institutes of Health Stroke Scale (NIHSS)	0-5	6-14	15-31	Govan L et al, 2009[1]
Canadian Neurological Scale	9-11.5	4.5-8.5	0-4	Nilanant Y et al, 2010[3]
Orgogozo				No reference found
Stroke Levity Scale	11-15	6-10	0-5	Owolabi MO et al, 2008[4]

1. Govan L, Langhorne P, Weir CJ. Categorizing stroke prognosis using different stroke scales. Stroke. 2009;40(10):3396-3399.
2. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989;42(8):703-709.
3. Nilanont Y, Komoltri C, Saposnik G, et al. The Canadian Neurological Scale and the NIHSS: development and validation of a simple conversion model. Cerebrovasc Dis. 2010;30(2):120-126.
4. Owolabi MO, Platz T. Proposing the Stroke Levity Scale: a valid, reliable, simple, and time-saving measure of stroke severity. Eur J Neurol. 2008;15(6):627-633.