FUNCTIONAL, COGNITIVE AND EMOTIONAL OUTCOMES AFTER TRANSIENT ISCHAEMIC ATTACK: A SYSTEMATIC REVIEW AND CONTROLLED COHORT STUDY

By

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ABSTRACT

Introduction

As neurological symptoms of transient ischaemic attack (TIA) subside, it is assumed that patients return to their "normal" health state. Patients are managed according to their risk of stroke and "success" is measured by time to clinic, prescription of prophylactics and prevention of further cardiovascular episodes and/or death. Very little attention has been given to patients' psychological well-being, cognitive functioning and physical functioning. The aim of this thesis was to examine these outcomes after TIA.

Methods

A systematic review was conducted to amalgamate and critique existing literature on health outcomes after TIA. A longitudinal, controlled cohort study (FACE TIA) was then designed to develop the evidence base further and examine interaction effects between cognition, feelings of affect and physical function in all patients referred to TIA clinics. The pilot results were analysed and discussed as part of this thesis.

Results

Fourteen publications, out 2007 generated by the initial search, were included in the systematic review. Evidence from these studies suggests that cognitive impairment and depression are higher in TIA patients than age-matched healthy individuals. However no evidence was found to suggest that basic daily functioning is compromised in TIA patients. The majority of studies were underpowered and used cross-sectional analysis. The FACE TIA trial is ongoing however the results of the pilot study are consistent with previous research. Feelings of depression were significantly higher in TIA patients (n=104) compared to healthy controls (n=30), but similar to levels of depression in other patient groups (possible TIA

(n=71), TIA “mimic” (n=41) and minor stroke (n=18)). This suggests that depression may be related to the experience of suffering a stressful event, rather than the cardiovascular event itself. Analyses also revealed that certain types of cognitive impairment were more prevalent in TIA patients (n=40) than published norms taken from a “healthy” population. Furthermore, increased anxiety and depression appeared to be associated with reduced independence and increased cognitive impairment.

Discussion

It is unclear how much of the observed association between cerebrovascular disease and cognitive dysfunction is mediated by cardiovascular risk factors, and/or whether TIA has a direct causal relationship. Regardless, such deficits could impact of the patient’s overall quality of life and their ability to learn, understand and remember new information, and adopt new health behaviours aimed at reducing stroke risk. Patients diagnosed with TIA may benefit from cognitive screening. Results into depression suggest that all patients attending TIA clinics may benefit from increased emotional support, regardless of their diagnosis. Further research should be directed at assessing the feasibility of screening patients for cognitive impairment and depression after referral to TIA clinics, and developing/evaluating interventions to facilitate patients whose screen is positive.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AIDS	Acquired immune deficiency syndrome
BDCS	Behavioural dyscontrol scale
BI	Barthel Index
BP	Blood pressure
BUCS	Birmingham University Cognitive Screen
CAMCOG	Cognitive part of the Cambridge examination for mental disorders of the elderly
CANTAB	Cambridge neuropsychological test automated battery
CEA	Carotid endarterectomy
CES-D	Centre for epidemiological studies depression scale
CI	Confidence intervals
CT	Computerised tomography
DARE	Database of abstracts of reviews of effects
DSM-IV	Diagnostic and statistical manual of mental disorders
DWI	Diffusion weighted MRI
FACE TIA	Functional, cognitive and emotional outcomes after transient ischaemic attack
GDS	Geriatric depression scale
GLM	General linear models
GP	General practitioners
HADS	Hospital anxiety and depression scale
HIV	Human immunodeficiency virus
HRDS	Hamilton rating scale for depression
HRQoL	Health related quality of life
ICD	International statistical classification of diseases and related health problems
MDAS	Mixed depression and anxiety score
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
MoCA	Montreal cognitive assessment
MOOSE	Meta-analysis of observational studies in epidemiology
MOS-SF	Medical outcomes study short form
NEADL	Nottingham extended activities of daily living
NICE	National Institute of Health and Clinical Excellence
OXVASC	Oxford Vascular Study
POMS	Profile of mood states
QOF	Quality and outcomes framework
RN	Research nurse
ROSIER	Recognition of stroke in the emergency room
SECF	Scale of elderly cognitive function
SF	Short form questionnaire
STROBE	Strengthening the reporting of observational studies in epidemiology
TIA	Transient ischaemic attack
TTO	Time trade-off utility
UK	United Kingdom
UoB	University of Birmingham

CHAPTER 1

BACKGROUND

1.1 Defining Transient Ischaemic Attack

Hankey & Warlow (1994) defined Transient Ischaemic Attack (TIA) as,

"an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply as a result of low blood flow, arterial thrombosis, or embolism". Only symptoms lasting longer than this were felt to represent tissue infarction and be considered a "completed stroke". There is a certain amount of controversy surrounding the somewhat arbitrary 24-hour threshold distinguishing TIA from stroke. Levy (1998) showed that the likelihood of symptoms resolving completely within 24 hours was less than 15 percent if symptoms lasted more than 1 hour. Thus, suggesting that symptoms lasting more than 1 hour are more likely to represent completed strokes than TIAs.

Advances in neuroimaging, particularly diffusion weighted MRI (DWI), have improved our understanding of the pathophysiology of TIA and highlighted an inconsistency between the concept of TIA (ischemia causing transient symptoms but no infarction) and the classic time-based definition of TIA. A pooled analysis of DWI-studied patients revealed cerebral infarction in a clinically relevant location in approximately one third of patients with classically defined TIA (Shah et al., 2007). The median duration of symptoms was longer among patients with DWI abnormality than those without DWI abnormality suggesting that stroke and TIA form a continuum rather than two distinct entities of cerebrovascular disease. Following such revelations, a shift from the arbitrary definition of TIA to tissue-based definitions was proposed. In 2002 the TIA Working Group re-defined TIA as: "a brief episode

of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction" (Albers et al., 2002).

1.2 Pathophysiology of Ischaemic stroke/TIA

The brain has a high demand for oxygen and glucose to function. Cerebral ischemia caused by vascular occlusion leads to a depletion of substrates within minutes. This is further compounded by the accumulation of toxicmetabolites (Mergenthaler et al., 2004). Neuronal damage is mild and reversible if flow is restored within a few hours. In these circumstances, a diagnosis of TIA would be given. The terms TIA and minor stroke are often used interchangeably. However, in explicit terms, stroke (cerebrovascular infarction) results from a series of metabolic processes which ensue if the blood flow is not re-established to the ischaemic area. Saver (2006) calculated that ischaemic stroke patients loose, in the absence of treatment, an average of 1.9 million neurons per minute. He paralleled this to 3.1 weeks of accelerated aging. The rate and extent of infarction however, will differ substantially depending on various factors including location and extent of vessel occlusion, degree of collateral blood supply, blood pressure, blood volume and degree of ischaemic preconditioning (Kidwell et al., 2003).

1.3 Epidemiology

1.3.1 Incidence

Transient Ischaemic Attack (TIA) affects a huge proportion of the population. The most robust study of TIA incidence in the UK is the Oxford Vascular study (OXVASC), carried out between 2002 and 2005 (Giles & Rothwell, 2007). When standardised to the 2005 population of England, the annual incidence rate of probable and definite TIA was 1.08 (0.95–1.21) and

the annual incidence rate of incident-definite TIA was 0.54 (0.44–0.63) per thousand. This translates into approximately 54,610 definite or probable TIAs and 26,280 incident-definite TIAs respectively in that year alone (Giles & Rothwell, 2007).

These figures are slightly higher than those reported in the Oxfordshire Community Stroke Project, carried out between 1981 and 1986, which reported annual incidence rates of 0.35 (0.30–0.40) per 100,000 for TIA (Dennis et al., 1989). This may reflect improved methods of case ascertainment in the OXVASC study. Equally, it may reflect an increased number of TIA patients seeking medical advice due to increased awareness of TIA as a medical emergency. Campaigns aimed at the general public like FAST (Face, Arms, Speech, Time) (Department of Health, 2007b), are likely to have triggered more individuals to recognise the symptoms of TIA and seek medical attention. Following recommendations for all front-line staff to be trained to recognise TIA and stroke symptoms, as part of the Department of Health's commitment to improving services for TIA and stroke (Department of Health, 2007a), practitioners ability to identify and act on TIA may have also improved. Diagnostic tools such as ROSIER (Recognition Of Stroke In the Emergency Room) (Department of Health, 2007b), and slogans like "time is brain" may have facilitated this.

Following the introduction of the quality and outcomes framework (QOF) in 2004 it is likely that the reporting TIA and minor stroke by practitioners improved, again contributing to the apparent increase in incidence of TIA. QOF is a voluntary incentive scheme for GP practices in the UK that rewards practices for how well they register, monitor and care for patients with different conditions, including stroke and TIA.

The mean age for patients experiencing their first ever TIA was reported by OXVASC to be 73 with a standard deviation 13 years (Giles & Rothwell, 2007). This is comparable to results

published from the Oxfordshire Community Stroke Project (Dennis et al, 1989), which reported highest incidence of TIA in the 75–84 age group.

It is suggested that there were approximately 150,000 new referrals to TIA clinics in England in 2005 with suspected TIA (Giles & Rothwell, 2007). Definite and probable TIA and stroke were found to account for only 62% of these referrals. The fact that many people with a suspected TIA turn out to have other diagnoses reflects the considerable challenge faced by GPs in accurately diagnosing TIA.

Although standardised admission rates for stroke in Oxfordshire are similar to mean overall rates in England, caution should be taken when generalising the results of these incidence-based studies to the rest of the country as the deprivation and ethnic mix of Oxfordshire may be very different.

Incidence (i.e. the number of people experiencing a first or recurrent TIA per year) is of interest because this has a bearing on initiation of treatment and secondary prevention. The prevalence (i.e. the number of people who have a history of a TIA) is also relevant as it highlights a group of people who may be living with the consequences of TIA and are receiving ongoing treatments including medical management and behaviour modification.

1.3.2 Prevalence

Extensive searches of electronic databases of medical literature revealed no UK-based prevalence studies of TIA. Current estimates for commissioning, planning and prioritizing healthcare, summarized in the Health Care Needs Assessment (Mant et al., 2004), are based on a Dutch study carried out between 1990 and 1993 (Bots et al., 1997). This population-based study of 7,983 individuals revealed a TIA prevalence of 1.9% in subjects aged 55-64 years, 3.5% in subjects aged 65-74 years, 4.3% in subjects aged 75-84 years and 5.1% in

subjects over 85 years. About half of these subjects were classified as having had non-specific TIAs.

1.4 Forming a diagnosis

The diagnosis of TIA is currently based on clinical judgement, formed by subjective assessment of risk factors and symptoms.

1.4.1 Risk factors

Modifiable risk factors are the same as for completed stroke and include atrial fibrillation, hypertension, smoking, diabetes mellitus and ischaemic heart disease (Mant et al, 2004). People may be at higher risk of stroke owing to inherent factors that cannot be altered, such as age, sex, family history and ethnicity.

1.4.2 Symptoms

Typically the symptoms associated with TIA arise suddenly, with maximal onset and last for only a short duration (Mant, 2011). Symptoms can be classified as "focal" and attributed to dysfunction to an arterial territory of the brain, or "non-focal" where cerebral symptoms cannot be anatomically localized. Symptoms most likely to predict a stroke or TIA include sudden change in speech, visual loss, diplopia, numbness or tingling, weakness or paralysis, and non-orthostatic dizziness(Goldstein & Simel, 2005). These are all focal symptoms. Non-focal symptoms, such as headache, confusion and loss of consciousness do not suggest a stroke or TIA unless they are clearly accompanied by focal symptoms (Warrior & Prabhakaran, 2009).

1.4.3 Diagnostic difficulties

Forming an accurate diagnosis of TIA is notoriously difficult. Agreement between assessors has been shown to be as low as 50% (Tomasello et al., 1982), and a high percentage of patients referred with suspected TIA are subsequently found to have a non-cerebrovascular diagnosis when assessed by stroke specialists (Dawson et al., 2009). In a recent cohort study of consecutive patients referred to TIA clinics over 5 years (Fonseca & Canhão, 2011), a specific diagnosis was not established in almost a quarter of patients, even after extensive investigation. In part diagnostic difficulties arise from the heterogeneity of TIA symptoms and variety of conditions that can mimic a TIA such as seizure, sepsis, metabolic disturbances, space occupying lesions, syncope and delirium and others (Dawson et al, 2009; Fonseca & Canhão, 2011; Goldstein & Simel, 2005; McArthur et al., 2011). Accurate diagnosis also relies on patients' ability to accurately recall their symptoms which would, by nature of the syndrome, have been short lived.

Although imaging modalities can significantly improve the clinical decision making and care of TIA and stroke patients, it is not always necessary and the results can be misleading. Infarcts, that are visible in brain scans are not always symptomatic and often go unnoticed, so called "silent strokes" (Lim & Kwon, 2010). In practice brain imaging is only recommended for diagnostic purposes when TIA is suspected yet vascular pathology is uncertain. For treatment purposes MR diffusion and perfusion imaging techniques have become indispensable for characterizing and dating acutely ischaemic tissue. Providing the critical time window has not lapsed, it can be used to identify individuals at risk of stroke who will benefit from thrombolysis (Ricci, 2000). Likewise, carotid imaging can be used to identify candidates for carotid endarterectomy (National Institute for Health and Clinical Excellence, 2008).

1.5 Management of Transient Ischaemic Attack and minor-stroke

National stroke guidelines and audits recommend that people with suspected TIA or minor stroke are immediately started on 300mg aspirin (daily) and managed according to their risk of further stroke (National Institute for Health and Clinical Excellence, 2008). Johnston and colleagues (2007) established and validated a tool, named $ABCD^2$, to predict the risk of stroke after TIA. The $ABCD^2$ evaluates five risk factors (age, blood pressure, clinical features, duration and diabetes) and is scored out of seven.

Patients that are considered to have a high risk of stroke (an $ABCD^2$ score of four or more, or more than one TIA in a week) should receive specialist assessment and investigation within 24 hours of symptom onset. For lower-risk patients specialist assessment and investigation should be performed as soon as possible and definitely within 1 week of onset of symptoms. In both cases measures for secondary prevention should be introduced as soon as the diagnosis is confirmed. Measures are usually aimed at managing hypertension, diabetes, atrial fibrillation, cholesterol and obesity through medication (e.g. antithrombotics and statins) and lifestyle advice (e.g. diet, exercise, smoking and alcohol advice). Carotid endarterectomy (CEA) is only advocated, within 2 weeks of symptom onset, in patients with symptomatic carotid artery stenosis of 50–99% (according to the North American Symptomatic Carotid Endarterectomy Trial criteria), or 70–99% (according to the European Carotid Surgery Trialists' Collaborative Group criteria).

"Success" with this group (that is patients with suspected TIA) appears to be measured in terms of time from event to clinic, prescription of prophylactic medications and prevention of further cardiovascular episodes and/or death. Given that TIA is associated with a very high risk of stroke (relative risk of 80, 95% confidence interval: 34–158) in the first month following the event (Dennis et al., 1990), this is hardly surprising.

Evidence for the role of rehabilitation after TIA is lacking and stroke-unit care is only advocated for those with a diagnosis of stroke. National stroke guidelines were developed by the Intercollegiate Working Party for Stroke, members of which were nominated by professional organisations and societies to give wide representation from all disciplines, including the views of patients and their families. Based on available evidence, the Intercollegiate Stroke Working Party (2008), recommend that a multidisciplinary assessment including assessment of consciousness level, swallowing, pressure sores risk, nutritional status, cognitive impairment, communication and the patient's needs in relation to moving and handling should be undertaken within 24–48 hours of admission for stroke. They acknowledge the importance of physiotherapists and occupational therapists in co-ordinating therapy to improve movement performance and address difficulties in activities of daily living following stroke. Within the first month of stroke the Intercollegiate Working Party highlight a need for screening patients for emotionalism, anxiety and depression. They state that "mood" should be kept under review and antidepressant should be considered as a possible treatment. The Edinburgh Consensus Conferences on stroke also support the use of antidepressants for depression or emotionalism, as well as psychological therapies; support mechanisms (including patient and carer support groups) after stroke (Mant et al., 2004).

1.6 Research Proposal

1.6.1 Rationale

While the physical, cognitive and psycho-social consequences of ischaemic stroke are extensively documented, as evidenced in the NICE guidelines (Swain et al., 2008), rather less is known about the consequence sequelae of TIA. This is hardly surprising given that TIA is defined in terms of "symptoms that resolve without obvious lasting damage" (Department of

Health, 2007b). Where there is data the emphasis tends to be on medical management and survival, reflecting the current focus of treatment for this group; the prevention of major stroke.

As discussed earlier, the boundary between TIA and stroke is not clear cut and it is possible that healthcare needs of people diagnosed with TIA and minor stroke are being overlooked. The World Health Organisation ‘‘biopsychosocial model’’ defines health as “a state of complete physical, mental and social well-being and not merely the absence of diseases and infirmity”. This has led to increased recognition that healthcare evaluations should incorporate patients’ perspectives and include self-report health rating scales as well as the inherent survival statistics and referral times.

Using Q-methodology, Spurgeon (2011) studied patients’ experiences of TIA. Q-methodology involves the development of a series of heterogeneous statements which capture subjective experiences. These statements are ranked by participants according to their own perspectives or experiences (Q-sort). The resulting Q-sorts are then subjected to correlation and factor analysis. Spurgeon (2011) identified eight themes that were pertinent to the experiences of TIA patients: lack of knowledge/awareness of TIA; life impact; anxiety; interpersonal impact; depression; physical consequences; cognitive avoidance (denial) and constructive optimism. Eminent comments including, “my memory did suffer quite a bit.....It’s better now, but still hasn’t returned to what it was before”; “I wonder whether I will ever be able to function normally again”, “the worry stopped me sleeping and functioning properly”; “I felt so very low for ages” and “I definitely felt I was a burden on my family” were particularly alarming. These personal experiences suggest that TIA is not as transient as once perceived.

The emergence of physical, psycho-social and cognitive sequalae of TIA warrants further attention, to see if the subjective experiences identified here translate to the wider TIA population, especially when potential influential factors are controlled.

1.6.2 Aim

A review will be conducted to systematically look for research which has investigated whether or not individuals who are diagnosed with TIA make a full physical and emotional recovery after the neurological symptoms subside. The extent and quality of research will be scrutinised and, if limited, a cohort study will be designed to better understand the consequences of TIA and provide clinically significant evidence to support the presence or absence of functional, cognitive and emotional impairments after TIA.

CHAPTER 2

SYSTEMATIC REVIEW

2.1 Aim

The aim of this systematic review was to analyse the results from any existing quantitative literature that used patient based outcome measures, psychosocial tests or clinical diagnoses to assess functional, emotional and/or cognitive outcomes after Transient Ischaemic Attack (TIA).

2.2 Scoping search

To avoid repetition, a scoping search was conducted across the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects (DARE), to identify any existing reviews that addressed the same aims as the proposed review. It was intended that any existing reviews would be updated, not repeated.

2.2.1 Findings of scoping search

No existing reviews were identified that addressed functional, emotional or cognitive outcomes after TIA.

2.3 Report strategy

This review has been conducted in accordance with the 'Meta-analysis of observational studies in epidemiology: a proposal for reporting' (MOOSE) statement, (Stroup et al., 2000) which provides a checklist for reporting meta-analyses and observational studies in epidemiology. The review also conformed to recommendations of the STROBE

(STrengthening the Reporting of OBservational studies in Epidemiology) guidelines (von Elm et al., 2008).

2.4 Methods

2.4.1 Search strategy

The following electronic databases were searched: MEDLINE (1948- May 2011), EMBASE (1947-May 2011), PsycINFO (1987-May 2011), HMIC (1979-May 2011), CINAHL (1982-May 2011), Science citation Index (1991- May 2011) and the Cochrane library (1991-May 2011). Grey literature, including unpublished trials and ongoing research was also searched for through the Stroke trials registry, the UK Stroke Research Network and reference lists of relevant articles. The search strategy, formulated in MEDLINE (Appendix 1), was adapted with the help of an experienced medical librarian to make it applicable to the other databases.

2.4.2 Eligibility criteria

Table 1: Criteria for including studies in the review

Item	Criteria
Study design	▪ cohort (prospective or retrospective) ▪ case-control
Study group	▪ persons with a confirmed diagnosis of TIA and no prior stroke
Comparison group	▪ ipsative (comparison of pre- and post-TIA data) ▪ normative (comparison with published norms or control data) *NB*. Only individuals without a cerebrovascular diagnosis were considered to be adequate controls.
Outcomes	▪ measures of cognitive function (e.g. memory, attention, executive function) ▪ measures of 'affect' (e.g. anxiety, depression, quality of life) ▪ measures of physical function (e.g. activities of daily living)

2.4.3 Identification of relevant trials

References yielded by the search strategy were merged in Reference Manager 11, and duplicates were subsequently removed. Two authors (NB and LH) independently screened all abstracts and titles to decide whether the full text should be sought. A third reviewer (CS) was consulted in the case of any disagreement. If discrepancy or indecision about eligibility of studies persisted following discussion, the full text was sought. Two authors (NB and GJ) independently examined the full text to make a final decision on their inclusion. Similarly, if no consensus was met a third reviewer (CS) had the casting vote.

2.4.4 Data extraction

Two authors completed a data extraction form for each study meeting the inclusion criteria. If the study design, methodology and/or data from published reports were unclear an effort was made to contact study authors to provide clarification.

2.4.5 Assessing methodological quality and risk of bias

Bias is defined as an error in the design or execution of a study, which produces results that are consistently distorted in one direction because of non-random factors.

A systematic review by Sanderson et al (2007) highlighted the lack of a single obvious tool for assessing quality and susceptibility to bias in observational epidemiological studies. Consequently, for this systematic review, the items of checklists reviewed by Sanderson were pooled, until saturation was reached, then refined to make them more specific to the needs of this systematic review, all the time keeping in mind the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines (von Elm et al, 2008). The items used to assess risk of bias in this review are summarised in Table 2, together with scoring the criteria. Rather than using an arbitrary scoring system, the quality of each study

was discussed against set criteria. This transparency, endorsed by Cochrane, allows the reader to come to their own conclusions about possible sources of bias. The methodological quality of the included studies was assessed by two independent reviewers (NB, GJ).

Table 2: Risk of bias scoring criteria

Category	Score "1"	Score "o"	Score "9"
Design	Cohort study (therefore able to infer causal relationship)	Cross-sectional data collection	Not enough information to judge/ not clear
Recruitment method of TIA group	Consecutive or random	Incentivised recruitment or subject to manipulation	Not enough information to judge/ not clear
Case diagnosis	Neuro-imaging (++), standardized clinical assessment (+) or medical notes used to diagnose TIA	Self-report	Not enough information to judge/ not clear
Recruitment method of control group	Consecutive or random	Incentivised recruitment or subject to manipulation	Not enough information to judge/ not clear
Were groups comparable at baseline for important characteristics?	Professional opinion (take into account "matching", inclusion criteria and statistical differences at baseline). If important statistical differences were factored into analysis e.g. Regression, score "1". If important statistical differences were not factored into analysis, score "0"		Not all potential confounders were addressed.
Were all subjects assessed using the same procedure and if longitudinal, were the same measures used at follow-up?	Yes	No	Not enough information to judge/ not clear
Were outcome measure choices appropriate?	Professional opinion (consider citations given for appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability or feasibility of outcome measures; evidence of inter/intra-rater reliability checks; measures of internal consistency; measurement to exposure in different ways)		Not enough information to judge/ not clear
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested?	Outcome measures self-completed by the participant or, if interviewer administered, evidence of blinding	Outcome measures administered by an un-blinded interviewer	Not enough information to judge/ not clear
Participation rates	≥80%	<80%	Not enough information to judge/ not clear
Attrition	No loss to follow-up, similar between groups or handled appropriately in the analysis	Loss to follow-up significantly different between groups and handled inappropriately in the analysis	Not enough information to judge/ not clear NB. For cross-sectional analyses score as "n/a"
Missing data	No missing data, similar between groups or handled appropriately in the analysis	Missing data significantly different between groups and handled inappropriately in the analysis	Not enough information to judge/ not clear
Was the study designed to have sufficient power to detect the effect(s) of interest? Were the numbers achieved?	Evidence of sample size planning or power calculation prior to recruitment, and target numbers achieved	Lack of evidence or admittance that neither a sample size nor power calculation were performed, or target numbers were not achieved	Not clear
Were confidence intervals provided in the analyses?	Yes	No	n/a
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective?	Major results directly related to the a priori hypothesis under investigation; significant and non-significant results reported in a balanced fashion or, if protocol available, intended and reported analyses match up	Evidence of "data dredging"; unbalanced reporting of results	n/a

2.4.6 Data Analysis

Due to the heterogeneity of studies a meta-analysis of results was not possible. Consequently a synthesis of study findings are presented and discussed.

2.5 Results

2.5.1 Study selection

Two thousand and seven titles and abstracts, generated from initial search, were screened. Full texts were sought for 55 of these publications, in addition to 15 publications identified through reference chaining. These 70 publications were reviewed by two independent reviewers. Agreement between reviewers was high; both independently identified the same 13 publications for inclusion. A further 9 publications were identified by just one reviewer. Following discussion 1 of these was included in the review and the remainder were rejected. Thus, 14 publications were included out of the 70 full texts reviewed. Fifty six publications were excluded for the following reasons: Five articles were published in a foreign language, 7 articles turned out to be reviews and for the remaining articles, the study population (n=29), objectives (n=9), design (n=3) or outcome measures (n=3) did not meet the inclusion criteria for this review. More detailed reasons for exclusion, by publication, can be found in Table 3.

2.5.2 Data extraction

A summary of the 14 included publications, detailing 12 different studies, can be found in Table 4. The three publications by Rao et al (1999; 2001; 2002), all refer to the same study and are therefore presented together.

Table 3: Summary of excluded studies

Reference	Reason for exclusion	Detail
(Acciarresi et al., 2006)	Study population did not meet brief	Stroke patients only (no TIA)
(Albright et al., 2009)	Study objectives did not meet brief	experimental study comparing weekend with weekday admission
(Bakker et al., 2003)	Study population did not meet brief- unable to differentiate between stroke and TIA	History of minor stroke in 27% TIA group and presence of ischaemic lesions on MRI in 68% TIA group.
(Barnes et al., 2006)	Study objectives did not meet brief	Association between depressive symptoms mild cognitive impairment Presence of TIA reported at baseline but no TIA group as such
(Berger et al., 2005)	Study population did not meet brief- unable to differentiate between stroke and TIA	TIA and stroke analysed together
(Cohen et al., 2011)	Study objectives did not meet brief	Highly selective cohort, studying the effects of patent foramen ovale closure on functioning, depression and anxiety
(Coutts et al., 2008)	Study population did not meet brief- unable to differentiate between stroke and TIA	TIA and minor stroke analysed together TIA group contaminated by stroke recurrence during follow-up
(Crisostomo et al., 2003)	Study objectives did not meet brief	Analyzed association between clinical characteristics and DWI scans in TIA patients
(Delcker et al., 2000)	Study objectives did not meet brief	Timing of transcranial Doppler monitoring on the microembolic signals and their possible prognostic value on the outcome of TIA or stroke symptoms
(Daffertshofer et al., 2004)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	22% TIA group had a history of prior stroke/TIA and 22% showed infarct on scan. No non-stroke comparison group
(Devuyst et al., 2002)	Study population did not meet brief	Highly selective cohort Inclusion defined by Degree of basilar artery stenosis (included TIA & stroke) No non-stroke comparator.
(Elwan et al., 1994)	Study population did not meet brief	stroke patients only (no TIA)
(Fagan, 2008)	Review	Review
(Falconer et al., 2010)	Study population did not meet brief- unable to differentiate between stroke and TIA	TIA and stroke analyzed together No comparison group
(Ferriero et al., 2006)	Study population did not meet brief	stroke patients only (no TIA)
(Ferro & Crespo, 1994)	Study design did not meet brief	No non-stroke comparator
(Flossmann & Rothwell, 2003)	Review	Review outcomes (survival and recurrent CV events) do not match brief
(Fonarow et al., 2010)	Study population did not meet brief- unable to differentiate between stroke and TIA	Prior stroke not excluded
(Frih et al., 2004)	Publication language	French
(Giles & Rothwell, 2007)	Study objectives/outcomes did not meet brief	Rate of recurrent stroke in suspected TIAs or strokes managed as outpatients versus inpatients
(Haacke et al., 2006)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	TIA and stroke analysed together no non-stroke comparator
(Hankey, 1993)	Study outcomes did not meet brief	Outcomes are survival and coronary/cerebrovascular events
(Hankey, 2003)	Review	Review outcomes (cerebrovascular/ coronary events) do not match brief
(Hankey et al., 2007)	Study population did not meet brief- unable to differentiate between stroke and TIA Study design did not meet brief	Highly selective cohort TIA and stroke analysed together Prior stroke not excluded in participants labelled as TIA No non-stroke comparator
(Harbison et al., 2009)	Study population did not meet brief- unable to differentiate between stroke and TIA	Stroke and TIA analysed together
(Hardie et al., 2004)	Study population did not meet brief	Only patients with a definite first-ever stroke were included (no TIA)
(Hart, 2008)	Review	Review of medical treatment studies
(Jiang et al., 2010)	Publication language	Chinese
(Kerr et al., 2011)	Study objectives did not meet brief	aimed to determine whether low-SES stroke/transient ischaemic attack (TIA) patients have a greater burden of vascular risk factors/co-morbidity and reduced health care access
(Luengo-Fernandez et al., 2009)	Study objectives did not meet brief	Aimed to compare the effects of access to outpatient clinics following TIA and minor stroke on disability (mRS, death) and hospital costs Stroke and TIA studied as one cohort
(Muus et al., 2010)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	TIA and stroke analysed together No non-stroke comparator
(Owens et al., 2002)	Study objectives did not meet brief	Examined the agreement between a self-reported and a performance-based measure of function and the ability of each measure to predict long-term health outcomes

(Pendlebury, 2009)	Review	Review
(Pendlebury et al., 2010)	No non-stroke comparator	No comparison group
(Pinto et al., 2006)	Study population did not meet brief	Stroke patients only (no TIA)
(Pokorski, 1996)	Review	Review
(Porsdal & Boysen, 1998)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	TIA group included patients with prior stroke No non-stroke comparison group
(Rao, 2000)	Review	Review
(Rola et al., 2008)	Study population did not meet brief- unable to differentiate between stroke and TIA	TIA and stroke analysed together (SDB v no SDB)
(Rotter, 2002)	Publication language	Polish
(Sachdev et al., 2004)	Study population did not meet brief- unable to differentiate between stroke and TIA	TIA and stroke analysed together
(Sachdev et al., 2007)	Study population did not meet brief- unable to differentiate between stroke and TIA	TIA and stroke analysed together
(Schnider et al., 1996)	Publication language	German
(Selvarajah et al., 2008)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	No non-stroke comparator TIA and minor stroke analysed together
(Silvestrelli et al., 2006)	Study population did not meet brief	Stroke
(Suenkeler et al., 2002)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	No non-stroke comparator TIA and minor stroke analysed together
(Takahashi et al., 2009)	Study population did not meet brief	Cases were those with memory impairment not TIA. TIA entered (as possible confounding variable) into multivariable logistic regression to examine risk factors for memory impairment
(Tham et al., 2002)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	No non-stroke comparator TIA and minor stroke analysed together
(Vang et al., 1999)	Study population did not meet brief	Stroke patients only (no TIA)
(Van Wijk et al., 2006)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	No non-stroke comparator TIA and minor stroke analysed together
(Van Wijk et al., 2007)	Study population did not meet brief- unable to differentiate between stroke and TIA	TIA and stroke analysed together
(Weimar et al., 2002)	Study population did not meet brief- unable to differentiate between stroke and TIA No non-stroke comparator	TIA group included patients with prior stroke No non-stroke comparator
(Winter et al., 2009)	Study outcomes did not meet brief No non-stroke comparator	Economic outcomes No non-stroke comparator (stroke v TIA)
(Winward et al., 2009)	Study design did not meet brief	no non-stroke comparator
(Xie et al., 2006)	Study population did not meet brief- unable to differentiate between stroke and TIA	Stroke and TIA grouped together
(Zhang et al., 2008)	Publication language	Chinese

Table 4: Summary of Included Studies

Reference	(Guyomard et al., 2011)	(Charoenkitkarn et al., 2009)	(Bos et al., 2007)	(Zinn et al., 2007)	(Howard et al., 2007)	(Bossema et al., 2006)	(Xin-rong et al., 2005)	(Hickie et al., 2003)	(Walters et al., 2003)	(Rao et al., 1999; Rao et al., 2001; Rao, 2002)	(Duncan et al., 1997)	(Iddon et al., 1997)
Design	Prospective, case-control	Prospective, cohort	Prospective, population-based, cohort	Prospective, case-control	Prospective, case-control	Prospective, case-control	Prospective, case-control	Prospective, cohort	Prospective, cohort	Prospective, case-control	Prospective case-control	Prospective, case-control
Location	UK (East of England)	Thailand, (Bangkok & Ayutthaya)	Holland (Rotterdam)	USA (South East)	USA (nationwide)	Holland (Nieuwegein, Utrecht)	China	Australia (Dubbo region)	UK (London)	UK (London)	USA (Kansas, North Carolina, NY)	UK (Cambridge & Newcastle)
Recruitment	Aug 2008 – Nov 2008	Not specified	1990-1993	Recruitment over 2..5 year period (exact years not specified)	Jan 2003 – Mar 2006	Not specified	Jan 2002 – Jun 2003	1988 – 1989	Not specified	Not specified	1992	Not specified
Time of recruitment relative to TIA	Recruited at clinic (assume within 1 week of symptom onset based on current guidelines)	At admission	Pre-TIA	Within 10 days of event	Variable	Not reported (1 day before CEA)	Within 72 hours of symptom onset	Pre-TIA	Within 15 days of event	Time since first TIA categorised as more/less than 5 years but exact numbers not presented	Not specified	Not reported (48–72 h before CEA)
Follow-up	n/a	3, 10 and 30 days after TIA or minor surgery (controls)	3 follow-up surveys (1993-1995, 1997-1999, and 2002-2004)	n/a	n/a	n/a	n/a	10 years	6 and 12 months	n/a	n/a	n/a (only pre-surgery scores meet review criteria)
TIA Group												
n	68	52	282 focal (TIA); 228 non-focal TNA, and 38 mixed TNA	9	818	41	35	19	60	25	184	30
Source of participants	Neurovascular clinic, Norfolk & Norwich University Hospital	Outpatient and emergency departments of 4 tertiary hospitals	Community-dwelling Rotterdam Study participants	Inpatient wards at veterans affairs medical centre	Subset of REGARDS cohort study (commercially available lists of residents)	Symptomatic patients on waiting list for unilateral Carotid endarterectomy (symptoms inc ≥1 episode of hemispheric/ retinal TIA)	Geriatric department, Urumqi General Hospital (inpatients and outpatients)	Community	Neurovascular clinic	Community within catchment of inner city teaching hospital, on waiting list for carotid endarterectomy	Academic Medical Center Consortium records (inpatients); United HC records (inpatients and outpatients); Bowman Gray site of the CV Health Study (community)	TIA patients admitted to Addenbrooke's Hospital for unilateral carotid endarterectomy

Reference	(Guyomard et al, 2011)	(Charoenkitkarn et al, 2009)	(Bos et al, 2007)	(Zinn et al, 2007)	(Howard et al, 2007)	(Bossema et al, 2006)	(Xin-rong et al, 2005)	(Hickie et al, 2003)	(Walters et al, 2003)	(Rao et al, 1999; Rao et al, 2001; Rao, 2002)	(Duncan et al, 1997)	(Iddon et al, 1997)
TIA Group continued..												
Selection criteria	First ever TIA; aged ≥ 45; No pre-existing cognitive impairment and/or depression; no history of stroke	≥24 years; able to read & write; able to take/ respond to tests/questions; without hearing loss, eye problems, history of substance abuse/dependency, Cancer, HIV/AIDS, head injury, ADHD or any other neurological disorder other than TIA; Not on meds to alter cognitive processing; Not depressed	≥55 years; free from stroke, myocardial infarction, and dementia at baseline Follow-up ended at time of outcome event (Stroke, ischaemic heart disease, or dementia) end of study, loss to follow-up or death, whichever occurred first	Ruled out for acute stroke; no prior stroke	Not reporting stroke but self reporting TIA ("Were you ever told by a physician that you had a ministroke or TIA, also known as a transient ischaemic attack?")	No history of minor or major stroke (evident from medical records)	Right-handed male TIA patients with no other inter-cranial disease visible on CT; normal visual and auditory functions; independent; no mental disorder, severe heart, lung, liver or kidney disease	Non-institutionalised residents born before 1930. Those who had a clinical stroke in the intervening decade were excluded.	First, isolated TIA; MMSE ≥ 28/30); no evidence of general/focal atrophy on MR imaging; no clinical/ radiological evidence of established stroke; Alcohol consumption ≤ 3 units daily; no severe hypertension, significant ischaemic heart disease, peripheral vascular disease, or carotid stenosis	History of ≥ 1 TIA and stenosis >70% on 1 or both internal carotid arteries; on waiting list for carotid endarterectomy; no history of stroke or clinical evidence of stroke during preoperative screening; no history of PVD, drug or alcohol misuse, Parkinson's disease, head injury, epilepsy, carcinomatosis or uncontrolled metabolic, endocrine, or respiratory disorders; >65 yrs	History of TIA but not stroke	Severe carotid artery stenosis (≥70%) no history of stroke, no depression or dementia at baseline
Case diagnosis	Focal neurological deficit < 24 hours duration of presumed vascular origin, confirmed by highly experienced stroke physician	Clinical diagnosis confirmed by neurologist	Consulted a neurologist, GP or another physician, or reported event at research centre Clinical diagnoses verified by experienced stroke neurologist	Clinical examination, chart review and CT scan by neurologist (where possible diffusion weighted MRI also performed)	Self-report	Degree of carotid stenosis assessed with duplex ultrasonography	Diagnosis conformed to classification & diagnostic criteria for Chinese National conference of cerebral vessels diseases; head CT excluded other intracranial diseases	Hospital discharge coding against usual criteria	Consultant neurologist with special interest in cerebrovascular disease; reinforced by neuro-imaging	Not clear	ICD-9 codes (verified by medical record review)	Not specified

Reference	(Guyomard et al, 2011)	(Charoenkitkarn et al, 2009)	(Bos et al, 2007)	(Zinn et al, 2007)	(Howard et al, 2007)	(Bossema et al, 2006)	(Xin-rong et al, 2005)	(Hickie et al, 2003)	(Walters et al, 2003)	(Rao et al, 1999; Rao et al, 2001; Rao, 2002)	(Duncan et al, 1997)	(Iddon et al, 1997)
Comparison Group n	68 non-vascular controls	52 non-vascular (minor-surgery) controls	5514 non-stroke/TIA controls	10 "at risk of stroke" controls	16,090 non-stroke/TIA controls	44 non-stroke/TIA controls	33 "healthy" controls	44 hypertensive & 45 normotensive controls	26 non-vascular controls	25 vascular & 25 orthopaedic controls	654 asymptomatic individuals at a high-risk of stroke	30 "healthy" volunteers
Source of participants	Dermatology and neurology clinics, Norfolk & Norwich University Hospital	Outpatient departments	Community-dwelling Rotterdam Study participants	Inpatient wards at veterans affairs medical centre	Subset of REGARDS cohort study (commercially available lists of residents)	Advert in local paper	Patients visiting hospital for physical examination	Community	Not stated	Community within catchment of inner city teaching hospital On waiting list for femoropopliteal bypass (vascular) or elective THR/TKR for OA (orthopaedic)	As TIA group	Not stated
Selection criteria	No vascular risk factors or evidence of vascular disease; No pre-existing cognitive impairment and/or depression (matched to TIA group by age & gender)	Minor surgery patients; no known hypertension, diabetes, vascular disease or Hx stroke/TIA (matched to TIA group by age, gender & education)	≥55 years; free from TNA, stroke, myocardial infarction, and dementia at baseline. Follow-up ended at time of outcome event (TNA, Stroke, ischaemic heart disease, or dementia) end of study, loss to follow-up or death, whichever occurred first	Not specified	Not specified	No history of Cerebro-vascular or psychiatric disease	"Healthy" right-handed male volunteers; no history of mental disorders (Matched to TIA group by age, gender, education, handedness)	*Hypertensive group:* using hypertensive medication at baseline *Normotensive group*: systolic BP<140mmHg and diastolic BP<90mmHg at baseline. *All groups:* Non-institutionalised residents born before 1930; no clinical stroke in the intervening decade	No history of stroke or TIA; no evidence of general/focal atrophy on MR imaging; no clinical/ radiological evidence of established stroke; Alcohol consumption ≤ 3 units daily; no severe hypertension, significant ischaemic heart disease, peripheral vascular disease, or carotid stenosis. (matched to TIA group by age & gender)	*Vascular (PVD) group:* On waiting list for femoropopliteal bypass ***Orthopaedic group:*** elective THR/TKR for OA (6-12 months before interview); no history of PVD *All groups:* no history of stroke/TIA, drug/alcohol misuse, Parkinson's, head injury, epilepsy, carcinomatosis, uncontrolled metabolic/endocrine/ respiratory disorders; not considered by GP or interviewer to be too frail, cognitively impaired, uncommunicative; >65 yrs	Asymptomatic individuals without neurological insult, at high-risk of stroke (based on ICD-9 codes)	"Healthy" volunteers with no depression or dementia at baseline (matched to TIA group by age and IQ)

Reference	(Guyomard et al, 2011)	(Charoenkitkarn et al, 2009)	(Bos et al, 2007)	(Zinn et al, 2007)	(Howard et al, 2007)	(Bossema et al, 2006)	(Xin-rong et al, 2005)	(Hickie et al, 2003)	(Walters et al, 2003)	(Rao et al, 1999; Rao et al, 2001; Rao, 2002)	(Duncan et al, 1997)	(Iddon et al, 1997)
Outcome Measures	*Cognition* MoCA (7 domains): (1) visuo-spatial, (2) naming, (3) attention, (4) language, (5) abstraction, (6) delayed recall, (7) orientation	*Cognition* (1) Necker cube pattern control test, (2) digit span forward test, (3) trail making A test, (4) Barrett impulsiveness scale, (5) visual analogue scale – irritability, (6) digit symbol substitution test, (7) digit span backward test, (8) Hopkins verbal learning test-revised	*Cognition* (1) Alzheimer disease, (2) vascular dementia (standardised clinical diagnosis)	*Cognition* Wechsler Adult Intelligence Scale subtests: (1) Digit span, (2) Picture arrangement Delis-Kaplan executive function system subtests: (3) symbol digit modalities test, (4) design fluency,(5) trail making (6) Hopkins verbal learning test-revised	*HR-QOL* SF-12: Physical and mental component scores	*Cognition* (1) digit span forward test, (2) digit span backward test, (3) dichotic listening test, (4) word learning test - immediate recall, (5) word learning test - delayed recall, (6) word learning test – recognition, (7) doors test A, (8) doors test B, (9) verbal fluency – letters, (10) verbal fluency – categories, (11) trail making A test, (12) trail making B test, (13) motor planning test - planning, (14) motor planning test - movement, (15) finger tapping test – dominant, (16) finger tapping test – non-dominant, (17) line orientation test *Mood* Dutch shortened POMS	*Cognition* SECF: (1) orientation, (2) memory, (3) recognition span, (4) recall 1 (association), (5) long-term memory, (6) naming of animals, (7) calculation, (8) classification), (9) copying, (10) language, (11) recall 2 (relationship)	*Depression* (1) CES-D tertiles, (2) DSM-lV codes, (3) MDAS	*Cognition* MMSE	***1999 & 2002 publications*** *Cognition* CAMCOG (9 Tests): (1) abstract thinking, (2) attention, (3) calculation, (4) language, (5) memory, (6) orientation, (7) praxis, (8) perception (recognition), (9) MMSE + (10) trail-making test, (11) BDCS, (12) controlled word association test ***2001 publication*** *Depression* (1) HRDS, (2) GDS-15, (3) DSM-IV codes, (4) wish to die, (5) suicidal ideation in past year *Handicap* (1) London handicap scale, *Social support* (1)social support scale	*Activities of daily living* (1) BI *Depression* (1) CES-D *HR-QOL* (1) MOS-36, (2) TTO	*Cognition* CANTAB: (1) pattern recognition, (2) spatial recognition, (3) spatial span, (4) spatial working memory,(5) attentional set shifting, (6) paired associates learning, (7) matching to sample

BDCS = Behavioral Dyscontrol Scale; BI = Barthel Index; CAMCOG = the cognitive, self-contained part of the Cambridge Examination for Mental Disorders of the Elderly; CANTAB = Cambridge Neuropsychological Test Automated Battery; CES-D = Centre for Epidemiological Studies Depression Scale; DSM-lV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GDS-15 = Fifteen-item Geriatric Depression Scale; HRDS = Hamilton Rating Scale for Depression; HR-QOL=Health Related Quality of Life; ICD=International Statistical Classification of Diseases and Related Health Problems; MDAS = Mixed Depression and Anxiety Score; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; MOS-SF36 = Medical Outcomes Study Short Form 36; POMS = Profile of Mood States; SECF = Scale of Elderly Cognitive Function; SF-12=12 item Short Form; TTO = Time Trade-off utility

2.5.3 Quality and risk of bias

The risk of bias of included studies is summarised in figure 1. Scoring sheets showing evidence, reasoning and judgement on the quality of reporting and risk of bias for each included study can be found in Appendix 2.

Figure 1: Risk of Bias Summary for Included Studies

	(Guyomard et al, 2011)	(Charoenkitkarn et al, 2009)	(Bos et al, 2007)	(Zinn et al, 2007)	(Howard et al, 2007)	(Bossema et al, 2006)	(Xin-rong et al, 2005)	(Hickie et al, 2003)	(Walters et al, 2003)	(Rao et al, 1999; Rao et al, 2001; Rao, 2002)	(Duncan et al, 1997)	(Iddon et al, 1997)
Design												
Recruitment method of TIA group												
Case diagnoses	+	+		++			++		++			
Recruitment method of control group												
Were groups comparable at baseline for important characteristics?												
Were all subjects assessed using the same procedure and if longitudinal, were the same measures used at follow-up?												
Were outcome measure choices appropriate?	Rel Res	Rel Val Acc	all	Rel Val App	Val Int	Rel		Res		Rel	App Res	Rel Val
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested?												
Participation rates	93%		99%	26%	>60%					65%	56%	
Attrition												
Missing data												
Was the study designed to have sufficient power to detect the effect(s) of interest? Were the numbers achieved?												
Were confidence intervals reported in the analysis?												
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective?												

Key: (please refer to Table 2 for scoring criteria) Low risk of bias; High risk of bias; Insufficient evidence to judge; n/a

2.5.3.1 Design

The majority of studies included in this review used cross-sectional analysis (Bossema et al, 2006; Guyomard et al, 2011; Howard et al, 2007; Rao et al, 1999; Rao et al, 2001; Rao, 2002; Xin-rong et al, 2005; Zinn et al, 2007). Consequently we cannot be sure of the direction of causation.

2.5.3.2 Recruitment

Most of the studies used samples of convenience, inviting patients from a particular neurovascular clinic (Guyomard et al, 2011; Walters et al, 2003), hospital ward (Xin-rong et al, 2005; Zinn et al, 2007), A&E department (Charoenkitkarn et al, 2009) or outpatient department (Charoenkitkarn et al, 2009; Xin-rong et al, 2005) that was easily accessible to the researcher. In doing so the researcher inadvertently excluded a great proportion of the TIA population. Some studies (Guyomard et al, 2011; Zinn et al, 2007) were less prone to bias than others as they invited all patients attending the clinic or ward, removing any possibility of manipulating the sample. Community samples (Bos et al, 2007; Hickie et al, 2003; Howard et al, 2007) and mixed samples (Duncan et al, 1997) would be considered more representative of the TIA population as a whole however these studies are more prone to bias associated with case diagnosis (discussed below). One study that was particularly prone to sampling bias rewarded the control group for their participation (Bossema et al, 2006). Volunteers who are incentivised with rewards are likely to exhibit different behaviours to those who are not rewarded, and as such they could influence the results of the study. The sampling strategy was further compromised here as the selection process was different for cases and controls. In terms of extrapolating the results of each study, time relative to TIA should be taken into account as patients recruited some time after their TIA (with no further incidents of TIA or

stroke) are likely to represent a healthier sample, leading to underestimations of functional, cognitive and emotional impairments.

2.5.3.3 Participation

Participation rates varied from poor (26%) (Zinn et al, 2007) to exceptional (99%) (Bos et al, 2007). Studies in which a higher percentage of people accept invitations to participate are likely to be more representative of the target population. Six studies failed to report participation rates (Bossema et al, 2006; Charoenkitkarn et al, 2009; Hickey et al., 2009; Iddon et al, 1997; Walters et al, 2003; Xin-rong et al, 2005).

2.5.3.4 Attrition

Attrition bias can result from a "survival of the fittest" effect or by altering the case and/or control group characteristics. Most studies in this review used cross-sectional analysis therefore loss-to-follow-up was not applicable. It should be noted however that in one cross-sectional study (Zinn et al, 2007) a patient was excluded from analysis on the basis of severely impaired scores suggestive of stroke. This rejection of data on arbitrary grounds, instead of according to previously stated or generally agreed criteria, should be considered biased. For longitudinal studies, loss-to-follow-up was less than 20% and similar between groups, with the exception of one study (Walters et al, 2003) which failed to report attrition rates or reasons.

2.5.3.5 Missing data

Almost all studies have some missing observations however seven of the included studies failed to report how complete their dataset was (Charoenkitkarn et al, 2009; Duncan et al, 1997; Guyomard et al, 2011; Hickie et al, 2003; Howard et al, 2007; Rao et al, 1999; Rao et al, 2001; Rao, 2002; Walters et al, 2003). The studies that did report missing data (Bossema et

al, 2006; Iddon et al, 1997; Zinn et al, 2007) were considered to have low risk of bias as missing data were similar between cases and controls and shown to be unrelated to the diagnosis and/or have no effect on outcome in the analysis.

2.5.3.6 Case diagnosis

Case diagnoses of the TIA group varied from self-report (Howard et al, 2007) to standardised clinical diagnosis (Charoenkitkarn et al, 2009; Guyomard et al, 2011) to brain scans (Walters et al, 2003; Xin-rong et al, 2005; Zinn et al, 2007). Due to the objective nature of brain scans they are the only method of completely ruling out stroke. However in terms of transferability of results to current clinical practice, standard clinical diagnosis would seem more appropriate. As most physicians are conditioned to look for focal symptoms, there is a chance that mixed Transient Neurological Attacks (TNAs) or TIA "mimics" may have been wrongly categorised as focal TNAs (TIAs). Reliability of clinical diagnosis could be considered higher if the diagnosis was formed by a stroke-physician or neurologist as they would be expected to have greater experience in forming such diagnoses. Although clinical diagnosis of TIA is largely based on the patient's ability to recall their symptoms, study groups formed by participant's self-reported history of TIA should be considered a greater risk of bias due to the time delay between the event and entry to the study (recall bias), and possible denial, exaggeration or misunderstanding of the diagnosis.

2.5.3.7 Confounding Bias

As TIA is usually predisposed by hypertension and other cardiovascular risk factors, observational studies looking at TIA are prone to clinical susceptibility bias, where outcomes may be erroneously linked to TIA rather than the predisposing condition or lifestyle e.g. smoking. Hypertension in particular has been linked to cognitive decline in previous research

(Bishop et al., 2010). To address this potential confounder, many of the studies included a cardiovascular control group, who exhibited risk factors for TIA and stroke but had never suffered one. Other studies factored cardiovascular risk factors into the analysis e.g. multiple regression. Three studies were however considered at risk of clinical susceptibility bias. In a study of depression after TIA (Hickie et al, 2003) variables including diabetes, heart disease and smoking status were significantly different between groups however as they were not addressed in the analysis we cannot attribute the results to TIA alone. In two other studies (Iddon et al, 1997; Xin-rong et al, 2005) cardiovascular risk factors were not measured at all. In terms of age, gender and other potential confounders eleven out of the twelve studies were found to have low risk of confounding bias based on individual inclusion criteria, "matching" of controls to TIA participants, comparability of baseline characteristics or, as with cardiovascular risk factors, factoring variables that were significantly different at baseline into the analysis. One study (Xin-rong et al, 2005) was considered at risk of confounding bias as inclusion criteria was less strict for the control group (normal visual and auditory functions, independence and no sever heart, lung, liver or kidney disease was only specified for the TIA group). These factors were not measured at baseline therefore we cannot be sure of their extent in the control group.

2.5.3.8 Assessment procedure

With the exception of two studies (Duncan et al, 1997; Hickie et al, 2003) cases and controls were assessed using the same procedures. In Hickie et al (2003) DSM-IV criteria was only reviewed if participants responded positively when asked about symptoms of depression. In addition different measures were used to assess depression at baseline and follow-up. Consequently any apparent temporal effects of TIA on depression cannot be assured. In Duncan et al (1997) participants from one database were interviewed face-to-face and others

were interviewed by phone. Phone interviews may have omitted individuals with language or cognitive dysfunction, leading to possible sampling bias. To reduce risk of bias the reviewers agreed that all participants should have been assessed using the same procedure.

2.5.3.9 Blinding

Where outcome measures were administered by an assessor, and that assessor was not blind to the case-control status of the participant, they may assertively look for impairments and/or classify vague or indeterminate responses negatively, thus overestimating the consequences of TIA. Only one study included in this review concealed case-control status to the investigator (Bos et al, 2007). Seven studies did not adequately blind the assessors (Bossema et al, 2006; Charoenkitkarn et al, 2009; Guyomard et al, 2011; Hickie et al, 2003; Rao et al, 1999; Rao et al, 2001; Rao, 2002; Xin-rong et al, 2005; Zinn et al, 2007) and the remaining four studies (Bos et al, 2007; Duncan et al, 1997; Iddon et al, 1997; Walters et al, 2003) did not provide enough information about whether the outcome measure was self- or interviewer-administered, and if interviewer-administered, whether the interviewer was "blind".

2.5.3.10 Outcome measures

With the exception of one study (Xin-rong et al, 2005) all studies justified their use of outcome measures to some extent. The study by Walters et al (2003) used the Mini Mental State Exam (MMSE) to measure cognitive function. In a seemingly uncompromised sample of TIA patients this measure was considered inappropriate by the reviewers due to the MMSE's low ceiling effect. The use of cut-off points in Zinn et al (2007) was also judged by reviewers to be susceptible to bias as it entails the risk of mis-categorisation, which may be magnified with small sample sizes.

2.5.3.11 Selective reporting

In one study (Xin-rong et al, 2005) only significant results seemed to be reported. All other studies appeared to avoid selective reporting.

2.5.3.12 Strength of evidence

Only four studies (Charoenkitkarn et al, 2009; Guyomard et al, 2011; Rao et al, 1999; Rao et al, 2001; Rao, 2002; Zinn et al, 2007) showed evidence of sample size planning and one of these failed to reach their target (Zinn et al, 2007). Without a pre-determined sample size the probability of a statistically significant effect being identified as a clinically significant effect could be manipulated by the investigator, in such a way that the desired results could be demonstrated. This is further compromised by the lack of reporting and/or referencing of what changes in outcome measure scores denote clinically significant changes. In defence of these studies, sample size planning requires prior information which may be lacking as many of the outcome measures used have not been tested in TIA populations before. The studies lacking sample size calculations could be considered pilot studies. Two studies (Bos et al, 2007; Howard et al, 2007), which failed to specify the required sample size prospectively did at least include confidence intervals in their analysis, allowing conclusions about the direction and strength of results to be made.

2.5.4 Summary of findings

The studies identified in this review were extremely varied in terms of design, study population, outcome measures and statistical methods (see Table 4). For cognitive assessments alone, seven different test batteries and over twenty individual tests were identified. Due to this heterogeneity, a meta-analysis was not possible. The findings of included studies are presented, by outcome of interest, in Table 5.

Table 5: Results of Included studies

Reference	Nature of deficits reported	Influential variables reported	Strength of evidence
COGNITION			
(Guyomard et al, 2011)	TIA patients were significantly more cognitively impairment than age/sex matched non-vascular controls in six out of seven domains including visuo-spatial ($p<0.0001$), attention ($p<0.0001$), language ($p<0.0001$), abstraction ($p=0.009$), delayed recall ($p<0.0001$) and orientation ($p<0.0001$).	The likelihood of cognitive impairment appeared to increase with increasing numbers of vascular risk factors however the study was underpowered for such sub-group analysis.	High
(Charoenkitkarn et al, 2009)	With the exception of irritability (visual analogue scale), all test scores covering areas of distractibility, impulsivity, working memory and learning and memory, were significantly more impaired in the TIA group compared to the non-vascular control group ($p<0.05$) in terms of group, time and interaction effects.	Cognitive impairments after TIA were found to worsen by day 10 but improve between day 10 and day 30.	High
(Bos et al, 2007)	No significant differences were found between patients with focal TNA and participants without TNA. However patients with non-focal TNA had a higher risk of dementia (HR, 1.59; 95% CI, 1.11-2.26), especially vascular dementia (HR, 5.05; 95% CI, 2.21-11.6), than participants without TNA. Patients with mixed TNA were also at increased risk of dementia (HR, 3.46; 95% CI, 1.72-6.98), especially vascular dementia (HR, 21.5; 95% CI 6.48- 71.3) than participants without TNA. Adjustment for confounding did not materially change these associations.		High
(Rao et al, 1999; Rao, 2002)	TIA patients with severe carotid stenosis showed greater global impairment on CAMCOG ($p<0.05$), MMSE ($p=0.001$), BDCS ($p<0.05$) and FRSS ($p<0.001$) than non-vascular controls. Forty percent of TIA patients showed scores on tests of attention, calculation and frontal lobe function lying within the bottom 5% of non-vascular control scores. TIA and PVD patients showed similar patterns of neuropsychological impairment, but the authors suggest that TIA may result in more prolonged cognitive impairment, particularly in frontal lobe function.	Frontal lobe impairment, suicidal thinking and age were all independent predictors of global cognitive impairment in the TIA group. There was no relationship between the MMSE and the length of time participants had been suffering TIAs but TIA patients scoring < 15 on the BCDS were more likely to have experienced TIAs for 5 years or more.	High
(Zinn et al, 2007)	On average patients with TIA were impaired in 48% of the tests completed, compared to 44% for stroke- risk-only patients. Larger sample sizes are required to show convincing results.		Low
(Bossema et al, 2006)	Patients with hemispheric TIA and severe occlusive disease of one or both carotid arteries scored significantly worse ($p<0.05$) than "healthy" controls on five of the seventeen test variables, including tests of attention (Digit Span forward), verbal fluency (letters and categories) and psychomotor speed and executive functioning (Trail Making Test B and Motor Planning). Patients with retinal TIA and severe occlusive disease of one or both carotid arteries also scored significantly worse ($p<0.05$) than "healthy" controls on five of the seventeen separate test variables, including tests of visual memory (Doors Test A and B), verbal fluency (categories) and psychomotor speed and executive functioning (Trail Making Test B and Motor Planning).	No effect of various vascular risk factors, such as hypertension and diabetes mellitus, was found on cognition.	Low
(Xin-rong et al, 2005)	TIA patients were significantly more impaired than "healthy" controls in terms of immediate, short-term and long-term memory, attention, concentration and capability of acquiring information ($p<0.05$). It is not clear how participants faired on tests that assessed spatial and temporal orientation, analyzing and synthesizing information and linguistic competence.		Low
(Walters et al, 2003)	During the first year after TIA the MMSE declined in 5% of participants compared to none of the non-vascular control participants. Although not the topic of this review Walters et al (2003) also found that patients presenting with a first isolated TIA had more than twice the rate of global brain atrophy as age matched controls during the year. This increased atrophy rate may reflect ongoing tissue damage at a subclinical level and would imply that these individuals are at higher risk of progressive cognitive decline.	A positive correlation was found between increased rates of cerebral atrophy and systolic blood pressure ($p = 0.02$) and diastolic blood pressure ($p = 0.002$).	Low
(Iddon et al, 1997)	No significant differences were found between TIA patients with carotid artery stenosis and age-matched controls on any of the CANTAB test scores.		Low

Reference	Nature of deficits reported	Influential variables reported	Strength of evidence
MOOD			
(Rao et al, 2001)	Statistical differences at the level of $p<0.01$ were found between the TIA group (with >80% stenosis) and the orthopaedic control group, as measured by the geriatric depression scale, modified Hamilton Rating Scale for Depression and DSM-IV major depression criteria. No significant differences were found between these groups on history of depression, family history of depression, suicidal ideation or wish to die. The prevalence of DSM-IV depressive disorder was not higher in the peripheral vascular disease group than in orthopaedic controls; however mean scores on the geriatric depression scale and modified Hamilton Rating Scale for Depression were significantly higher in the PVD group.	Time between first TIA and assessment did not have any significance on DSM-IV depression	High
(Duncan et al, 1997)	The TIA group were more depressed than the asymptomatic control group at risk of stroke, as measured by the CES-D, however the differences were not significant.		Med
(Bossema et al, 2006)	Patients with severe occlusive disease of one or both carotid arteries showed significantly less vigor and more tension, fatigue and depression than "healthy" controls ($p<0.05$). The patient group included asymptomatic patients as well as symptomatic TIA patients. This may have diluted the effect size.		Low
(Hickie et al, 2003)	Significantly more new cases of depression were reported in the TIA group than in the hypertensive and normotensive control groups ($p<0.05$) during the 10-year follow-up period. However, depression was categorised differently at baseline and follow-up so the results are difficult to interpret.		Low
QUALITY OF LIFE			
(Howard et al, 2007)	Participants reporting a history of TIA had a 6.0 point (95% CI: 5.3 to 6.7) lower physical component summary score than the control group with no symptoms of TIA. In the fully adjusted model (adjusting for demographics, cerebrovascular disease risk factors, exercise, body mass index, and socioeconomic status), those reporting TIA had a 3.7 point (95% CI: 3.0 to 4.4) lower score. TIA participants had an average mental component summary score 0.5 (95% CI: : 0.0 to 1.1) points lower than those without symptoms with no attenuation after adjustment for confounders to a difference of 0.6 with 95% CI: -0.1 to 1.2)		High
(Duncan et al, 1997)	TIA patients reported health states significantly below that of asymptomatic individuals on 7 out of 8 domains of the MOS-36, including general health, mental health, physical role, social function, vitality, bodily pain and physical function. No significant differences were found between TIA and asymptomatic groups, as measured by TTO (trade-offs between time in their current health state and time in excellent health).	In the regression analysis, Barthel Index and diagnosis were the strongest and most consistent predictors of health status.	Med
ACTIVITIES OF DAILY LIVING			
(Duncan et al, 1997)	No significant differences were found between TIA and asymptomatic groups in basic activities of daily living, as measured by the Barthel Index.		Med

2.5.4.1 Cognitive deficits

Five out of nine studies found that, on average, individuals with TIA had significantly more cognitive impairment than non-vascular controls (Bossema et al, 2006; Charoenkitkarn et al, 2009; Guyomard et al, 2011; Rao et al, 1999; Rao, 2002; Xin-rong et al, 2005). Specific domains that were implicated included immediate, short-term and long-term memory (including visual, working and learning memory), attention/concentration, orientation/spatial awareness/perception, abstract thinking, impulsivity, language (including verbal fluency), praxis, psychomotor speed and executive functioning. The three studies that found no significant difference in cognition between TIA and non-vascular control groups had not performed sample size calculations prior to recruitment (Iddon et al, 1997; Walters et al, 2003; Zinn et al, 2007) and one of the studies used the Mini Mental State Exam (MMSE) to measure cognition (Walters et al, 2003). The MMSE is known to have low ceiling effects and is also less sensitive to small changes in cognition. Interestingly, both of the studies that compared TIA patients to individuals with cardiovascular risk factors did not find any significant differences in cognition between groups (Rao et al, 1999; Rao, 2002; Zinn et al, 2007). One of these studies, however had a very small sample size of just nine TIA patients (Zinn et al, 2007) and is therefore likely to be underpowered to detect any change. The correlation between cardiovascular risk factors and cognitive decline is supported by two studies through regression analysis (Guyomard et al, 2011; Walters et al, 2003). On the contrary, no effect of vascular risk factors, including hypertension and diabetes mellitus, was found by Bossema et al (2006). It should be noted that these studies were underpowered for regression analysis and the associations therefore lack weight.

2.5.4.2 Mood

One out of four studies found that TIA patients with severe occlusive disease of one or both carotid arteries showed significantly less vigour and more tension, fatigue and depression than "healthy" controls ($p<0.05$) as measured by the Dutch shortened Profile of Mood States (Bossema et al, 2006). Another study (Hickie et al, 2003) reported that during the first ten years after TIA, the number of new cases of major depression was significantly higher than in hypertensive and normotensive control groups ($p<0.05$), however depression was categorised differently at baseline and follow-up so the results are difficult to interpret. Rao et al (2001) showed that although TIA patients (with >70% carotid stenosis) showed significantly less handicap than an orthopaedic control group, the prevalence of DSM-IV major depressive disorder was significantly higher in the TIA group. The TIA group also scored significantly higher on the geriatric depression scale and modified than the orthopaedic control group, as did the asymptomatic vascular control group. The TIA group were more depressed than the asymptomatic vascular controls, as measured by the CES-D; however the differences were not significant. Similar findings were reported by Duncan et al (Duncan et al, 1997).

2.5.4.3 Quality of life

Two studies addressed quality of life after TIA. In one study, on average, participants with a history of TIA scored their physical health significantly lower than "healthy" individuals, as measured by the physical component summary score of the SF-12 (mean=6.0 points; 95% CI=5.3 to 6.7).(Howard et al, 2007) Adjustment for demographics, cerebrovascular disease risk factors, exercise, body mass index, and socioeconomic status only partially attenuated these effects. Based on previous research, the authors speculate that the observed decline in health-related quality of life in TIA patients could translate into a public health burden on the same order of magnitude as that imposed by type 2 diabetes. In the same study TIA patients

scored their mental health significantly lower than "healthy" individuals, as measured by the mental component summary score (mean=0.5 points; 95% CI=0.0 to 1.1). After adjustment for confounding variable the differences in mental score were no longer significant. In another study (Duncan et al, 1997) TIA patients reported health states significantly below that of asymptomatic individuals on 7 out of 8 domains of the Medical Outcomes Study Short Form 36, including general health, mental health, physical role, social function, vitality, bodily pain and physical function. No significant differences were found between groups when using trade-offs between time in present health state and time in excellent health. This emphasises the need for careful selection of outcome measures, as some are more sensitive to change than others.

2.5.4.4 Activities of daily living

One study (Duncan et al, 1997) measured activities of daily living after TIA and found no significant differences between TIA and asymptomatic, as measured by the Barthel Index. The Barthel Index focuses on dependence in basic daily activities such as toileting and washing, which are unlikely to be affected by TIA. Consequently the Barthel Index is likely to have a ceiling effect in this population.

2.6 Discussion

In this systematic review, the results of 12 studies were analysed to identify cognitive, physical and/or emotional outcomes in patients who had been diagnosed with TIA and not stroke. Cognitive deficits and depression were significantly higher in TIA patients than age-matched "healthy" individuals. However, it is unclear how much of the observed association between cerebrovascular disease and cognitive dysfunction and/or depression is mediated by cardiovascular risk factors. Although cognitive dysfunction and depression were higher in

TIA patients than patients at risk of cerebrovascular insult, the differences were not significant. In addition, although underpowered, regression analyses suggest that TIA patients who exhibited a higher number or higher severity of cardiovascular risk factors were more likely to show signs of depression and cognitive decline than TIA patients with fewer or less severe cardiovascular risk factors.

Links between cardiovascular risk factors and cognitive decline have also been expressed in non-TIA cohorts: Diabetes mellitus has been shown to have a significant independent effect on abstract reasoning and visuo-spatial dysfunction and hypercholesterolaemia has been shown to have a significant independent effect on memory dysfunction (Desmond et al., 1993). Furthermore, hypertension has been associated with cerebral atrophy (Hatazawa et al., 1984; Salerno et al., 1992) and has been linked to speed of cognition, episodic and working memory, and executive function (Saxby et al., 2003). Hypertension is now thought to be an independent risk factor for Alzheimer's disease (Kivipelto et al., 2001) and has also been raised as a possible correlate of depression (Krishnan et al., 1994). Minor reductions in blood pressure have been associated with improvements in MMSE score and logical memory (Birns et al., 2006). A recent review by McGuinness et al (2006) found some evidence that midlife hypertension was related to cognitive decline. However, they found no convincing evidence that lowering blood pressure prevents the development of dementia or cognitive impairment in hypertensive patients without apparent prior cerebrovascular disease. In another review, Bakker et al (2000) found evidence to suggest that carotid stenosis may also be a risk factor for cognitive impairment. Together, this evidence suggests that cardiovascular risk factors may be the cause of cognitive impairment in TIA patients, rather than the insult itself.

The majority of studies included in this review used cross-sectional analysis and recruited their participants post-TIA. It is therefore difficult to know the temporal relationship between TIA and cognitive, physical or emotional impairment.

To conclude, this review found no evidence to suggest that basic activities of daily living are compromised after TIA. However, there is evidence to suggest that many aspects of quality of life are significantly lower in TIA patients than in "healthy" individuals, including physical function. The results also suggest that TIA patients have more cognitive impairment and depression than the general population without TIA. It is unclear how much of the observed association between cerebrovascular disease and cognitive dysfunction and/or depression is mediated by cardiovascular risk factors, and/or whether TIA has a direct causal relationship.

2.6.1 Suggestions for future research

This systematic review has highlighted the need for more research, with larger sample sizes that allow further examination of possible mediators such as cardiovascular risk factors. Associations between cognition, mood and function, and whether these outcomes are predictive of future stroke should also be explored, using longitudinal designs to determine the direction of causation.

Researchers should take advantage of published guidelines such as STROBE to strengthen the quality of future research. Where possible, sample size calculations should be conducted prior to recruitment and mean differences should be reported with confidence intervals to provide more meaningful results. Researchers should endeavour to blind assessors to the diagnosis of study participants and a concerted effort should be made to recruit participants on a consecutive basis, without incentives. Outcome measures should also be chosen carefully. For instance, the Barthel Index has been shown to have a ceiling effect in this population and the MMSE has appeared to lack sensitivity. Future studies are therefore advised to examine

functional dependence by measuring extended rather than basic activities of daily living. Psychological tests that are capable of detecting subtle changes in specific areas of cognition should also be used, over and above the MMSE.

CHAPTER 3

COHORT STUDY DESIGN

3.1 Introduction

The FACE TIA cohort study arose from the systematic review, to further develop the research into residual problems after TIA, namely anxiety, depression, cognition and daily function. As well as studying TIA outcomes in relation to healthy control and minor stroke outcomes, FACE TIA also studies TIA outcomes in relation to patients with transient neurological symptoms not suggestive of TIA. This, so-called "TIA-mimic" population has scarcely been studied but represent approximately half of those referred to TIA clinic. In terms of vascular risk, TIA mimics have been found to have a poorer outcome than patients at risk of TIA or stroke (Cameron et al., 2011).

The FACE TIA study addresses limitations of previous studies by using a larger (national) sample to provide sufficient power to justify any findings. The study is also longitudinal in design to allow trends and interactions to be studied over time.

The study was approved by Birmingham East, North and Solihull Research Ethics committee on 30/06/2010 (Ref. 10/H1206/36) and has since been co-adopted by the stroke and primary care research networks. It is being funded by the West Midlands Strategic Health Authority (WM NMAHP Research Training Fellowship) and the National School for Primary Care Research (Monitoring and management of long-term conditions). Sponsorship is provided by the University of Birmingham.

The FACE TIA cohort study is ongoing. The objectives and methods reported here relate to the full trial, however only preliminary (baseline) results are reported in Chapter 4.

3.2 Objectives

The objectives of this study were:

a) To investigate the effect of a clinical diagnosis of TIA on physical function, cognition and feelings of anxiety and depression, in relation to minor-stroke, TIA "mimics" and "healthy" controls (or population norms).
b) To examine interaction effects between cognition, feelings of affect and physical function.
c) To examine whether these outcomes change over time and/or are predictive of future stroke

Null Hypothesis: After the neurological symptoms of TIA subside, there is no difference between TIA patients, minor stroke patients, "mimics" or "healthy" individuals in relation to cognition, emotion and physical function. Individuals who are more impaired, (cognitively, physically and emotionally) do not have increased risk of stroke, compared to less impaired individuals.

3.3 Trial Design

This study followed a prospective cohort design with three control groups. To ensure the trial was well reported the STROBE guidelines were adhered to (Von Elm et al., 2008).

3.4 Setting

Participants were recruited from 12 TIA clinics (hospital sites) and 4 GP practices in the West Midlands. The study is now being rolled out to TIA clinics and GP practices in London, Yorkshire and the South West.

3.5 Participants

The main study group (group A), included people attending TIA clinics diagnosed with their first TIA. The control groups included:

- People attending TIA clinics diagnosed with minor stroke (group B)
- People attending TIA clinic diagnosed as NOT having had a TIA or stroke. This group were labelled as TIA "mimics" (group C)
- Age and postcode matched controls from GP registers (group D)

3.5.1 Eligibility

3.5.1.1 Eligibility Criteria

i. Clinical diagnosis formed by consultant stroke physician or neurologist at the TIA clinic [Groups A, B, C]

ii. Diagnosis made within 14 days of event [Groups A, B, C]

iii. New episode (not follow-up appointment) [Groups A, B, C]

iv. Patient deemed able to self-complete postal questionnaires by consultant stroke physician or neurologist [Groups A, B, C] or general practitioner [Group D]

v. No past medical history of stroke/TIA (confirmed by GP records and by including a screening question on baseline questionnaires) [Groups A, C, D]

3.5.1.2 Rational for eligibility criteria

One of the main criteria for this study was forming clear separation between the different clinical diagnoses so we could be confident that the outcomes of interest were not influenced by previous cerebrovascular events. Consequently, with the exception of group B, patients were not eligible if they had previously been diagnosed with TIA or stroke. Although the

reliability of diagnoses can be improved with imaging (as discussed earlier), it is not routinely available to all individuals who are seen at TIA clinics. Consequently, to ensure that the results were transferrable to current practice, diagnoses were formed by the professional judgement of consultant stroke physicians or neurologists at participating clinics. The findings of any investigations (including diagnostic imaging) requested at clinic were however collected to help describe any covariance in the results.

To rule out inappropriate referrals, patients diagnosed after 14 days of their event were not included in the study. Patients attending follow-up appointments were also rejected to avoid repetition of data collection. To minimize the amount of incomplete data, patients that were deemed unable to self-complete questionnaires were not invited to participate. However patients that were able to communicate their responses indirectly or by other means (e.g. verbally or via an interpreter) were not excluded.

3.5.2 Recruitment and consent

Groups A, B and C were recruited at participating TIA clinics. Consecutive patients attending the clinics were informed about the study and invited to participate if they were judged by their consultant/neurologist to meet the selection criteria. A research nurse was made available to answer any questions asked by the patient. As the study is not experimental and would not impact on usual treatment in any way, participants were given the opportunity to consent at their clinic appointment. This was encouraged, to increase recruitment rates and therefore achieve a more representative sample. Patients that wanted more time to consider participation were given the option of consenting via post. By definition, TIA and minor stroke are minor vascular events; therefore potential participants did not have impaired capacity to consent. Each participant was given an information sheet with details about study, rights to withdraw consent at any stage, and contact details for the research team (should they

have any queries about the study after leaving the clinic). A copy of the Participant information sheet and consent form can be found in Appendix 3 and 4 respectively.

Potential "healthy" controls (group D) were identified from GP registers. Eligible patients who were found to be a suitable match for the main study group were sent participant information and consent forms by post with prepaid return envelope. As with clinic patients, a contact telephone number was provided, allowing patients the opportunity to ask questions pertaining to the study. If individuals did not respond within three months, it was assumed that they did not wish to participate.

As part of the consent process, permission was sought from participants to inform their GP that they were taking part in the study. A copy of the letter that was sent out to inform GPs of their patient's participation can be found in Appendix 5.

Recruitment of participants at TIA clinics began on 13th September 2010 and recruitment at GP practices began on 3rd May 2011.

3.5.3 Matching controls

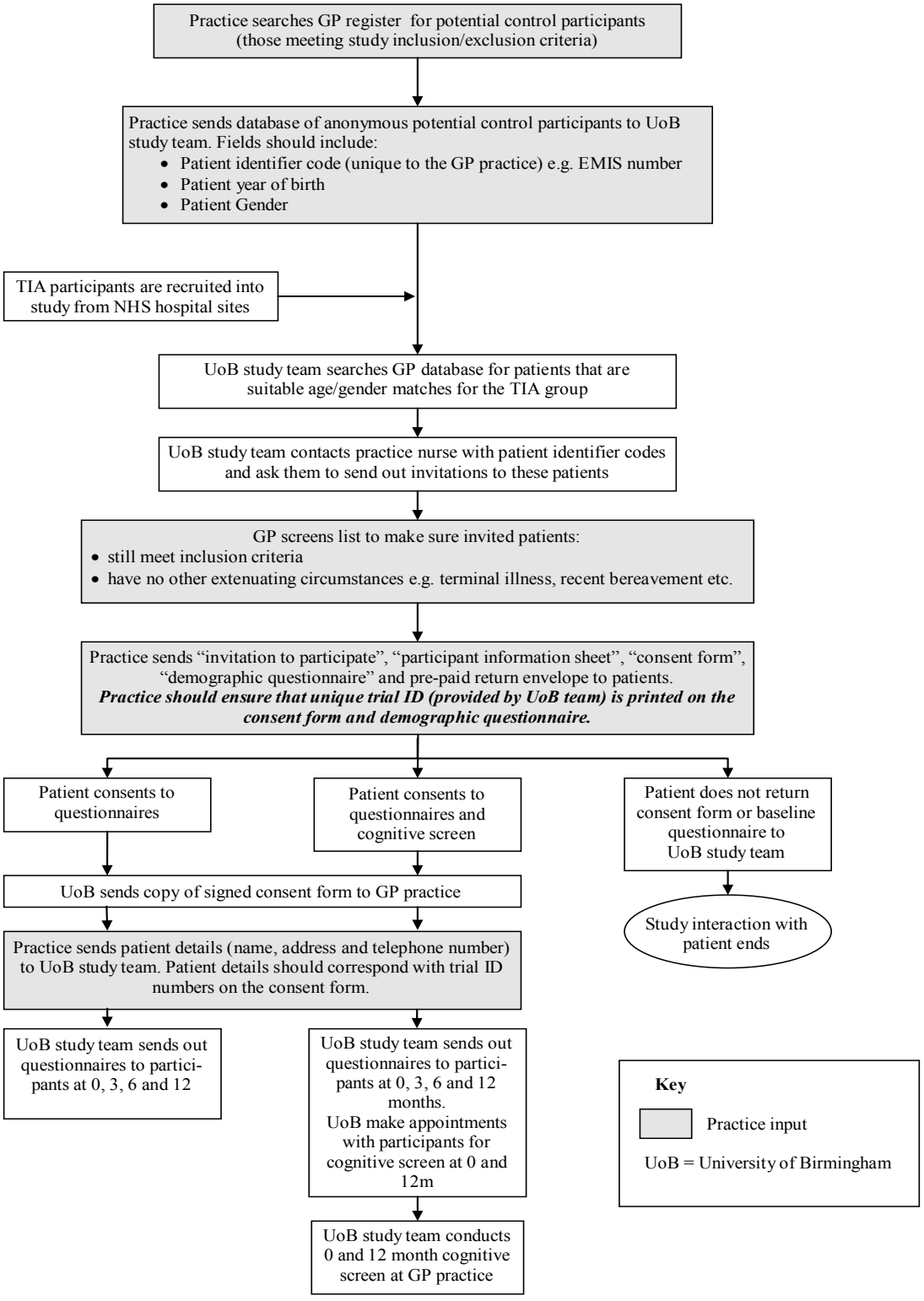
GP practices were chosen based on their postcode meta-data, namely urban-rural indicators and indices of multiple deprivation. Participating practices provided the study team with an anonymous database containing year of birth, gender and a unique ID for each of their patients. For every TIA participant entering into the trial, GP databases were searched at random for five age, gender, urban-rural and deprivation matched controls. Following approval from their GP, invites were then sent out to the five potential controls. If recruitment was unsuccessful the process was repeated.

Figure 2 illustrates the recruitment pathways in more detail, for participants recruited via TIA clinics and GP practices.

Figure 2

TIA Clinic Recruitment Pathway
Patient referred to TIA Clinic
Patient assessed by consultant
Patient meets inclusion criteria
Patient does not meet inclusion criteria
Study interaction with patient ends
Patient asked by consultant whether they would be willing to talk to someone about taking part in a q'aire based study
Patient willing
Patient NOT willing
Study interaction with patient ends
Patient speaks to RN
RN should go through Participant information sheet and answer questions asked by patients
Patient happy to consent there and then
Patient needs more time to consider participation
Patient does not want to participate in study
Study interaction with patient ends
Pt should be given 1 and 2 to take home.
Pt should sign 3 and complete 4 now.
Pt can either complete 5 now or take it away to complete at home (with pre-paid return envelope)
RN should complete 6.
RN should assign pt with unique identifier code and ensure that it is printed on 3, 4 and 5 and 6.
Pt should be given 1, 2, 3, 4 and 5 to take home (with pre-paid return envelope for 3, 4 and 5)
RN should complete 6.
RN should assign pt with unique identifier code and ensure that it is printed on 3, 4 and 5 and 6.
RN should send 3, 4, 5 (if completed in clinic) and 6 to UoB study team.
UoB study team receive signed consent form
UoB do not receive signed consent form
UoB study team will contact RN with unique identifier code and ask for clinic baseline data collection form for that participant.
Study interaction with patient ends
Key
1 = Invitation to Participate
2 = Participant Information Sheet
3 = Consent Form
4 = Demographic Questionnaire
5 = Baseline Questionnaire
6 = Clinic Data Collection Form

GP Practice Recruitment Pathway



3.6 Data sources/measurement

Data was collected from medical records, postal questionnaires and direct contact.

3.6.1 Variables

Outcome (dependent)	Exposure (independent)	Potential confounders
• Function • Anxiety • Depression • Cognition	• Diagnosis	• Age • Gender • $ABCD^2$ score (stroke risk)

The outcome variables were studied in relation to exposure to the four different diagnoses making up the study groups. Measures used to capture these outcomes are described in section 3.6.4. Age, gender and stroke risk were identified as the variables most likely to correlate with both exposure and outcome variables. These potential confounders would need to be factored into the analysis to minimise threat to internal validity of the study.

3.6.2 Baseline assessment

For participants in groups A, B and C, details of their presenting condition, investigations, stroke risk and medical management were collected. Stroke risk was predicted using the $ABCD^2$ score, derived from the Oxfordshire Community Stroke Project (Dennis et al, 1990) and validated in the Oxford Vasular study (Rothwell et al., 2004). The six-point score uses the patient's age, blood pressure, clinical features, duration of symptoms and history of diabetes mellitus to predict seven-day stroke risk (Rothwell et al., 2005).

The proposed "clinic" data collection form was informed by preliminary liaison with consultants from TIA clinics in the West Midlands. Discussions were held with participating clinics at site set-up visits to ensure these data formed part of the routine assessment. A copy of the clinic form can be found in Appendix 6.

All participants were asked to self-complete a form yielding information on demographics, social history and past medical history. Patients' perception of their past medical history may differ slightly from that documented in medical records. However for consistency across groups, patient perception was chosen to reduce potential bias that may have occurred form gathering information from different medical sources (GP records for group C and hospital records for other groups).

A copy of the form sent to participant can be seen in Appendix 7.

3.6.3 Outcome Assessment

Physical function and feelings of affect were measured using the Nottingham Extended ADL Scale (Nouri & Lincoln, 1987) and the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) respectively. These were completed by the participant at home and returned by post. Questionnaires that had not been returned within two weeks of consent were followed up with telephone reminders. Any missing data from postal returns was also sought by telephone interview. Cognition was measured using the Birmingham University Cognitive Screen (Humphreys et al., 2007). This was administered by trained assessors at the participant's GP practice or own home within four weeks of consent. The cognitive screen takes approximately one hour to administer and could be considered burdensome, however it was chosen above others as it measures a broad range of cognition. To address the issue of burden and increase consent rates the cognitive screen was made optional. BUCS assessors were trained by members of the BUCS development team and detailed guidelines were provided for guidance and to increase standardisation of administration, interpretation and scoring. In attempt to increase intra-rater reliability, a random sample of the completed BUCS assessments were marked by a second assessor and any inconsistencies in marking were addressed.

3.6.4 Selection of Outcome measures

Patient-based outcome measures (NEADL and HADS) were selected to provide a means of addressing patients' perception of their own health. This has become increasingly important with the emergence of patient autonomy in relation to their healthcare. Patient based outcome measures are also invaluable for quantifying quality of life and measures of affect, such as anxiety and depression, which are of increasing concern as the prevalence of long-term conditions increase. The NEADL and HADS were also chosen based on their content and psychometric properties for use in stroke and/or TIA populations.

To find evidence for the psychometric properties of the outcome measures, an electronic search was carried out across MEDLINE (1990- July 2011) and EMBASE (1990-July 2011), in relation to the following dimensions: reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility. These dimensions were identified as important in a report commissioned by the Health Technology Assessment board for evaluating patient based outcome measures (Fitzpatrick et al., 1998). The electronic databases were searched using the following terms: validity.mp.; appropriateness.mp.; exp "Reproducibility of Results"/ or reliability.mp.; exp "Sensitivity and Specificity"/ or accuracy.mp.; precision.mp.; responsiveness.mp.; exp Data Interpretation, Statistical/ or interpretability.mp.; acceptibility.mp.; exp Feasibility Studies/ or feasibility.mp.; floor effects.mp.; ceiling effect.mp. Reference lists of the relevant articles were also searched in order to locate further publications that were omitted from the initial search. The search was limited to articles published in English and relating to TIA populations. No results were generated therefore the search was widened to include stroke patients. In total, 44 articles relating to the NEADL and 92 articles relating to the HADS were identified. Of these, 29 were studied in full. The remaining articles were considered inappropriate based on their abstract. Of the 29 articles

studied in full, 15 were included in the critique, one being a review. To avoid repetition, articles that were identified by the search but also included in the published review (n=7) were only reported in the context of the review.

The content of the chosen outcome measures and relevant findings of the review are discussed below:

3.6.4.1 Nottingham Extended Activities of Daily Living Scale

The Nottingham Extended Activities of Daily Living Scale (NEADL) is a self-report measure of level of activity actually performed. It was developed by Nouri and Lincoln (1987) to assess activities which may be important to stroke patients who have been discharged home. The NEADL assesses function at a higher level than measures like the Barthel Index, which is limited to basic self-care tasks such as washing and dressing. The NEADL encompasses tasks such as shopping, housework and managing money which are important for functioning independently in a community and would therefore seam more suited to more able individuals. The questionnaire is composed of 22 items of higher functional self-care independence, each of which is scored on a four-point scale: 0 (when answered as “not at all”); 1 (“with help”) 2 (“on my own”) or 3 (“on my own with difficulty”). A higher total score indicates greater independence.

A recent review of stroke outcome measures by Teale and Young (2010) concluded that the NEADL was one of 5 out of 36 instruments that had acceptable psychometric properties for postal administration in stroke populations. The authors reported response rates ranging from 82-98% for patients recruited face-to-face and 46-88% for patients recruited by post. In 14 out of 15 included studies, 98-100% of NEADL questionnaires were well completed. Teale and Young suggest that telephone reminders reduce the volume of missing data. In terms of responsiveness a floor effect was observed in the mobility subscales in more dependant

institutionalized patients however this should not be a problem in our population. No ceiling effects were found. Variability in test-retest statistics suggest that the NEADL may be unreliable for detecting change in individual patients and therefore potentially limits the use of the NEADL to group rather than individual comparisons (Gompertz et al., 1993). The results of studies that were not included in review by Teale and Young are summarised in Table 6. The results confirm the variability in test-retest reliability (Green et al., 2001) identified by Teale and Young (2010) but emphasise the high validity and responsiveness of the NEADL, over and above related outcome measures (Jacob-Lloyd et al., 2005; Wu et al., 2011).

3.6.4.2 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) was developed in the early 1980s as a tool to identify emotional disorders in non-psychiatric patients within a hospital setting. However it has since been shown to perform well in other populations. HADS is made up of an anxiety (HADS-A) and depression subscale (HADS-D), each comprising seven questions that relate to the patient's emotional state over the last 7 days. For each question the patient is asked to choose one response from the four given. Responses are scored from 0-3, with 3 points indicating maximum impairment. The authors recommended that a score above 8 on each individual scale should be regarded as a possible case and a score above 10 a probable case of anxiety or depression (Zigmond & Snaith, 1983).

The psychometric properties of the HADS are summarised in Table 6. One study (Aben et al., 2002) observed ischaemic stroke outpatients in the UK, 1 month post-stroke (n=171), and found the optimal screening cut-off for major depression to be 8 (Se = 73.1, Sp =81.6) for HADS-D and 11 (Se = 91.7, Sp =65.3) for HADS-total. For major or minor depression, the

optimal screening cut-off was 7 (Se = 72.5 Sp =78.9) for HADS-D and 11 (Se = 86.8, Sp =69.9) for HADS-total. The other study (Tang et al., 2004) conducted in 100 Chinese geriatric patients with first-ever stroke, found the optimal cut-off point for any depression disorder to be slightly lower at 6/7 on HADS-D (Se=0.88, Sp=0.53). Another study, published after the meta-analysis reported lower optimal cut-offs for HADS in 104 patients, 4 months after stroke (Sagen et al., 2009). For Depression, the optimal cut-off was 4 (Se=0.84, Sp=0.73) for HADS-D and 11 (Se=0.9, Sp=0.83) for HADS-total. For Anxiety, the optimal screening cut-off was 4 (Se=0.83, Sp=0.65) for HADS-A and 6 (Se=0.83, Sp 0.60) for HADS-total.

The HADS shows high levels of internal consistency and there is little evidence that removing items would improve it. Reported correlations between different items on the HADS-D, as measured by Cronbach's α, have ranged from 0.70 to 0.85 in stroke populations (Aben et al, 2002; Johnston et al., 2000; Sagen et al, 2009). For HADS-A, Cronbach's α has ranged from 0.76 to 0.89 (Johnston et al, 2000; Sagen et al, 2009) and for HADS-total Cronbach's α has ranged from 0.79 to 0.91 (Johnston et al, 2000; Sagen et al, 2009). Confirmatory factor analyses confirmed the separation of anxiety and depression (Johnston et al, 2000).

Table 6: Psychometric properties of NEADL and HADS

Source	N	Validity	Reliability	Responsiveness	Precision	Interpretability	Acceptability	Feasibility	Conclusions
NEADL									
(Wu et al, 2011)	N=70 stroke patients (assessed before and after treatment)	Good to excellent correlation With the Frenchay Activities Index (spearman p=0.8) and after treatment (p=0.8). Fair correlations with the stroke Impact scale (p=0.3–0.4)		Standardized response mean = 0.9					The NEADLand Frenchay Activities index are both valid outcome measures but theNEADL is more responsive.
(Jacob-Lloyd et al, 2005)				The NEADL and the Rivermead mobility index were found to be more responsive than the Barthel Index and lower limb motricity index					The NEADL is more suitable than other measures for tracking change in function after discharge from hospital, for a wide case mix of people who have experienced a stroke.
(Green et al, 2001)	N=22 (15 months post-stroke; tested Twice at an interval of 1 week)		Test-retest reliability Differences between the first and Second assessments were not significant Percentage agreement was >60% and kappa values 0.3-0.89 for individual Items						Measurements used to assess basic activities of daily living were more reliable in this study.

HADS					
(Sagen et al, 2009)	N=101 (4 months post stroke)	For anxiety, the optimal screening cut-off was 4 (se=0.83, sp=0.65) for HADS-A and 6 (se=0.83, sp 0.60) for HADS-total For depression, optimal cut-offs were 4 (se=0.84, sp=0.73) for HADS-D and 11 (se=0.9, sp=0.83) for HADS-total	Internal consistency Cronbach's α = 0.89 for HADS-A, 0.83 for HADS-D and 0.91for HADS- total.		HADS-D and HADS-A perform acceptably for screening depression and anxiety after stroke. However, lower HADS cut-offs than recommended for the general population should be considered for stroke patients.
(Tang et al, 2004)	N=100 chinese stroke patients	Optimal cut-off point of HADS was 6/7 (se=0.88, sp=0.53)			The optimal cut-off point for HADS was 6/7 in chinese older adults.
(Aben et al, 2002)	N=171 (1 month post-stroke)	For major depression, the optimal screening cut-off was 8 (se = 73.1, sp =81.6) for HADS-D and 11 (se = 91.7, sp =65.3) for HADS-total For major& minor depression, the optimal screening cut-off was 7 (se = 72.5 sp =78.9) for HADS-D and 11 (se = 86.8, sp =69.9) for HADS-total		Response rate= 84.7%	The recommended cut-off level of 8 for the depression subscale turned out to be optimal.
(Johnston et al, 2000)	N=68 (1 month and 6 months post stroke discharge)		Internal consistency 1 month cronbach's α = 0.76 for HADS-A, 0.70 for HADS-D and 0.79 for HADS-total 6 month cronbach's α = 0.87 for HADS-A, 0.76 for HADS-D and 0.89 for HADS-total		The HADS showed high levels of internal consistency and there was little evidence that removing items would improve it. Confirmatory factor analyses confirmed the separation of anxiety and depression. The objective of the HADS of measuring psychological states with minimal confounding by symptoms of somatic disease is adequately achieved.

3.6.4.3 Birmingham University Cognitive Screen

The Birmingham University Cognitive Screen (BUCS) (Humphreys et al, 2007) is a new test instrument developed to screen patients for a 'broad but shallow' range of cognitive problems. The test takes one hour to administer and cover 5 domains:

domain:	**impairment:**
Language	Speech impairment (3 items) Reading impairment (4 items) Writing impairment (1 item)
Mathematical/Number abilities	Number reading (1 item) Number writing (1 item) Calculation (1 item)
Praxis/control and planning of action	Visuo-constructive impairment (1 item) Gesture recognition, production and imitation (3 items) Action organization (1 item)
Memory	Orientation impairment (2 items) Episodic memory impairment (6 items)
Attention and executive functions	Spatial attention impairment (14 items) Controlled attention impairment (including executive functions) (2 items)

Each item on the BUCS is scored as "impaired" or "not impaired" using age-adjusted cut-off scores derived from a population-based healthy control sample. Cut-off scores were assembled across 3 decades (<64, 65-74, 75+), based on scores two Standard Deviations or more from the means of the "healthy" population. See Appendix 8.

The BUCS was chosen above other cognitive outcome measures because of its ability to pinpoint specific areas of cognition. This was identified as important in the systematic review (chapter 2). The BUCS tests were also designed to be relatively difficult within their domain to increase the chance of identifying problems if they exist. This is important in TIA patients where impairments may not be outwardly noticeable. The BUCS was chosen over and above other comprehensive cognitive screening tools such as the Montreal Cognitive Assessment,

identified in the review (chapter 2), as it was designed with stroke patients in mind. It is therefore laid out to be as neglect friendly' and 'aphasia friendly' as possible. These design qualities are important in longitudinal studies of TIA patients where full stroke is often imminent. As the BUCS was developed at the University of Birmingham, collaboration and support from the BUCS team was also a huge asset.

Performance of BUCS has been validated against standardized tests from the literature including: the AMT (to validate the BUCS orientation test); sentence reading from the BDAE (validate sentence reading), story recall from the WMS-R (validate story recall test, immediate and delayed), star cancellation (BIT), Rey figure (complex figure copy), elevator task from the Test of Everyday Attention (to validate our test of auditory sustained attention), the Brixton (to validate the Birmingham Frontal test), PALPA test of nonword reading (for the BUCS nonword reading), picture naming from BORB (for BUCS picture naming), BDAE writing short-form (BUCS writing), CAT calculation (number processing), spoken picture description (sentence construction).

3.6.5 Addressing diversity

The above mentioned questionnaires have not all been validated in different languages however, to make the results more pertinent the study population should reflect the cultural diversity of the West Midlands. Consequently we enclosed a brief cover letter, translated into several languages (Bengali, Guajarati, Punjabi, Hindu and Urdu), encouraging the participant to seek help in completing the questionnaires from a friend or family member if necessary. An English version of the cover letter can be found in Appendix 9.

For the cognitive screen, participants with language difficulties were encouraged to bring a friend or family member with them to act as a translator.

3.6.6 End points

Participants remained in the study until TIA (groups C and D), stroke or death (all groups). Events were identified through a screening question on all postal questionnaires, and confirmed through GP records.

3.7 Accrual and Analysis

3.7.1 Statistical Methods

After cleaning the database, summary statistics were produced for nominal variables. For each continuous variables (interval and ratio), the data were represented graphically (Appendix 10). This facilitated the interpretation of the distributions of data and provided an opportunity to double-check "outliers", to see if they were data entry errors. It also allowed us to test the assumptions for statistical analysis (i.e. that linear relationships existed between exposure and outcome variables).

For each questionnaire (NEADL and HADS) a total score was calculated from the individual item scores. For the HADS two component scores were also computed, giving rise to an anxiety and depression sub-score. The data collected on the NEADL and HADS were analyzed in SPSS for windows (SPSS Inc, 2006). Multiple regression was performed to examine whether the total scores (for NEADL, HADS-total, HADS-Anxiety and HADS-depression) were influenced by exposure (diagnosis) after adjusting for age and gender differences. Missing or ambiguous responses to items on questionnaires were pro-rated.

As the exposure variable was nominal and included more than two categories, dichotomous dummy variables were created (for example: TIA "mimic"/not TIA "mimic" and minor stroke/not minor stroke). A diagnosis of definite TIA was used as the constant variable, to which comparisons were made.

As mentioned previously the FACE TIA study is ongoing. For preliminary analysis, BUCS data was only available for the definite TIA group. Consequently, between-group analysis was not possible for this outcome. Instead, published cut-off scores, derived from a "healthy" population, were used to transform BUCS item scores into more meaningful "impaired"/ "not impaired" categories. Multiple regression was then performed to see whether number of cognitive impairments (as measured by the BUCS) or stroke risk (as measured by $ABCD^2$ score) influenced NEADL and HADS scores, after adjusting for age and gender. Interaction effects between HADS and NEADL were also assessed using multiple regression. The level of significance was set to 0.05.

3.7.2 Sample size

As there were no existing data for the NEADL and HADS in the desired TIA population, on which to base the sample size calculation, a target sample size of 600 for the full FACE-TIA cohort was defined by available resources. This sample size was reviewed and adjusted using the results of the pilot data, analysed in Chapter 4. Sample size predictions were calculated from the effect size of the difference in means between diagnostic groups for the HADS and NEADL, after adjusting for age and gender. Software (G*POWER, 2004) was used to perform the sample size calculation.

CHAPTER 4

RESULTS

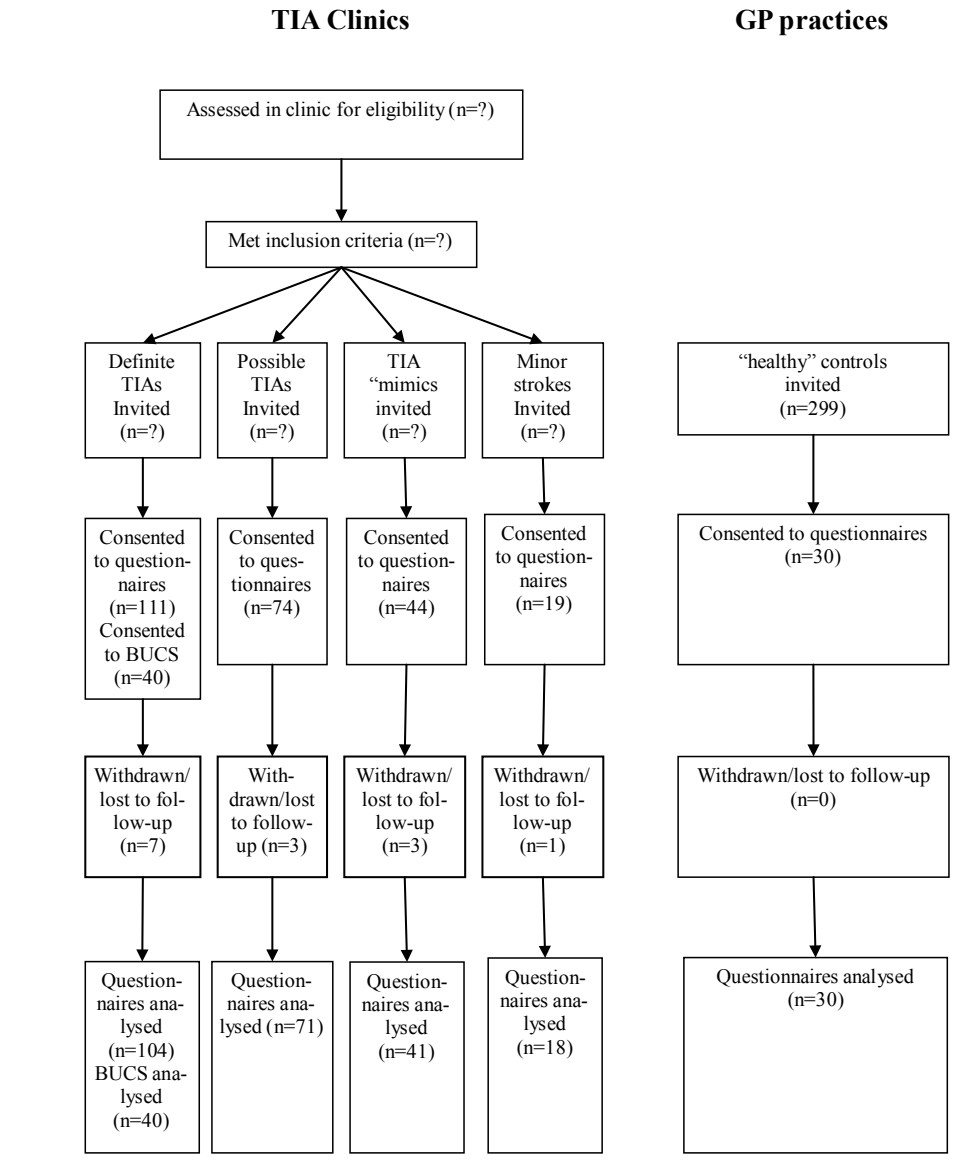
The FACE TIA trial is ongoing. The results reported in this chapter relate to data collected before July 2011. This includes baseline data only. The results of the three, six and twelve-month follow-up will be reported in subsequent publications.

4.1 Participants

To date, one hundred and eleven patients diagnosed with definite TIA have consented to participate in the FACE TIA trial. Patients diagnosed with possible TIA (n=74), TIA "mimic" (n=44), minor stroke (n=19), and 30 "healthy" controls have also agreed to take part. Furthermore, 40 participants out of 111 who had suffered a definite TIA have consented to participate in the Birmingham University Cognitive Screen (BUCS). The TIA "mimic" group included patients who were given a differential diagnosis to TIA, such as migraine, syncope, orthostatic hypotension, vertigo, transient global amnesia, transient speech arrest, lazy eye, dyspraxia and conversion syndrome.

A flow diagram of all the participants is presented in Figure 3.

Figure 3: Flow diagram of participants



? Number is currently unknown as reports from clinics have not yet been received

Seven definite TIA participants were lost to follow-up before submitting their baseline questionnaire; two participants withdrew their consent without stating a reason, three participants failed to return their questionnaire and did not respond to telephone/postal

reminders and two participants were excluded as further investigation revealed that they had actually suffered a major stroke. Three participants diagnosed with possible TIA were lost to follow-up before submitting their baseline questionnaire; one participant became hospitalized and did not want to continue, one participant withdrew their consent as they needed assistance to complete the questionnaire and felt uncomfortable in doing so, and one participant withdrew their consent without stating a reason. Three participants diagnosed with TIA "mimic" were lost to follow-up before submitting their baseline questionnaire: two found the study irrelevant as they had not suffered a TIA and one withdrew their consent without stating a reason. One minor stroke patient also withdrew their consent without reason before submitting their baseline questionnaire.

4.2 Baseline Characteristics

The definite TIA group were significantly older than the possible TIA group, and included significantly fewer males than the control group. However they were comparable to the other groups in terms of age and gender. No significant differences were found between the definite TIA group and other groups with regards to ethnicity, living situation or formal education, with the exception of "other qualification/level unknown", which was significantly higher in the control group. In terms of stroke risk factors, no significant differences were found between the definite TIA group and other groups with regards to obesity and smoking status. However a significantly higher proportion of the "healthy" control group admitted to drinking alcohol on a regular basis, compared to the definite TIA group. The demographic characteristics of the study sample are presented by diagnosis in Table 7.

Table 7: Demographic characteristics

	Definite TIA (n=111)		Possible TIA (n=74)		Mimic (n=44)		Minor stroke (n=19)		Healthy control (n=30)	
Age (mean ± SD; range)	74±14; 43-109		69±12; 31-88*		69±11; 41-91		70±12; 50-89		73±8; 61-89	
	(n)	**(valid %)**	**(n)**	**(valid %)**	**(n)**	**(valid %)**	**(n)**	**(valid %)**	**(n)**	**(valid %)**
Gender										
Male	56	(53.8%)	33	(44.6%)	25	(56.8%)	10	(52.6%)	25	(83.3%)*
Missing	7		0		0		0		0	
Ethnicity										
White	101	(97.1%)	70	(95.9%)	44	(100%)	18	(94.7%)	30	(100%)
Black	2	(1.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Asian	1	(1.0%)	3	(4.1%)	0	(0.0%)	1	(5.3%)	0	(0.0%)
Missing	7		1		0		0		0	
Education										
No formal qualification	38	(37.3%)	22	(30.6%)	7	(15.9%)	10	(55.6%)	6	(20.0%)
GCSE or equivalent	27	(26.5%)	26	(36.1%)	19	(43.2%)	1	(5.6%)	4	(13.3%)
A'level or equivalent	10	(9.8%)	11	(15.3%)	4	(9.1%)	3	(16.7%)	2	(6.7%)
Degree	7	(6.9%)	6	(8.3%)	7	(15.9%)	1	(5.6%)	1	(3.3%)
Postgraduate qualification	2	(2.0%)	1	(1.4%)	4	(9.1%)	0	(0.0%)	3	(10.0%)
Other	18	(17.6%)	6	(8.3%)	3	(6.8%)	3	(16.7%)	14	(46.7%)*
Missing	9		2		0		1		0	
Lives with										
Spouse/partner	63	(60.6%)	44	(60.3)%	32	(72.7)%	17	(89.5)%	24	(80.0)%
Dependents	2	(1.9%)	2	(2.7)%	0	(0.0%)	0	(0.0%)	0	(0.0%)
Alone	34	(32.7%)	24	(32.9)%	10	(22.7)%	2	(10.5)%	5	(16.7)%
Other	5	(4.8%)	3	(4.1)%	2	(4.5)%	0	(0.0%)	1	(3.3)%
Missing	7		1		0		0		0	
Residence										
Domestic	98	(94.2%)	70	(95.9%)	40	(90.9%)	19	(100%)	30	(100%)
Sheltered	2	(1.9%)	2	(2.7%)	4	(9.1%)	0	(0.0%)	0	(0.0%)
Residential	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Nursing	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other	4	(3.8%)	1	(1.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Missing	7		1		0		0		0	
Anxiety and Depression										
Anxious (HADS-A>4)	53	(51.5%)	43	(60.6%)	22	(53.7%)	11	(64.7%)	7	(23.3%)
Depressed (HADS-D>4)	31	(30.1%)	23	(32.4%)	11	(26.8%)	7	(41.2%)	6	(20.0%)
Missing	8		3		3		2		0	
Health										
Obese	24	(29.6%)	10	(18.9%)	15	(37.5%)	4	(30.8%)	8	(27.6%)
Missing	30		21		4		6		1	
Lifestyle										
Smokes	14	(13.6%)	7	(9.9%)	3	(7.3%)	2	(11.1%)	0	(0.0%)
Drinks alcohol	61	(59.2%)	39	(55.7%)	33	(80.5%)	12	(66.7%)	27	(90.0%)*
Missing	8		3		3		1		0	

* Significantly different to definite TIA group ($p<0.05$)

Additional clinical findings for the four patient groups are presented in Table 8.

Table 8: Clinic findings

	Definite TIA (n=111)		Possible TIA (n=74)		Mimic (n=44)		Minor stroke (n=19)	
Days to consent (median: IQR)	4: 1-8		7: 4-11		6: 3-7		4: 1-11	
	(n)	**(valid %)**	**(n)**	**(valid %)**	**(n)**	**(valid %)**	**(n)**	**(valid %)**
Referral source								
A&E	49	(45.8%)	21	(28.4%)	13	(29.5%)	8	(42.1%)
GP	47	(43.9%)	48	(64.9%)	29	(65.9%)	6	(31.6%)
Other	11	(10.3%)	5	(6.8%)	2	(4.5%)	5	(26.3%)
Missing	4		0		0		0	
Duration symptoms								
≤ 1 hour	70	(71.4%)	43	(71.7%)	29	(80.6%)	4	(36.4%)
1-24 hours	28	(28.6%)	16	(26.7%)	6	(16.7%)	3	(27.3%)
24-48 hours	0	(0.0%)	1	(1.7%)	0	(0.0%)	3	(27.3%)
> 48 hours	0	(0.0%)	0	(0.0%)	1	(2.8%)	1	(9.1%)
Missing	13		14		8		8	
Symptoms								
Right weakness	31	(27.9%)	17	(23.0%)	12	(27.3%)	5	(26.3%)
Left weakness	45	(40.5%)	21	(28.4%)	4	(9.1%)	9	(47.4%)
Bilateral weakness	4	(3.6%)	9	(12.2%)	12	(27.3%)	0	(0.0%)
Speech	12	(10.8%)	5	(6.8%)	8	(18.2%)	4	(21.1%)
Visual	9	(8.1%)	6	(8.1%)	9	(20.5%)	0	(0.0%)
Other	7	(6.3%)	4	(5.4%)	1	(2.3%)	2	(10.5%)
Missing	0		0		0		0	
ABCD^2								
≥4 (high risk of stroke)	44	(51.2%)	18	(36.7%)	16	(40.0%)	7	(77.8%)
Missing	25		25		4		10	

The proportion of patients at high risk of future stroke, as measured by the ABCD^2 score, was greatest in the minor stroke group (77.8%), followed by the definite TIA group (51.2%). Fewer patients diagnosed with possible TIA and TIA "mimic" were considered to be at high risk of stroke (36.7% and 40.0% respectively).

In accordance with the time-based definition of TIA, the symptoms recalled by all definite TIA patients lasted less than 24 hours. The majority of TIAs (71.4%) actually lasted less than 1 hour. Although the number of participants in the minor stroke group was small, less than half of the group reported symptoms lasting more than 24 hours. This emphasises the discrepancy between the arbitrary cut-off time between TIA and minor stroke, and clinical judgement.

4.3 Outcome Results

4.3.1 Extended Activities of Daily Living

After adjusting for age and gender, the minor stroke group scored significantly lower than the definite TIA group on the NEADL (mean: -5.05 points, CI: -9.63 to -4.63). The results suggest that patients diagnosed with minor stroke are likely to be more dependent in extended activities of daily living, than patients diagnosed with TIA. All other groups had similar mean NEADL scores to the definite TIA group (Table 9).

Table 9: Differences in NEADL score, compared to the definite TIA group[†]

Constant: Definite TIA (n=104)				
	B	**SE (B)**	**95% CI (B)**	**Sig (B)**
Comparison group				
Healthy Control (n=30)	2.14	1.93	-1.66 to 5.93	0.268
Mimic(n=41)	1.44	1.70	-1.90 to 4.79	0.396
Possible TIA (n=71)	-0.02	1.43	-2.84 to 2.80	0.990
Minor Stroke (n=18)	-5.05	2.33	-9.63 to -0.46	0.031

[†] age and gender adjusted model
B = regression coefficient
Note: $R^2 = 0.075$
Lower NEADL score = greater dependence in ADL

4.3.2 Anxiety and Depression

After adjusting for age and gender, the HADS-total scores (Table 10) of the "healthy" control group were significantly lower than the HADS-total scores of the definite TIA group (mean: 2.90 points higher, CI: 0.24 to 5.55). After dividing the HADS into its component anxiety and depression sub-scores, the "healthy" control group were found to have significantly less feelings of depression than the definite TIA group (mean: -1.35 points, CI: -2.65 to -0.06), as shown in Table 12. The anxiety scores were not significantly different between the "healthy" controls and definite TIA group; however there appears to be a trend towards less anxiety in the "healthy" control group (Table 11). The other patient groups (possible TIAs, TIA

"mimics" and minor stroke) scored similarly to the definite TIA group in terms of anxiety (Table 11) and depression (Table 12).

Table 10: Differences in HADS-Total score, compared to the definite TIA group†

Constant: Definite TIA (n=104)				
	B	**SE (B)**	**95% CI (B)**	**Sig (B)**
Comparison group				
Healthy Control (n=30)	-2.90	1.35	-5.55 to -0.24	0.033
Mimic(n=41)	-0.60	1.19	-2.94 to 1.75	0.617
Possible TIA (n=71)	0.62	1.00	-1.35 to 2.60	0.534
Minor Stroke (n=18)	2.08	1.67	-1.21 to 5.37	0.215

† age and gender adjusted model
B = regression coefficient
Note: $R^2 = 0.081$
Lower HADS-total score = less anxious/depressed mood

Table 11: Differences in HADS-Anxiety score, compared to the definite TIA group†

Constant: Definite TIA (n=104)				
	B	**SE (B)**	**95% CI (B)**	**Sig (B)**
Comparison group				
Healthy Control (n=30)	-1.54	0.84	-3.19 to 0.12	0.067
Mimic(n=41)	-0.16	0.74	-1.61 to 1.23	0.830
Possible TIA (n=71)	0.70	0.62	-0.53 to 1.93	0.263
Minor Stroke (n=18)	1.14	1.04	-0.91 to 3.12	0.273

† age and gender adjusted model
B = regression coefficient
Note: $R^2 = 0.141$
Lower HADS-anxiety score = less anxious mood

Table 12: Differences in HADS-Depression score, compared to the definite TIA group†

Constant: Definite TIA (n=104)				
	B	**SE (B)**	**95% CI (B)**	**Sig (B)**
Comparison group				
Healthy Control (n=30)	-1.35	0.66	-2.65 to -0.06	0.041
Mimic(n=41)	-0.44	0.58	-1.58 to 0.71	0.452
Possible TIA (n=71)	-0.08	0.49	-1.04 to 0.89	0.878
Minor Stroke (n=18)	0.94	0.82	-0.67 to 2.54	0.251

† age and gender adjusted model
B = regression coefficient
Note: $R^2 = 0.044$
Lower HADS-depression score = less depressed mood

The order of outcome was similar across all measures, with the minor stroke group having the worst outcome (most dependence; most anxiety and most depressed mood), followed by the possible TIA group, then the definite TIA group, then the TIA "mimics" and finally the "healthy" controls.

4.3.3 Cognition

Cognitive impairment, scored as “impaired” or “not impaired” on the BUCS was determined using cut-off scores, based on scores two Standard Deviations or more from the means of the “healthy” population (Humphreys et al, 2007). From Table 13 it can be seen that, on several items (highlighted in grey), 5-21% of definite TIA participants were impaired. This equates to 5-21% of definite TIA participants scoring within the bottom 5% of the normal population. Thus, indicating that definite TIA patients might be more impaired than “healthy” controls in these areas of cognition.

Table 13: Cognitive impairments in the definite TIA group (n=40)

		Assessed (n)	Impaired (n)	Impaired (%)
LANGUAGE				
Speech	Instruction comprehension	39	0	0.0%
	Picture naming	40	2	5.0%
	Sentence construction	40	4	10.0%
Reading	Nonwords – accuracy	39	1	2.6%
	Nonwords – time	39	0	0.0%
	Sentence – accuracy	39	4	10.3%
	Sentence – time	39	1	2.6%
Writing	Words + nonword	39	1	2.6%
NUMBER				
Reading	Total	39	0	0.0%
Writing	Total	39	2	5.1%
Calculation	Total	39	0	0.0%
PRAXIS				
visuo-constructive	Figure copy	39	3	7.7%
Limb	Multi-step	39	0	0.0%
	Gesture production	39	1	2.6%
	Gesture recognition	39	0	0.0%
	Imitation	39	8	20.5%
LONG-TERM MEMORY				
Orientation	Personal	40	0	0.0%
	Time and space (MC)	40	1	2.5%
Episodic	Story - immediate recall	39	6	15.4%
	Story – immediate recognition	39	3	7.7%
	Story – delayed recall	39	3	7.7%
	Story – delayed recognition	39	1	2.6%
ATTENTION				
Spatial	Apple cancellation -total	37	1	2.7%
	Apple asymmetry - full	37	0	0.0%
	Apple asymmetry - incomplete	37	0	0.0%
	Left visual neglect	39	1	2.6%
	Right visual neglect	39	0	0.0%
	Left visual bilateral	39	1	2.6%
	Right visual bilateral	39	0	0.0%
	Left tactile neglect	39	2	5.1%
	Right tactile neglect	39	1	2.6%
	Left tactile bilateral	39	0	0.0%
	Right tactile bilateral	39	1	2.6%
	Auditory – WM2 – recall	39	2	5.1%
	Auditory – accuracy	39	5	12.8%
Control	Auditory – sustained attention	39	4	10.3%
	B'ham – rule finding - accuracy	39	7	17.9%
	B'ham – rule finding - rules	39	3	7.7%

Sentence construction was impaired in 10% of TIA participants, compared to 5% in the normal population. In this task participants were instructed to construct a sentence which describes what a person is doing in a photograph, incorporating 2 given words. Difficulty with

this task suggests problems in semantic and syntactic processes, along with problems in articulation. Sentence reading accuracy was impaired in 10.3% TIA participants, compared to 5% in the normal population. This is unlikely to be a reflection on neglect or visual disorientation as sentences are presented across several lines in central alignment. Again, it is more likely to reflect problems in syntactic processes and articulation. Over one fifth of TIA participants were impaired in the imitation task, compared to one in twenty in the normal population. In this task participants were asked to "mimic" four meaningless hand gestures. Difficulties with this task suggest problems with proprioception and coordination. Immediate story recall was impaired in 15.4% of TIA participants compared to 5% in the normal population. This suggests that TIA patients have more problems with episodic memory for newly learned verbal information. In the auditory attention task, over 10% of TIA participants demonstrated impairments in sustaining their attention, and storing items in their memory over the short-term, when engaged in another activity (a measure of working memory). This is more than double the proportion of impairments found in the normal population on this task. A higher proportion of TIA participants than "healthy" norms also demonstrated impairments in the rule finding and switching test, which measures the participant's ability to find an abstract rule and to switch the rule across stimuli within and across dimensions.

4.3.4 Predictors of functional, emotional and cognitive outcomes

4.3.4.1 Predictors of functional outcome

After adjusting for age, gender and diagnosis, the HADS-total score was found to be a strong predictor of the NEADL score. An increase of one in the HADS-total predicted a decrease of 0.35 (CI: -0.52 to -0.17) in the NEADL (Table 14). A higher score on the HADS reflects greater anxiety and feelings of depression, and a lower score on the NEADL reflects less

independence. Therefore the negative correlation between scores indicates that as anxiety and feelings of depression increase, independence decreases.

The number of BUCS impairments was not a significant predictor of NEADL scores in the definite TIA group, after adjusting for age and gender (mean: 1.72, CI: -0.18 to 3.61). This suggests that cognitive impairment is not related to independence in extended daily activities in this population.

In the definite TIA group, after adjusting for age and gender, an increase of one on the $ABCD^2$ score resulted in a significant decrease in the NEADL (mean: -1.78, CI: -3.59 to 0.04), showing that increased stroke risk is linked to reduced independence (Table 14).

Table 14: Predictors of the NEADL score

Predictor variable	B	SE (B)	95% CI (B)	Sig (B)
BUCS ¶ (n=40)	1.72	0.93	-0.18 to 3.61	0.075
HADS† (n=264)	-0.35	0.09	-0.52 to -0.17	0.000
$ABCD^2$ ¶ (n=234)	-1.78	0.91	-3.59 to 0.04	0.054

B = regression coefficient
† all groups (age, gender and diagnosis adjusted models)
¶ TIA group only (age and gender adjusted)
Note: R^2 (BUCS) = 0.111; R^2 (HADS) = 0.119; R^2 ($ABCD^2$) = 0.117
Lower NEADL score = greater dependence in ADL

4.3.4.2 Predictors of emotional outcomes

After adjusting for age, gender and diagnosis, the NEADL was found to be a strong predictor of the HADS score. An increase of one in the NEADL score predicted a decrease of 1.17 (CI: -0.26 to -0.09) in the HADS-total score (Table 15). A higher score on the NEADL reflects greater independence and a lower score on the HADS reflects a less anxious/depressed mood. Therefore the negative correlation between scores indicates that as independence increases, anxiety and feelings of depression decrease.

In the definite TIA group, after adjusting for age and gender, an increase of one impairment on the BUCS resulted in a significant increase in the HADS-Total score (mean: 1.60, CI: 0.27 to 2.92), HADS-Anxiety score (mean: 0.87, CI: 0.13 to 1.60) and HADS-Depression score

(mean: 0.73, CI: 0.08 to 1.38). These results are presented in Tables 15, 16 and 17 respectively. The results suggest a positive correlation between cognitive impairment and anxiety and depression.

In the definite TIA group, an increase of one on the $ABCD^2$ score did not influence the HADS-total score (Table 15) or HADS sub-scores (Tables 16-17) after adjusting for age and gender. This suggests that stroke risk is unrelated to feelings of anxiety and depression.

Table 15: Predictors of the HADS-Total score

Predictor variable	B	SE (B)	95% CI (B)	Sig (B)
BUCS ¶ (n=40)	1.60	0.65	0.27 to 2.92	0.020
NEADL† (n=264)	-1.17	0.04	-0.26 to -0.09	0.000
$ABCD^2$ ¶ (n=234)	-0.06	0.65	-1.35 to 1.23	0.932

B = regression coefficient
† all groups (age, gender and diagnosis adjusted models)
¶ TIA group only (age and gender adjusted)
Note: R^2 (BUCS) = 0.215; R^2 (NEADL) = 0.135; R^2 ($ABCD^2$) = 0.033
Lower HADS-total score = less anxious/depressed mood

Table 16: Predictors of the HADS-Anxiety score

Predictor variable	B	SE (B)	95% CI (B)	Sig (B)
BUCS ¶ (n=40)	0.87	0.36	0.13 to 1.60	0.022
NEADL† (n=264)	-0.08	0.03	-0.13 to -0.03	0.004
$ABCD^2$ ¶ (n=234)	-0.03	0.37	-0.77 to 0.71	0.939

B = regression coefficient
† all groups (age, gender and diagnosis adjusted models)
¶ TIA group only (age and gender adjusted)
Note: R^2 (BUCS) = 0.233; R^2 (NEADL) = 0.169; R^2 ($ABCD^2$) = 0.072
Lower HADS-anxiety score = less anxious mood

Table 17: Predictors of the HADS-Depression score

Predictor variable	B	SE (B)	95% CI (B)	Sig (B)
BUCS ¶ (n=40)	0.73	0.32	0.08 to 1.38	0.029
NEADL† (n=264)	-0.09	0.02	-0.13 to -0.05	0.000
$ABCD^2$ ¶ (n=234)	-0.03	0.32	-0.66 to 0.60	0.932

B = regression coefficient
† all groups (age, gender and diagnosis adjusted models)
¶ TIA group only (age and gender adjusted)
Note: R^2 (BUCS) = 0.203; R^2 (NEADL) = 0.337;R^2 ($ABCD^2$) = 0.048
Lower HADS-depression score = less depressed mood

4.3.4.3 Predictors of cognitive outcomes

An increase of one on the HADS-total score predicted a significant increase in number of BUCS impairments, after adjusting for age and gender (Table 18). This suggests that patients

with a more anxious/depressed mood are likely to exhibit more cognitive impairments. A trend towards more cognitive impairments with increased NEADL and $ABCD^2$ scores was also demonstrated (Table 18), suggesting that increased stroke risk and greater independence in extended daily activities could be associated with increased cognitive impairment.

Table 18: Predictors of BUCS impairments

Predictor variable	B	SE (B)	95% CI (B)	Sig (B)
NEADL¶ (n=40)	0.05		-0.01 to 0.11	0.075
HADS¶ (n=40)	0.09		0.02 to 0.17	0.020
$ABCD^2$¶ (n=40)	1.30		-0.18 to 2.79	0.083

¶ TIA group only (age and gender adjusted)
Note: R^2 (NEADL) = 0.119; R^2 (HADS) = 0.182; R^2 ($ABCD^2$) = 0.184

4.4 Sample size calculations

Based on the effect size of the NEADL (r=0.274) and a significance level of 0.05, a total sample size of 458 participants would be needed to achieve 90% power. For the HADS (r=0.285), only 424 participants would be needed to achieve 90% power at the 0.05 level of significance. As the full FACE TIA study continues, attrition rates would need to be considered and the target sample size of 458 should be adjusted accordingly.

CHAPTER 5

DISCUSSION AND EPILOGUE

5.1 Discussion

This cohort study was designed to analyse functional, cognitive and emotional outcomes in patients diagnosed with their first TIA, compared to "healthy" individuals. The study also sought to analyse how patients with suspected TIA faired after being given a differential diagnosis, compared to those whose TIA diagnosis was confirmed. Although the study is under-powered at this stage, the preliminary findings of the ongoing FACE TIA study demonstrate some strong emerging themes.

Previous research has found TIA to have no impact on basic activities of daily living (Duncan et al, 1997). In this study we sought to examine the effect of TIA on extended activities of daily living, which require increased interaction with the environment than basic ADL, and appear to be a prerequisite for independent living in the community. The results provide no evidence to suggest that extended ADL are compromised in TIA patients compared to controls. However, minor-stroke patients were significantly more impaired in this area than TIA patients. This evidence supports the classic understanding of TIA, distinguishing it from stroke, as "symptoms that resolve without obvious lasting damage" (Department of Health, 2007b). A strong trend was found between the $ABCD^2$ score and NEADL suggesting that clinical populations at high risk of stroke are likely to more impaired in extended activities of daily living, than patients at lower risk of stroke.

It is generally accepted, by health professionals, that patients make a complete recovery after TIA. However recent findings into depression and cognition after TIA suggest otherwise

(Bossema et al, 2006; Charoenkitkarn et al, 2009; Guyomard et al, 2011; Hickie et al, 2003; Rao et al, 1999; Rao et al, 2001; Rao, 2002; Walters et al, 2003; Xin-rong et al, 2005).

The HADS-depression score is largely related to the loss of pleasure responses (anhedonia) which is one of the two required components of the official definition of 'major depressive disorder' (Snaith, 2003). In this study, patients diagnosed with TIA scored significantly worse on the depression component of the HADS than "healthy" controls. This finding suggests that TIA is associated with depression, and is consistent with previous research (Bossema et al, 2006; Rao et al, 2001). Although an association between feelings of depression and TIA is evident, the temporal relationship is unclear. Our findings, of depressed mood in TIA patients, is also consistent with subjective accounts of depression reported by TIA patients in qualitative research (Spurgeon, 2011).

Depression has been linked to low physical activity and smoking, that may increase vascular risk (Jonas & Mussolino, 2000). Depressive symtoms have also been shown to be an independent risk factor for incident stroke/TIA in a community-based study (Salaycik et al., 2007). These findings suggest that depression may provoke TIA, rather than TIA being the causative factor. Interestingly, our results found the $ABCD^2$ score to be a poor predictor of depression. In addition, mean depression scores were similar between TIA patients and patients who were referred to TIA clinics, but given an alternative diagnosis. This suggests that depression may be related to the experience of suffering a stressful event, whether that is stroke, TIA or another condition entirely. This finding implies a need to explore the potential for psychological screening and support in all patients attending TIA clinics, regardless of their final diagnosis.

In previous research Duncan et al (1997) found that depression significantly impacted on the quality of life, family functioning and psychological health of all concerned. Our research

supports this. A significant correlation was found between the HADS and NEADL, with feeling of anxiety and depression increasing with reduced independence. A significant correlation was also found between the HADS and BUCS, with feeling of anxiety and depression increasing with increasing cognitive impairment. This finding suggests that addressing depression could have an all-round impact on the patients' health.

Although not statistically significant, an emerging trend towards increased anxiety in definite TIA patients, compared to "healthy" controls, is evident. This trend should not be dismissed, especially as the results of the preliminary analyses were underpowered. Furthermore, anxiety emerged as a strong theme in qualitative research (Spurgeon, 2011).

In the FACE TIA study, preliminary analysis revealed that certain types of cognitive impairment were more prevalent in definite TIA patients than in the normal "healthy" population. The impact of TIA on cognitive functioning has already been documented by several authors and although different test batteries were used, the areas of impairment seem to be consistent. Impaired language has been reported by Bossema et al (2006) and Guyomard et al (2011); impaired memory has been reported by Xin-rong et al (2005), Bossema et al (2006), Charoenkitkarn et al (2009) and Guyomard et al (2011); visuo-spatial impairement has been reported by Guyomard et al (2011) and attention deficits have been reported by Rao et al (1999; 2002), Xin-rong et al (2005), Bossema et al (2006) and Guyomard et al (2011). In addition, Rao et al (1999; 2002) and Guyomard et al (2011) identified impairments in areas of calculation and orientation respectively. To date, no substantial impairments in these two dimensions have been identified in the FACE TIA cohort. In previous research some authors have demonstrated a possible correlation between cardio vascular risk factors and cognition. This theme was explored in the FACE TIA cohort using the $ABCD^2$ score, as a measure of stroke risk, to predict cognitive impairment.

Although not statistically significant, a positive correlation was observed between stroke risk and number of cognitive impairments. This emerging trend suggests that higher risk patients attending TIA clinics may benefit from cognitive screening.

No significant relationship was found between cognition and extended activities of daily living in this study however there was a positive correlation between the BUCS and HADS suggesting that cognitive impairments may provoke feelings of anxiety and depression. Green and King (2007) imply that this may result from the implication of reduced cognition on employment and social activities. Although not the topic of this research, cognitive impairments could impact on the patient's ability to attend to, learn, understand and remember new information and adopt new health behaviours. This could potentially have an effect on patient management. If patients are unable to comprehend the severity of TIA or respond and adhere to stroke prevention strategies, such as lifestyle advice and preventative medication, it could increase their risk of future stroke. Finding ways to manage cognitive decline could have a huge impact on patient prognosis.

5.2 Strengths and Limitations

5.2.1 Extrapolating the results to a wider population

The results have been adjusted for age and gender to reduce any effects resulting from differences in the demographics between groups. In terms of the population studied, participants were recruited from a wide geographical area within the UK, reflecting a variety of urban and rural locations, ranging in levels of socioeconomic status. However, the sample was predominantly White British, perhaps reflecting that this ethnic group is more likely to seek medical attention for TIA-like symptoms or perhaps reflecting a greater willingness to participate in research. Researchers should be aware of this and make additional arrangements

to engage and facilitate involvement of people form ethnic minorities in research. Care should also be taken when extrapolating the results of this study to ethnic minority groups. Participants were grouped according to their clinical diagnosis. However to increase consistency of diagnoses between clinicians some additional constraints were enforced; for example, minor stroke patients were differentiated from major stroke patients based on length of admission to hospital. These constrains were formed in collaboration with stroke consultants. Radiographic evidence was used to inform diagnoses at the discretion of stroke consultant assessing the patient. This was a practical decision by the research team to ensure that the results were relevant to current practice where scans are not mandatory and are often deemed unnecessary.

5.2.2 Study design

Only baseline results of the FACE TIA study are reported in this thesis. However, as 3, 6 and 12 month follow-up data are collected and analysed, the results will provide a more insightful account of the course of TIA, and provide a greater understanding of the prognosis after TIA. This will add to the current evidence base, not only in terms of time-to-stroke and survival, but also in terms of patients' perceptions of their physical and mental health after TIA, and how this changes over time. The latter has scarcely been reported before (Hickie et al, 2003). In terms of recruitment, patients meeting the inclusion criteria were recruited from TIA clinics consecutively to eliminate selection bias. "Healthy" control patients from GP practices were identified as suitable matches for TIA patients using anonymous databases containing essential information only (year of birth, GP postcode, gender and unique ID). "Healthy" control patients were then selected at random using a quasi-computerised random number generator in Microsoft Office Excel (Microsoft Corporation, 2007).

The main limitation of the results reported here stems from the small sample size, which has a huge implication on the effect size and power of the results. Consequently the preliminary findings need to be interpreted with caution. From the sample size calculation, yielded from this analysis, a sample size of 458 (almost double) is needed to achieve 90% power at a 0.05 level of significance.

5.2.3 Response rates

From the results it can be seen that the recruitment rate of "healthy" controls was very low. Only one in ten individuals consented to participate. In part this may be due to the recruitment method. Controls were invited by post rather than face-to face, by a medical professional whom they trust. The low recruitment rate may also reflect reduced incentive; as they have not suffered a cerebrovascualr event they may be less interested in the results of the study. There is a chance that the small proportion of "healthy" individuals that did respond reflected the "worried-well" population, especially given that the prevalence of anxiety in this group exceeded 20% (HADS-A > 4). The "worried-well" have an obsessional preoccupation with the idea or the thought that they are currently (or will be) experiencing a physical illness (Criqui et al., 1979). Consequently self-reflection on their health is likely to be more negative. To reduce the chances of obtaining a "worried-well" control group in the future, participants could be screened for hyphochondriasis. Alternatively, a more representative sample could be achieved by recruiting in person or by phone. Recruitment could be performed during routine check-up appointments at the GP practice. However patients should not be recruited during GP consultations resulting from self-referral, as the latter would favour an un-well population.

5.2.4 Outcome measures

So far the BUCS has only been administered to participants who have a confirmed TIA. No BUCS data is currently available for "healthy" control participants who have been recruited to the study. Consequently the effect of TIA on cognition has been assessed using published cut-off scores for "healthy" controls, collected as part of a previous study, rather than actual scores. In addition, although the BUCS is highly standardised in terms of administration and scoring, inter-rater reliability has not been formally assessed. Certain measures were undertaken to try and maximise inter-rater reliability; BUCS administers were all required to attend a 2-day training course, refresher courses were also provided and assessments were chosen at random for triple-marking and any discrepancies/inconsistencies were discussed with all BUCS assessors to encourage uniform marking.

Although some scientists are sceptical about the use of patient-based outcome measures, patients' perspectives of their own health are being recognised as increasingly important in research. This is illustrated by the World Health Organisation (1947), who describe health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". Patients' perspectives are particularly relevant to health related quality of life, which "in clinical medicine represents the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" (Schipper et al., 1996). The psychometric theory e.g. validity, reliability etc. of patient-based measures provides further theoretical support for their use. The psychometric properties of the HADS and NEADL in stroke patients have been discussed chapter 3. The measures appear to perform well in the population studies here, with no obvious ceiling effects.

5.2.5 Statistical methods

To avoid selective reporting, pre-specified predictor variables were entered into multiple regression models using forced entry, rather than getting the computer software to search for predictors based on mathematical criteria, which takes advantage of random sampling variation. Meaningful predictor variables were chosen based on study aims, previous research and theoretical reasoning: Thus, minimising statistical biases.

5.3 Epilogue

The increasing evidence base emerging from quantitative and qualitative research offers insights into the impact of TIA on different dimensions of health status including psychological well-being, cognitive functioning and physical functioning.

The baseline data collected from the FACE TIA cohort to date supports previous research suggesting that patients diagnosed with TIA are likely to be more depressed and more cognitively impaired than the general population. It is unclear how much of the observed association between cerebrovascular disease and cognitive dysfunction and/or depression is mediated by cardiovascular risk factors, and/or whether TIA has a direct causal relationship. However it is likely that TIA patients would benefit from targeted health education campaigns and active management. Strong interactions between cognition, feelings of anxiety and depression and activities of daily living, infer that improving one outcome could potentially improve other outcomes.

The FACE TIA study aims to follow-up participants at 3, 6 and 12 months after their diagnosis. It will be interesting to see how depressed mood and cognitive impairments in TIA patients change over time, compared to other clinical groups and "healthy" controls. It will also be interesting to see how these outcomes affect participants' health in terms of service

use (contact with health-care providers) and the occurrence of clinically significant events including stroke.

5.3.1 Future research

Patients with suspected TIA are routinely screened for stroke risk, and are managed according to this risk. The visible neurological symptoms associated with TIA should not only act as an alarm for impending stroke but could be used as an opportunity to screen for depression and cognitive function. Attending to and treating such conditions is important. Not only could this improve patients' quality of life after TIA but it could also improve compliance to medical management and behaviour modification aimed at reducing stroke risk. Future research could be aimed at developing and evaluating interventions such as cognitive reappraisal and developing effective coping strategies.

Modest changes in a large proportion of the population can have a greater impact on public health compared to dramatic changes in a smaller "high-risk" population (Rose, 1988). Consequently, a large proportion of the general population experiencing minor deficits associated with TIA may pose a significant public health burden through a shift of a substantial proportion of the population to lower levels of health status.

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APPENDICES

Appendix 1: Systematic review search strategy (formulated in Ovid MEDLINE)

1	exp *Ischemic Attack, Transient/ep, mo, pc, rh, th, co, di, nu [Epidemiology, Mortality, Prevention & Control, Rehabilitation, Therapy, Complications, Diagnosis, Nursing]
2	exp "Activities of Daily Living"/
3	exp "Quality of Life"/
4	exp Depression/
5	exp Fatigue/
6	exp Emotions/
7	exp Cognition/
8	disab$.ab,hw,ot,ti,nm.
9	handicap$.ab,hw,ot,ti,nm.
10	function$.ab,hw,ot,ti,nm.
11	dependen$.ab,hw,ot,ti,nm.
12	mobil$.ab,hw,ot,ti,nm.
13	exp Dysarthria/
14	exp Aphasia/
15	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	1 and 15
17	exp brain ischemia/ or exp stroke/ or exp brain infarction/
18	"TIA".ab,hw,ot,ti.
19	(transient adj3 ischem$).ab,hw,ot,ti.
20	18 or 19
21	1 or 17
22	20 and 21
23	15 and 22
24	23 and 1991:2012.(sa_year).
25	24 and "Humans" [Subjects]
26	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort studies/ or exp longitudinal studies/ or exp cross-sectional studies/ or exp control groups/
27	25 and 26
28	(transient adj3 isch?emi$ adj3 (brain$ or cerebral or attack)).ab,hw,ot,ti.
29	18 or 28
30	21 and 29
31	15 and 30
32	26 and 31
33	32 and 1991:2012.(sa_year).
34	33 and "Humans" [Subjects]

Appendix 2: Data extraction forms

Reference: (Bos et al., 2007)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, population-based, cohort		1
Location *Urban/rural?* *Country?*	Holland (Rotterdam)	1	
Sampling frame *(period of recruitment, follow-up)*	1990-1993 3 follow-up surveys (1993-1995, 1997-1999, and 2002-2004)	1	
Study group			
Sample size	282 focal TNA (TIA); 228 non-focal TNA, and 38 mixed TNA	1	
source of participants *(e.g. community, hospital, GP practice)*	community-dwelling Rotterdam Study participants	1	
recruitment method Consecutive or random?	Population (all inhabitants of Ommoord district, Rotterdam)	1	1
Inc/exc criteria	≥55 years; free from stroke, myocardial infarction, and dementia at baseline	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Variable - consulted a neurologist, GP or another physician, or reported event at research centre Clinical diagnoses verified by experienced stroke neurologist No brain-imaging therefore not able to rule out possible stroke	1	1
Time of recruitment relative to TIA	Pre-TIA (although participants with TNA before baseline were not excluded)	1	
Control group			
Sample size	5514 non-stroke/TIA controls	1	
source of participants *(e.g. community, hospital, GP practice)*	community-dwelling Rotterdam Study participants	1	
recruitment method Consecutive or random?	Population (all inhabitants of Ommoord district, Rotterdam)	1	1
Inc/exc criteria	≥55 years; free from TNA, stroke, myocardial infarction, and dementia at baseline	1	
Measurement of outcome			
Outcome Measures and end-points	Outcome measures: Alzheimers disease; vascular dementia (diagnosis made by criteria by a panel consisting of a neurologist, a neuropsychologist, and a research physician in accordance with internationally accepted criteria, and in combination with information from general practitioners, the Regional	1	

	Institute for Outpatient Mental Health Care, the municipality, and the hospitals) End-points: Stroke, ischemic heart disease, dementia and death		
Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	Criteria for diagnosing and classifying dementia are internationally accepted (references given)		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Yes. The panel had "no adequate information on TNAs at baseline."		1
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	6125 invited, 6062 consented	1	
N Lost to follow-up + reasons: Similar between groups?	High retention (follow-up completed for 96.2% of potential person-years) Reasons for loss to FU not given	1/2	1
Missing data (n for each outcome) Similar between groups?	Data appears to be complete	0	1
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Age, gender, BP, Intima-media thickness, C-reactive protein, Cholesterol, High-density lipoprotein, Uric acid, Waist-hip ratio, BMI, Mini-Mental State Examination, smoking history, Atrial fibrillation, Diabetes mellitus, Hypertension, heart surgery, Angina pectoris, education	1	1
Were p values and confidence intervals reported at baseline? Were groups comparable on all important	Neither P values nor CI reported at baseline Both groups ≥55 years and free from myocardial infarction, and dementia at	0	1

confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	baseline (selection criteria) Associations between baseline characteristics and risk of TNA assessed with adjusted Cox proportional hazards models		
Interpretation of results – other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	No evidence of sample size/ power calculation		0
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Hazard Ratios for the Association Between Incident TIA and Risk of Subsequent Dementia	1	
Were confidence intervals provided in the main and subsidiary analyses?	Yes	1	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Bossema et al., 2006)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, case-control cross-sectional analysis therefore not able to infer causal relationship		0
Location *Urban/rural?* *Country?*	Holland (Nieuwegein, Utrecht)	1	
Sampling frame *(period of recruitment, follow-up)*	Not specified	0	
Study group			
Sample size	41	1	
source of participants *(e.g. community, hospital, GP practice)*	Symptomatic patients on waiting list for unilateral Carotid endarterectomy (symptoms inc ≥1 episode of hemispheric/ retinal TIA)	1	
recruitment method Consecutive or random?	Not clear	0	9
Inc/exc criteria	No history of minor or major stroke (evident from medical records)	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Degree of carotid stenosis assessed with duplex ultrasonography TIA diagnostic criteria not specified No brain-imaging therefore not able to rule out possible stroke	1	9
Time of recruitment relative to TIA	Not reported (1 day before CEA)	0	
Control group			
Sample size	44 non-stroke/TIA controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Advert in local paper	1	
recruitment method Consecutive or random?	Controls rewarded for participation (possible source of incentive bias)	1	0
Inc/exc criteria	No history of Cerebrovascular or psychiatric disease	1	
Measurement of outcome			
Outcome Measures and end-points	Battery of neuropsychological tests: Attention and working memory –Digit Span forward and backward Tests and Dichotic Listening Test Verbal memory - Word Learning Test and The Doors Test Verbal Fluency Psychomotor speed and executive functioning - Trail Making Test parts A and B	1	

	and the Motor Planning test Manual dexterity - The Finger Tapping Test Visuospatial function - Line Orientation Test Dutch shortened Profile of Mood States (POMS) - measures anger, tension, depression, vigor, and fatigue		
Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	All tests were referenced Reliability: Reproducibility enhanced as all administrators trained by experienced neuropsychologist		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Doesn't appear so as patients and controls examined in different locations (Tests are interviewer-administered therefore blinding is important)		0
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Not reported	0	
N Lost to follow-up + reasons: Similar between groups?	n/a – cross sectional	n/a	n/a
Missing data (n for each outcome) Similar between groups?	11 patients and 4 controls did not complete Dichotic listening test due to hearing problems (used linear regression analysis to impute scores) 3 patients did not complete Trail making test (replaced with arbitrary high scores)	1	1
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a – cross sectional		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Age, gender, education, hypertension, Hypercholesterolaemia, Diabetes mellitus, Heart disease	1	1
Were p values and confidence intervals reported at baseline?	P values reported for age, gender and education, but not CV risk factors. No CI reported at baseline.	1/2	1

Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	Age, gender & education were comparable between groups at baseline. Hypertension, hypercholesterolaemia, diabetes mellitus, and heart disease greater in patient group (analyzed with multiple post-hoc comparisons using the Bonferroni correction). Also corrected for significant differences in mood scores by entering these as covariates in the analyses (MANCOVA and ANCOVA)		
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	No evidence of sample size/ power calculation		0
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	MANOVA and ANOVA	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Charoenkitkarn et al., 2009)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, cohort		1
Location *Urban/rural?* *Country?*	Thailand, (Bangkok & Ayutthaya)	1	
Sampling frame *(period of recruitment, follow-up)*	Year of recruitment not specified. TIA group recruited at admission & followed up 3, 10 and 30 days after TIA or minor surgery (controls)	1/2	
Study group			
Sample size	52	1	
source of participants *(e.g. community, hospital, GP practice)*	Outpatient and emergency departments of 4 tertiary hospitals	1	
recruitment method Consecutive or random?	"convenience"	1	9
Inc/exc criteria	≥24 years; able to read & write; able to take/ respond to tests/questions; without hearing loss, eye problems, history of substance abuse/dependency, Cancer, HIV/AIDS, head injury, ADHD or any other neurological disorder other than TIA; Not on meds to alter cognitive processing; Not depressed	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Clinical diagnosis confirmed by neurologist No brain-imaging therefore not able to rule out possible stroke	1	1+
Time of recruitment relative to TIA	At admission for TIA	1	
Control group			
Sample size	52 non-vascular (minor-surgery) controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Outpatient departments	1	
recruitment method Consecutive or random?	"identified by way of their patient record, while they were being seen in an outpatient's department" Susceptible to bias	1	0
Inc/exc criteria	Minor surgery patients; no known hypertension, diabetes, vascular disease or Hx stroke/TIA	1	
Measurement of outcome			
Outcome Measures and end-points	**ATTENTION** **Distractibility** Necker Cube Pattern control test (NCPCT)	1	

	digit span forward (DSFT) trail making A test (TMAT) **Impulsivity** Barratt impulsiveness scale (BIS) **Irritability** visual analogue scale (VAS) **MEMORY** **Working Memory** digit symbol substitution test (DSST) digit span backward (DSBT) **Learning and Memory** Hopkins verbal learning test-revised (HVLT-R)		
Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	English versions of cognitive tests are referenced All instruments translated into Thai. Reliability/acceptability: Pilot run to assess test-retest reliability (all acceptable r=0.812-0.985). Reproducibility enhanced as tests appear to have been administered to all by same assessor Validity: Content and face validity of Thai versions assessed and modified accordingly.		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	No (Tests are interviewer-administered therefore blinding is important)		0
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Not reported	0	
N Lost to follow-up + reasons: Similar between groups?	4 TIA participants had stroke within 30 days. They were subsequently removed from analysis with their matched controls and replaced.	1	1
Missing data (n for each outcome) Similar between groups?	Not reported	0	9
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics	Gender, age, education	1	0

given (list) All necessary baseline characteristics reported?			
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	Neither p-values nor CIs reported at baseline Controls matched to TIA group by age, gender and education Authors state that, "no significant differences were found among the demographics between those who had experienced a TIA and those who had experienced minor surgery"	0	1
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	Power calculation to .8, p=.05, effect size of .25 carried out		1
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Repeated measures ANOVA	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Duncan et al., 1997)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective case-control cross-sectional analysis therefore not able to infer causal relationship		0
Location *Urban/rural?* *Country?*	USA (Kansas, North Carolina, New York)	1	
Sampling frame *(period of recruitment, follow-up)*	1992	1	
Study group			
Sample size	184	1	
source of participants *(e.g. community, hospital, GP practice)*	Academic Medical Center Consortium records (inpatients); United HealthCare records (inpatients and outpatients); Bowman Gray site of the Cardiovascular Health Study (community sample)	1	
recruitment method Consecutive or random?	A percentage of individuals who met the inclusion criteria were selected, to ensure equal sample groups Not clear if random	1	9
Inc/exc criteria	History of TIA but not stroke	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	ICD-9 codes (verified by medical record review), supplemented by information from prospective follow-up No brain-imaging therefore not able to rule out possible stroke	1	1
Time of recruitment relative to TIA	Not specified	0	
Control group			
Sample size	654 asymptomatic individuals at a high-risk of stroke	1	
source of participants *(e.g. community, hospital, GP practice)*	As TIA group	1	
recruitment method Consecutive or random?	A percentage of individuals who met the inclusion criteria were selected, to ensure equal sample groups Not clear if random	1	9
Inc/exc criteria	Asymptomatic individuals without neurological insult, at high-risk of stroke (based on ICD-9 codes)	1	
Measurement of outcome			
Outcome Measures and end-points	Activities of daily living: Barthel Index (BI)	1	

	Depression: Medical Outcomes Study Short Form 36 (MOS-36) Health status: Centre for Epidemiological Studies Depression Scale (CES-D) Utility for current health state: Time Trade-off utility (TTO)		
Were all subjects assessed using the same procedure?	No (participants from one database were interviewed face-to-face; others were interviewed by phone) To ensure that responses from the two interview methods were comparable, telephone interviews were conducted on a 10% sample of CHS respondents. Responses did not differ significantly between telephone and in-person interviews. However phone interviews may have omitted individuals with language or cognitive dysfunction, leading to possible sampling bias.		0
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	All measures were referenced Appropriateness/responsiveness: Breadth and ceiling effects taken into account	1	1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Not stated (Tests are interviewer-administered therefore blinding is important)		9
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Consented 1253; invited 2247	1	
N Lost to follow-up + reasons: Similar between groups?	n/a – cross-sectional	n/a	n/a
Missing data (n for each outcome) Similar between groups?	Not reported	0	9
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a – cross-sectional		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Gender, race, education, living arrangement, employment status, social support & co-morbid diseases	1	1

Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	P-values reported. CI not reported. "Asymptomatic group was older and included a relatively higher percentage of whites" "The TIA group had relatively less social support" "TIA group were more likely to have diabetes, ischemic heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, renal disease, and rheumatoid arthritis" than the asymptomatic group Regression analysis was used to determine whether patient group (stroke, TIA, asymptomatic), other comorbid diseases, and/or Barthel scores were predictive of responses to any of the eight different domains of the MOS-36 and/or the CESD	1/2	1
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	No evidence of sample size/ power calculation		0
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Groups were compared with X^2 statistics for categorical variables and ANOVA for continuous variables	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Referencce: (Guyomard et al., 2011)

		Quality of reporting*	Quality of design, conduct & analysis[†]
Design	Prospective, case-control cross-sectional analysis therefore not able to infer causal relationship	1	0
Location *Urban/rural?* *Country?*	UK (East of England)	1	
Sampling frame *(period of recruitment, follow-up)*	Aug 2008 – Nov 2008	1	
TIA group			
Sample size	68	1	
source of participants *(e.g. community, hospital, GP practice)*	Neurovascular clinic, Norfolk & Norwich University Hospital	1	
recruitment method Consecutive or random?	invitation letter sent by post from the out-patient department to patients attending TIA clinic for suspected TIA (supplementary material)	1	1
Inc/exc criteria	First ever TIA; aged ≥ 45; No pre-existing cognitive impairment and/or depression; no history of stroke	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Focal neurological deficit < 24 hours duration of presumed vascular origin, confirmed by highly experienced stroke physician No brain-imaging therefore not able to rule out possible stroke	1	1+
Time of recruitment relative to TIA	Recruited at clinic (assume within 1 week of symptom onset based on current national guidelines)	0	
Control group			
Sample size	68 non-vascular controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Dermatology and neurology clinics, Norfolk & Norwich University Hospital	1	
recruitment method Convenience, consecutive, random?	identified age and sex-matched controls from urology and dermatology clinic lists, and invited potential controls prior to their clinic appointment (supplementary material)	1	1
Inc/exc criteria	No vascular risk factors or evidence of vascular disease; No pre-existing cognitive impairment and/or depression	1	
Measurement of outcome			
Outcome Measures and end-points	Cognition: MoCA (Montreal Cognitive Assessment)	1	

Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	MoCA referenced Appropriateness: Authors acknowledge that MoCA lacks breadth Reliability: Reproducibility enhanced as MoCA administered to all by same assessor and specific instructions provided to standardize assessment. Responsiveness: Authors cite that MoCA is more specific and sensitive in detecting early cognitive decline than other measures such as MMSE		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Not reported (MoCA is interviewer-administered therefore blinding is important)		0
Interpretation of results - completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	146 invited, 136 consented (5 declined in each group) Reasons not reported	1	
N Lost to follow-up + reasons: Similar between groups?	n/a – cross sectional	n/a	n/a
Missing data (n for each outcome) Similar between groups?	Not reported	0	9
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	Cross-sectional.		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Age, gender, hypertension, hypercholesterolaemia, diabetes, atrial fibrillation, family history of TIA/stroke, history of MI, smoking status.	1	1
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	P-values reported. CI not reported. Control group matched to TIA group by age (+/- 1 year), gender No pre-existing cognitive impairment and/or depression in both groups (inclusion criteria) Association between cog impairment and vascular risk factors assessed using Chi-squared tests.	1/2	1

Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	Yes (only adequate to detect overall group differences. Underpowered for sub-group analysis)		1
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Group comparison with student t-test	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Hickie et al., 2003)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, cohort		1
Location *Urban/rural?* *Country?*	Australia (Dubbo region)	1	
Sampling frame *(period of recruitment, follow-up)*	Baseline measures 1988-1989; Follow-up in 1998	1	
Study group			
Sample size	19	1	
source of participants *(e.g. community, hospital, GP practice)*	Community	1	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	Non-institutionalized residents born before 1930 Those who had a clinical stroke in the intervening decade were excluded.	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Hospital discharge coding against usual criteria No brain-imaging therefore not able to rule out possible stroke	1	1
Time of recruitment relative to TIA	Pre-TIA	1	
Control group			
Sample size	89 (44- hypertensive; 45 – normotensive) controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Community	1	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	Non-institutionalized residents born before 1930 Hypertensive: using hypertensive medication at baseline Normotensive: systolic BP<140mmHg and diastolic BP<90mmHg at baseline Those who had a clinical stroke in the intervening decade were excluded.	1	
Measurement of outcome			
Outcome Measures and end-points	Depression: Centre for Epidemiological Studies Depression Scale (CES-D), Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) codes, Mixed Depression and Anxiety Score (MDAS)	1	
Were all subjects assessed using the same	Yes although DSM-IV only reviewed if participants responded positively when		0

procedure?	asked about symptoms of depression NB. Different measures used to assess depression at baseline and FU.		
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	References given for outcome measures Responsiveness: Identifies on-going debate with DSM-IV threshold – as justification of using @ least one of two key features for at least 2 weeks		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	No (may result in unintentional biases when scoring participants/ forming diagnoses)		0
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Not reported	0	
N Lost to follow-up + reasons: Similar between groups?	TIA=3/19 Hypertensive=6/44 Normotensive=5/45 Reasons not given	1/2	1
Missing data (n for each outcome) Similar between groups?	Not reported	0	9
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Age, gender, diabetes, prior coronary heart disease, cholesterol, smoking status, depression	1	1
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or*	Significance recorded as $p<0.05$ or $p<0.01$(specific p-values and CI not reported) Reporting of potential confounding factors for depression is limited however one could assume equal distribution between groups due to chance (potential confounders that are likely to vary between groups due to cardiovascular origin are reported) Diabetes, heart disease and smoking status are significantly different between	1/2	0

sensitivity analysis to correct, control or adjust for confounding factors.	groups at baseline. This is not accounted for in the analysis.		
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	No evidence of sample size/ power calculation		0
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Descriptive statistics Significance assessed using Chi-squared	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Howard et al., 2007)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, case-control cross-sectional analysis therefore not able to infer causal relationship		0
Location *Urban/rural?* *Country?*	USA (nationwide) Twenty percent of the sample was selected from the "buckle" of the Stroke Belt (coastal plain region of NC, SC, and Ga), 30% from the Stroke Belt states (remainder of NC, SC, and Ga plus Ala, Miss, Tenn, Ark, and La), and the remaining 50% from the other 48 contiguous United States.	1	
Sampling frame *(period of recruitment, follow-up)*	Jan 2003 – Mar 2006	1	
Study group			
Sample size	818	1	
source of participants *(e.g. community, hospital, GP practice)*	Subset of REGARDS cohort study (commercially available lists of residents)	1	
recruitment method Consecutive or random?	all eligible individuals approached to participate	1	1
Inc/exc criteria	Not reporting stroke but self reporting TIA ("Were you ever told by a physician that you had a mini-stroke or TIA, also known as a transient ischemic attack?")	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Self-report	1	0
Time of recruitment relative to TIA	Assume variable based on recruitment methods	0	
Control group			
Sample size	16,090 non-stroke/TIA controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Subset of REGARDS cohort study (commercially available lists of residents)	1	
recruitment method Consecutive or random?	all eligible individuals approached to participate	1	1
Inc/exc criteria	Those not reporting stroke, TIA, or stroke symptoms	1	
Measurement of outcome			
Outcome Measures and end-points	physical function (PCS-12) Mental function (MCS-12)	1	
Were all subjects assessed using the same	Yes		1

procedure?			
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	All measures referenced Validity: "well-validated and widely used indices" Interpretability: "Relatively small differences in these scores are associated with substantial health impacts"		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Not reported (Tests are interviewer-administered therefore blinding is important)		9
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	21959 invited, 21803 consented (participants who refused to answer questions relating to stroke history/symptoms, or answered "don't know" were removed from the analysis) NB. These figures include stroke patients who formed another study group	1	
N Lost to follow-up + reasons: Similar between groups?	n/a – cross sectional	n/a	n/a
Missing data (n for each outcome) Similar between groups?	Not reported	0	9
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a – cross sectional		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Ethnicity, Hypertension, Diabetes, Smoking status, Lipoproteins, Heart disease, Atrial fibrillation, Exercise, BMI, Income, Education	1	
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust*	P-value stated but CI not reported Baseline characteristics sufficiently detailed to account for many potential confounding factors. Authors indentify 4 classes of potential confounders (demographic, cerebrovascular, physical fitness & socioeconomic) Adjustments made in set of incremental linear regression models with additional analyses at each stage	1/2	1

for confounding factors.			
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	No evidence of sample size/ power calculation		1
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Type of analysis not disclosed.	0	
Were confidence intervals provided in the main and subsidiary analyses?	Yes, 95% CI reported	1	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Iddon et al., 1997)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, cohort however only pre-surgery scores meet review criteria therefore cross-sectional analysis (not able to infer causal relationship)		0
Location *Urban/rural?* *Country?*	UK (Cambridge & Newcastle)	1	
Sampling frame *(period of recruitment, follow-up)*	Not specified	0	
Study group			
Sample size	30	1	
source of participants *(e.g. community, hospital, GP practice)*	TIA patients admitted to Addenbrooke's Hospital for unilateral carotid endarterectomy	1	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	Severe carotid artery stenosis (≥70%) no history of stroke, no depression or dementia at baseline	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Not specified	0	9
Time of recruitment relative to TIA	Not reported (48–72 h before CEA)	0	
Control group			
Sample size	30 Healthy volunteers	1	
source of participants *(e.g. community, hospital, GP practice)*	Not stated	0	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	Healthy volunteers with no depression or dementia at baseline	1	
Measurement of outcome			
Outcome Measures and end-points	Cambridge Neuropsychological Test Automated Battery (CANTAB)	1	
Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability,	CANTAB is referenced Reliability/Validity: Evidence given for validity and test-retest reliability		1

acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*			
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Not reported (although CANTAB is computerised the experimenter controlled the computer therefore blinding is important)		9
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Not stated	0	
N Lost to follow-up + reasons: Similar between groups?	n/a – cross-sectional	n/a	n/a
Missing data (n for each outcome) Similar between groups?	Numbers reported in table 1 (missing data equal between groups)	1	1
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a – cross-sectional		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	None reported	0	0
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	Baseline/demographic characteristics not listed Controls matched to TIA group by age and IQ None of the patients included were demented or depressed at baseline as measured by MMSE and Beck depression index CV risk factors not measured (have been associated with increased cognition in other studies)	0	9
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	No evidence of sample size/ power calculation		0

Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Comparisons between preoperative scores and control scores using unmatched *t*-tests	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Rao et al., 1999; Rao et al., 2001; Rao, 2002)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, case-control cross-sectional analysis therefore not able to infer causal relationship		0
Location *Urban/rural?* *Country?*	UK (London)	1	
Sampling frame *(period of recruitment, follow-up)*	Not specified	0	
Study group			
Sample size	25	1	
source of participants *(e.g. community, hospital, GP practice)*	Community within catchment of inner city teaching hospital, on waiting list for carotid endarterectomy	1	
recruitment method Consecutive or random?	"consecutive patients aged 65 years or older who were on the waiting list for carotid endarterectomy"	1	1
Inc/exc criteria	History of ≥ 1 TIA and stenosis >70% on 1 or both internal carotid arteries; on waiting list for carotid endarterectomy; no history of stroke or clinical evidence of stroke during preoperative screening; no history of PVD, drug or alcohol misuse, Parkinson's disease, head injury, epilepsy, carcinomatosis or uncontrolled metabolic, endocrine, or respiratory disorders; >65 yrs	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Not stated	0	9
Time of recruitment relative to TIA	affect of time since first TIA (categorised as more/less than 5 years) on outcomes reported in analysis but exact numbers not presented	0	
Control group			
Sample size	25 vascular & 25 orthopaedic controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Community within catchment of inner city teaching hospital On waiting list for femoropopliteal bypass (vascular) or elective THR/TKR for OA (orthopaedic)	1	
recruitment method Consecutive or random?	Authors specify PVD group recruited consecutively. Recruitment method of orthopaedic controls not explicit.	1	1/2
Inc/exc criteria	**Vascular (PVD):** On waiting list for femoropopliteal bypass **Orthopaedic:** elective THR/TKR for OA (6-12 months before interview); no history of PVD **All:** no history of stroke/TIA, drug/alcohol misuse, Parkinson's, head injury,	1	

	epilepsy, carcinomatosis, uncontrolled metabolic/endocrine/respiratory disorders; not considered by GP or interviewer to be too frail, cognitively impaired, uncommunicative; >65 yrs		
Measurement of outcome			
Outcome Measures and end-points	**1999 & 2002** CAMCOG: (1) abstract thinking, (2) attention, (3) calculation, (4) language, (5) memory, (6) orientation, (7) praxis, (8) perception (recognition), and (9) MMSE; Trail-Making Test; BDCS; Controlled Word Association Test. **2001** Depression: Hamilton rating Scale for Depression (HRSD), Fifteen-item Geriatric Depression Scale (GDS-15), Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) codes, wish to die and suicidal ideation in past year Handicap: London Handicap scale Social support: Social support scale	1	
Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	References given for all outcome measures Reliability: Reproducibility enhanced as all participants were interviewed by the same assessor		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	No (Tests are interviewer-administered therefore blinding is important)		0
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Invited 155; Consented 100	1	
N Lost to follow-up + reasons: Similar between groups?	n/a – cross-sectional	n/a	n/a
Missing data (n for each outcome) Similar between groups?	Not reported	0	9

If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a – cross-sectional		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Age, sex, marital status, education, race, handedness, physical illness scale score, BP reported in table. Others e.g. diabetes, drug intake not reported in tables but used to test for associations in results.	1	1
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	Significance recorded as p<0.05 (specific p-values and CI not consistently reported) No significant difference in mean age, gender, educational status, racial origin, or handedness found between groups Exclusion criteria comparable between groups Variables entered in logistic regression (in descending order of P value) including verbal fluency (F); diastolic blood pressure; verbal fluency (A); Trail-Making B time; verbal fluency (S); systolic blood pressure; BDCS; age; suicidal thinking; depression (per Diagnostic and Statistical Manual of Mental Disorders); diabetes; cardiovascular disease, hyperlipidemia.	1/2	1
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	Powered to .8 for GDS and HRS (Rao, 2001)		1
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	ANOVA	1	
Were confidence intervals provided in the main and subsidiary analyses?	Yes	1	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Walters et al., 2003)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, cohort		1
Location *Urban/rural?* *Country?*	UK (London)	1	
Sampling frame *(period of recruitment, follow-up)*	Year of recruitment not specified. TIA group recruited within 15 days of event & followed up at 6 and 12 months	½	
Study group			
Sample size	60	1	
source of participants *(e.g. community, hospital, GP practice)*	Neurovascular clinic	1	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	First, isolated TIA; MMSE ≥ 28/30); no evidence of general/focal atrophy on MR imaging; no clinical/ radiological evidence of established stroke; Alcohol consumption ≤ 3 units daily; no severe hypertension, significant ischaemic heart disease, peripheral vascular disease, or carotid stenosis	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Consultant neurologist with special interest in cerebrovascular disease; reinforced by neuro-imaging	1	1++
Time of recruitment relative to TIA	Within preceding 15 days	1	
Control group			
Sample size	26 non-vascular controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Not stated	0	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	No history of stroke or TIA; no evidence of general/focal atrophy on MR imaging; no clinical/ radiological evidence of established stroke; Alcohol consumption ≤ 3 units daily; no severe hypertension, significant ischaemic heart disease, peripheral vascular disease, or carotid stenosis.	1	
Measurement of outcome			
Outcome Measures and end-points	Dementia: Mini-Mental State Examination (MMSE)	1	

	(new lesion occurrence & atrophy rates also recorded through MRI)		
Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	Reference given for MMSE Responsiveness: MMSE has a known ceiling effect in this population		0
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Not clear (MMSE is interviewer-administered therefore blinding is important)		9
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Not reported	0	
N Lost to follow-up + reasons: Similar between groups?	Not reported	0	9
Missing data (n for each outcome) Similar between groups?	Not reported	0	9
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	Not reported		9
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Age, gender, BP	1	1
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or*	Significance recorded as $p<0.001$ (specific p-values and CI not consistently reported) Controls matched to TIA group by age & gender Exclusion criteria comparable between groups Patients had non-significantly higher systolic and diastolic blood pressure than controls however regression techniques were used to demonstrate any	1	1

sensitivity analysis to correct, control or adjust for confounding factors.	relation between atrophy and blood pressure in the patient group		
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	No evidence of sample size/ power calculation		0
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	Descriptive stats for MMSE t-tests for imaging outcomes	1	
Were confidence intervals provided in the main and subsidiary analyses?	CI only reported for imaging outcomes	0 (1 for imaging outcomes)	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Xin-rong et al., 2005)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, case-control cross-sectional analysis therefore not able to infer causal relationship		0
Location *Urban/rural?* *Country?*	China	1	
Sampling frame *(period of recruitment, follow-up)*	Jan 2002-June 2003	1	
Study group			
Sample size	35	1	
source of participants *(e.g. community, hospital, GP practice)*	Geriatric department, Urumqi General Hospital (inpatients and outpatients)	1	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	Right-handed male TIA patients with no other inter-cranial disease visible on CT; normal visual and auditory functions; independent; no mental disorder, severe heart, lung, liver or kidney disease	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Diagnosis conformed to classification & diagnostic criteria for Chinese National conference of cerebral vessels diseases; head CT excluded other intracranial diseases	1	1++
Time of recruitment relative to TIA	within 72 hours of symptom onset	1	
Control group			
Sample size	33 healthy controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Patients visiting hospital for physical examination	1	
recruitment method Consecutive or random?	Not stated	0	9
Inc/exc criteria	Healthy right-handed male volunteers; no history of mental disorder	1	
Measurement of outcome			
Outcome Measures and end-points	Scale of elderly cognitive function (SECF)	1	
Were all subjects assessed using the same procedure?	Yes		1
Have appropriateness, reliability,	Not clear. No justification for outcome measure choice or references given		9

validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*			
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	Doesn't appear so as patients and controls examined in different locations (SECF is interviewer-administered therefore blinding is important)	0	0
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	Not reported	0	
N Lost to follow-up + reasons: Similar between groups?	n/a – cross sectional	n/a	n/a
Missing data (n for each outcome) Similar between groups?	None	1	1
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a – cross sectional		n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	gender, handedness (selection criteria) age (mean, range and SD), education (cases) given for both groups		0
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	P values & CI not reported at baseline but control group matched to TIA group by age, gender, education & handedness Inclusion criteria state no history of mental disorder (both groups) Inclusion criteria less strict for control group (normal visual and auditory functions, independence, and no severe heart, lung, liver or kidney disease only specified for TIA group) BP not reported but possible confounder (has been identified as a risk factor for cognitive decline in other studies)	0	9
Interpretation of Results – Other			
Was the study designed to have sufficient power to detect the effect(s) of interest?	No evidence of sample size/ power calculation		0

Was a sample size calculation or power calculation performed?			
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	No. Not all SECF item results reported.		0
What statistical test was used to measure effect?	T-test	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Reference: (Zinn et al., 2007)

		Quality of reporting*	Quality of design, conduct & analysis†
Design	Prospective, case-control cross-sectional analysis therefore not able to infer causal relationship		0
Location *Urban/rural?* *Country?*	USA (South East)	1	
Sampling frame *(period of recruitment, follow-up)*	Recruitment over 2..5 year period (exact years not specified)	1/2	
Study group			
Sample size	9	1	
source of participants *(e.g. community, hospital, GP practice)*	Inpatient wards at veterans affairs medical centre	1	
recruitment method Consecutive or random?	"Consecutive"	1	1
Inc/exc criteria	ruled out for acute stroke; no prior stroke Stroke risk factors "included hypertension, diabetes, hyperlipidemia, cardiovascular disease, peripheral vascular diseases, migraine, smoking, cocaine or alcohol dependence, and sleep apnea."	1	
Case diagnoses *How/who assessed this?* *(standard criteria, definition, clinical judgement)*	Clinical examination, chart review and CT scan by neurologist (where possible diffusion weighted MRI also performed) "Stroke was confirmed by diffusion-weighted MRI, or in several cases where MRI was precluded or inconclusive, from clinical examination, chart review and computed tomography scan by a neurologist. Recruitment of the TIA sample was similar"	1	1++
Time of recruitment relative to TIA	within 10 days of event	1	
Control group			
Sample size	10 "at risk of stroke" controls	1	
source of participants *(e.g. community, hospital, GP practice)*	Inpatient wards at veterans affairs medical centre	1	
recruitment method Consecutive or random?	"convenience"	1	9
Inc/exc criteria	Patients ruled out for stroke and TIA, who had several stroke risk factors (supplemented with additional inpatients, recruited from inpatient general	1	

	medical wards, with a minimum of 3 stroke risk factors.)		
Measurement of outcome			
Outcome Measures and end-points	Battery of neuropsychological tests: • Digit span and picture arrangement subtests from the Wechsler Adult Intelligence Scale, Third Edition • Symbol Digit Modalities Test (SDMT, oral version) • The design fluency and trail making subtests from the Delis-Kaplan Executive Function System (DKEFS) • The Hopkins Verbal Learning Test-Revised (HVLT)	1	
Were all subjects assessed using the same procedure?	yes		1
Have appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility been considered in relation to the outcome measures?*(consider citations, measurement to exposure in different ways, inter/intra-rater reliability checks, measures of internal consistency e.g. cronbach's alpha)*	References given for tests Appropriateness: "Selection of particular tests was guided in part by clinical experience with vascular disease patients". "Battery was deliberately multidimensional in order to measure the various components of executive functioning through multiple tasks, making it possible to obtain at least partial measurement of executive functioning on every patient irrespective of focal symptoms" Reliability/ Validity: "tests all have well-established validity and reliability." Administrators trained in standard administration of the instruments, enhancing inter-rater reliability. Cut-off scores used for analysis (*N.B.* problems of being borderline)		1
Were interviewers and data collectors blind to the case/control status of study subjects and to the hypothesis being tested? Does this matter?	No (tests are interviewer-administered therefore blinding is important)		0
Interpretation of results – completeness			
What percentage of eligible individuals agreed to participate? *(consented/invited)*	325 screened, 83 enrolled + 6 (additional controls), 66 completed test battery (9 didn't meet inclusion criteria, 2 became too ill and 8 refused testing or were discharged prior to testing) NB. These figures include stroke patients who formed another study group One TIA patient had several severely impaired test scores that were outliers, suggestive of a "silent" stroke, and was subsequently excluded from the analyses.	1	
N Lost to follow-up + reasons:	n/a - cross-sectional	n/a	n/a

Similar between groups?			
Missing data (n for each outcome) Similar between groups?	Missing data was as follows: Digit span, 0 missing; HVLT, 1 missing (stroke); design fluency, 11 missing (10 stroke, 1 TIA); picture arrangement, 15 missing (13 stroke, 1 TIA, 1 risk)); SDMT, 21 missing (18 stroke, 2 TIA, 1 risk); and trail making, 25 missing (20 stroke, 4 TIA, 1 risk). "Completion of testing was sometimes precluded by clinical treatment procedures, patient fatigue, or hospital discharge. Sequelae of stroke, such as paresis, aphasia or visual dysfunction, also precluded administration of certain instruments to particular patients." "We assessed whether there was a difference in executive function test performance between those who completed the battery and those who did not complete it, using a t test on the composite impairment ratio (CIR). We also examined whether stroke severity affected battery completion by examining the relationship of severity and number of tests completed." " tests administered toward the end of the battery were less likely to be completed. There was no relationship between stroke severity and number of tests completed, nor was there any difference in the CIR between those who completed the battery and those who did not, for whatever reason".	1	1
If loss-to-follow-up exceeded 20% was this accounted for in the analysis?	n/a	n/a	n/a
Interpretation of results – confounding bias			
Demographic and other baseline characteristics given (list) All necessary baseline characteristics reported?	Age, Years of education, IQ, ethnicity, No. of stroke risk factors, ability to follow commands, ADLs prior to stroke, IADLs prior to stroke	1	1
Were p values and confidence intervals reported at baseline? Were groups comparable on all important confounding factors including demographic characteristics, co-morbid conditions etc? *NB. Take into account matching of control group* OR *have* authors taken account of the confounding factors in the analysis? *E.g. Modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors.*	Neither p-values nor CI reported at baseline Authors state that, "The groups did not differ significantly on any of the listed characteristics"	0	1
Interpretation of Results – Other			

Was the study designed to have sufficient power to detect the effect(s) of interest? *Was a sample size calculation or power calculation performed?*	Target was 100 stroke patients – never achieved. "Original target enrolment was 100 stroke patients, funding and administrative considerations prevented the extension of our enrollment period when recruitment rates fell below our predictions."		0
Did the report avoid selective reporting of results or inappropriate use of methods to achieve a stated or implicit objective? *E.g. were the major results directly related to the a priori hypothesis under investigation? Are both significant and non-significant results reported in a balanced fashion? If, protocol available, do intended and reported analyses match up?*	Yes. Major results directly related to the a priori hypothesis under investigation. Both significant and non-significant results reported in a balanced fashion.		1
What statistical test was used to measure effect?	"We calculated the composite impairment ratio as the percentage of tests failed divided by the number of tests completed". ANOVA was used to compare CIR across groups. Cut-off scores used for analysis (N.B. problems of being "borderline")	1	
Were confidence intervals provided in the main and subsidiary analyses?	No	0	

* 1=reported, 0=not reported, 9=n/a

† 1=Y, 2=N, 9="unclear"

Appendix 3: Participant Information Sheet

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Attach Trust Logo

A Study of Functional, cognitive and emotional outcomes after "mini stroke"

PARTICIPANT INFORMATION SHEET

Invitation

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 is involved. Please take time to read the information below carefully, and discuss it with friends, relatives, and your GP if you want to. If there is anything that is not clear, or if you would like more information, please ask us.

What is the purpose of the study?

A transient ischemic attack (TIA), also known as "mini stroke," produces stroke-like symptoms that usually resolve within 24 hours. Symptoms can include: numbness or weakness in the face, arm or leg, especially on one side of the body; confusion or difficulty in talking or understanding speech; trouble seeing; difficulty walking, dizziness, or loss of balance and coordination. It is assumed that quality of life improves and functional problems (e.g. difficulty in carrying out normal domestic/leisure activities) resolve as these medical symptoms subside. However some research has reported that this is not the case.

The aim of this study is to investigate whether or not patients have a reduced quality of life and/or residual functional problems that adversely influence day to day living, after being diagnosed with TIA. The study will also examine the costs associated with TIA, including personal economic losses e.g. time off work due to illness, and health and social care service provision.

Why have I been invited?

You have been chosen either because:

a) You were referred to a TIA clinic with a suspected TIA.

OR b) Your medical records show that you have never suffered a stroke or TIA and you are a suitable match (in terms of age, gender and place of residence) for someone who has recently suffered a TIA. A group of individuals that closely resemble the group of interest (those with suspected TIA) have an essential role in the study: They serve as a comparison group when the results are evaluated.

In total we aim to recruit 600 individuals to take part in this study.

Do I have to take part?

No, it is up to you. Take time to read this information sheet and decide whether or not you would like to participate. You may wish to discuss your views with friends or family members. If you have any questions feel free to contact a member of the study team (details below).

If you decide you would like to take part please complete the consent form and return it to the University of Birmingham in the pre-paid envelope. You would be free to withdraw at any time and without reason if you later decide that you no longer wish to participate. Your decision would not affect your normal medical care or future access to healthcare in any way.

What would happen to me if I take part?

If you chose to take part we would ask you to complete 4 questionnaires (listed below) and return them to us in a pre-paid, stamped, addressed envelope. In total you would be asked to complete the questionnaires 4 times: straight away and then 3 months, 6 months and 12 months after agreeing to take part. Each set of questionnaires should take no longer than 30 minutes to complete. We might contact you by telephone to answer questions that have been left blank.
The set of questionnaires would include:

i. Nottingham Extended ADL Scale: A measure of independence in performing domestic and leisure activities.
ii. Hospital Anxiety and Depression Scale: A measure of emotion.
iii. Client service receipt inventory: A questionnaire yielding information on use of health and social care services, economic impacts (such as time off work due to illness) and socio-demographic aspects (such as living arrangements).
iv. Cardiovascular risk factors (questions on exercise, smoking and alcohol intake)

In addition to completing these questionnaires we would ask you to take part in cognitive screening. This would include a series of simple tasks to measure your communication, memory, perception and attention skills. The cognitive screen would be administered by a member of the research team that has been trained to conduct the assessment. We would ask you to complete 2, 1 hour sessions at your home, GP practice, hospital or the University of Birmingham, at times convenient to you (within the 1st month after consenting to participate and approximately 12 months later). You would be reimbursed for any travel expenses incurred.

What are the possible benefits of taking part?

Through dissemination of study findings, participants diagnosed with symptoms suggestive of TIA would find out more about the holistic implications of their condition that could have previously been overlooked. Findings could also change future practice and healthcare provision.

Expenses and payments

All of the questionnaires would be sent out with a pre-paid, stamped, addressed return envelope. For the cognitive screening, we would reimburse you for any travel expenses incurred. For travel by car, mileage would be reimbursed at a rate of 40 pence per mile.

What are risks of taking part?

This study does not involve any testing of drugs, devices or procedures therefore there are no real risks or side-effects of taking part. Some of the questionnaires enquire about potentially sensitive issues. You would have the option to refrain from answering these questions. You might wish to contact a member of the research team if you find any of the questions particularly difficult or distressing to answer. Each case would be reviewed and managed on an individual basis.

What if something goes wrong?

If you wish to complain, or have any concerns about any aspect of the way you might have been approached or treated during the course of this study, the normal National Health Service and University complaints mechanisms would be available to you.

Foreseeable circumstances under which the subject's participation might be terminated

The maximum length of participation in the study would be 12 months. As the study is looking at a specific group of people, you would no longer be required participate if you experience a stroke or TIA during the follow-up period. The questionnaires you might have completed would remain in the analysis providing that you were still happy for us to use them.

What happens when the research study stops?

After having completed the last set of questionnaires your participation in the study would end. If you are interested in the study findings we would be happy to send you a report.

Would my taking part in this study be kept confidential?

Yes, all information that is collected about you during the study would be kept strictly confidential.
Your contact details (needed for mail-outs and follow-up telephone calls) would be stored in a locked filing cabinet in a secure, restricted access building in the department of Primary care Clinical Sciences at the University of Birmingham. Information stored electrically would be saved as password protected documents on network restricted computers.
Other personal information such as past medical history and results of TIA clinic assessments (if applicable), would have your name and address removed so that you cannot be identified from it – we use a unique code instead. The questionnaires and results of cognitive screening would also be anonymised.
No identifying information would appear in our published results.

With your permission your GP will be notified of your participation in the study.

Who might have access to my personal information?

Named members of the study team would have access to the information that is collected about you during the study.
To monitor the quality and conduct of research, studies might be chosen at random for audit. There is a chance that this study would be subject to review, in which case members of the Independent Review Board / Research Ethics Committee (REC) / regulatory authorities would be granted direct access to your personal information for verification of clinical trial procedures and/or data collection. These authorities would treat any information about you as strictly confidential.

What would happen to the results of the research study?

The results of this study are likely to be presented to other health professionals and researchers. The results may also be published in medical or scientific journals and used as part of PhD theses. You would not be identified in any of the presentations or publications. If you would like copies of the publications please let a member of the study team know. Contact details are provided below.

Who is organising and funding the research?

The research has been funded by the West Midlands Strategic Health Authority. It has been designed and will be implemented by the University of Birmingham.

Who has reviewed the study?

The study has been reviewed and ethical approval has been granted by the Local Research Ethics Committee (LREC). Research ethics committees safeguard the rights, safety, dignity and well-being of research participants, independently of research sponsors.

Contact details for further information

If you have any questions or queries relating to the study please contact the study coordinator:

Ms Jenny O'Donnell & Ms Grace Turner
Primary Care Clinical Sciences Department
School of Health and Population Sciences
University of Birmingham
Edgbaston campus,
Birmingham
B15 2TT
Tel. 0121 414 5465/ 0121 414 5463
Office hours: Monday to Friday 8.30am-4.30pm (or leave a message on the answer phone)

For general independent advice about taking part in research please contact PALS (The Patient Advice and Liaison Service) on_____.

Thank you for reading this

Appendix 4: Consent form

Patient Identification Number for this Trial: ☐

CONSENT FORM

A study of functional, cognitive and emotional outcomes after "mini stroke"

Chief Investigator: Professor Catherine Sackley (University of Birmingham)

Principal Investigator:

Initial box

1. I confirm I have read and understand the information sheet dated 21/06/2010 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand my participation is voluntary and I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals conducting the trial at the University of Birmingham, by regulatory authorities or by the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study (optional). ☐

5. I agree to take part in the above study (postal questionnaires and cognitive screen). ☐

OR I agree to take part in the above study (Postal questionnaires only). ☐

_____	_ _/_ _ _/_ _ _ _	_____
Name of Participant	Date	Signature
_____	_ _/_ _ _/_ _ _ _	_____
Name of Person taking consent	Date	Signature

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Appendix 5: GP Letter

GP Address ***UoB Letter headed paper***

Date:

Dear Dr _____

RE: Functional, cognitive and emotional outcomes after Transient Ischemic Attack: A prospective, controlled cohort study to inform future rehabilitative interventions

Patient Name: _____ DOB: _ _/_ _ _/_ _

The above patient has recently consented to enter a prospective cohort study analysing whether TIA patients have residual functional impairment and/or psychosocial issues compared to;
a) Patients referred to TIA clinics and given a differential diagnosis, and
b) Healthy age/gender/postcode matched controls.
In total the study aims to recruit 600 individuals from NHS trusts throughout the West Midlands.
Patients will be asked to complete a series of postal questionnaires at 0, 3, 6 and 12 months, yielding data on activities of daily living, handicap, quality of life, service use and vascular events. A subset of the study population will also undergo cognitive screening.
This is purely an observational study. Although some of the questionnaires enquire about potentially sensitive issues, the study will not involve testing of drugs or any prophylactic, diagnostic or therapeutic procedures; therefore it does not pose any real risk to the participant.
Please find enclosed a patient information sheet for your enlightenment. If you have any queries about the trial please contact Nicola Brittle (details below).

Yours sincerely,

Ms Nicola Brittle
Primary Care Clinical Sciences Department
School of Health and Population Sciences
University of Birmingham
Edgbaston campus,
Birmingham
B15 2TT
Email: n.brittle@bham.ac.uk
Tel: 0121 414 5483

Appendix 6: Clinic data collection form

Patient Identification Number for this Trial: ☐

CLINIC DATA COLLECTION FORM

Affix hospital sticker here

(Patient name, address, postcode, DOB, GP name)

Patient Telephone: _____

GP Address: _____

1. Date of incident: _ _ / _ _ / _ _ _ _ (d d / m m / y y y y) **Time (if known):** _ _ : _ _ (h h : m m)

2. Date of referral to TIA clinic: _ _ / _ _ / _ _ _ _ (d d / m m / y y y y) **Time (if known):** _ _ : _ _ (h h : m m)

3. Date seen in TIA clinic: _ _ / _ _ / _ _ _ _ (d d / m m / y y y y) **Time (if known):** _ _ : _ _ (h h : m m)

4. Referral source: ☐ A&E ☐ GP ☐ Other, please specify

5. Duration of symptoms: ……hours

6. Symptomatic side: ☐ Left ☐ Right ☐ Both

7. Handedness: ☐ Left ☐ Right

8. Have imaging or other investigations been performed or requested?

		Date performed or scheduled for (_ _ / _ _ / 20_ _)	Result (if known)
Imaging			
☐	CT		
☐	MRI		
☐	Carotid scan		
☐	Other, please specify		
☐	No imaging		
Investigations			
☐	BP		...../……..mmHg
☐	Cholesterol		……..mg/dL
☐	BMI		……..kg/m^2
☐	ABCD2 score		……..points
☐	Other, please specify		……
☐	No investigations		

9. Final clinic diagnosis:

☐ Stroke

☐ Definite TIA

☐ Possible TIA, treated as TIA ☐ OR non-TIA ☐

☐ TIA mimic, please specify ……..

10. Medical Management:

	On at time of incident	**Started by referrer**	**Started in clinic**	**Intolerant of drug**
Aspirin 75-150mg	☐	☐	☐	☐
Dipyridamole 200mg MR (2 years)	☐	☐	☐	☐
Clopidogrel 75mg	☐	☐	☐	☐
Warfarin (if in AF)	☐	☐	☐	☐
ACE inhibitor (inc ARBs)	☐	☐	☐	☐
Thiazide diuretic	☐	☐	☐	☐
Statin / lipid lowering agent	☐	☐	☐	☐
Other antihypertensive	☐	☐	☐	☐

11. Has/will the patient been referred?

☐ Cardiology

☐ Neurology

☐ Neurosurgery

☐ Vascular surgery

☐ Falls / Syncope clinic

☐ Other, please specify ……

12. Has the patient ever suffered a TIA or stroke prior to this incident?

☐ Yes, Stroke

☐ Yes, TIA

☐ No

Thank you

Appendix 7: Demographic questionnaire

Patient Identification Number for this Trial: ☐

A Study of Functional, cognitive and emotional outcomes after "mini stroke"

Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT
(Telephone: 0121 414 5483)

DEMOGRAPHIC QUESTIONNAIRE

CONFIDENTIAL

Please answer the following questions about your social background and medical history. This information will help us interpret the results of the study. All the information you provide will remain anonymous and strictly confidential. Thank you for your co-operation.

1. What is your date of birth? _ _ / _ _ / _ _ _ _
d d m m y y y y

2. What is your Gender? (*Please* ☐ male ☐ female

3. What is your Ethnicity? (*Please tick one box)*

☐ White ☐ Black ☐ Asian
☐ Mixed ☐ Other, please specify……..

4. What is the highest qualification you have attained? (*Please tick one box)*

☐ GCSE, CSE, 'O' level or equivalent ☐ School Certificate ☐ A' level or equivalent
☐ Higher school certificate ☐ Degree ☐ Postgraduate qualification e.g. Masters degree, PhD, PGCE
☐ No formal qualification ☐ Other qualification/ level unknown

5. Who do you live with? (*Please tick all that apply)*

☐ Spouse/partner ☐ Dependants (e.g. children under 18 yrs, elderly relatives)
☐ I live alone ☐ Other, please specify…….

6. What is your primary place of residence? (*Please tick one box)*

☐ Domestic housing (e.g. house, flat) ☐ Sheltered housing ☐ Residential home
☐ Nursing home ☐ Other, please specify…….

Please turn over

7. Have you ever been diagnosed with any of the following medical conditions?
(Please tick all that apply)

☐	Arthritis (rheumatoid and osteoarthritis)
☐	Osteoporosis
☐	Asthma
☐	Chronic obstructive pulmonary disease (COPD), acquired respiratory distress syndrome (ARDS) or emphysema
☐	Angina
☐	Congestive heart failure (or heart disease)
☐	Heart attack (myocardial infarct)
☐	Neurological disease (such as multiple sclerosis or Parkinson's)
☐	Stroke or TIA
☐	Peripheral vascular disease
☐	Diabetes types I and II
☐	Upper gastrointestinal disease (ulcer, hernia, reflux)
☐	Depression
☐	Anxiety or panic disorders
☐	Visual impairment (such as cataracts, glaucoma, macular degeneration)
☐	Hearing impairment (very hard of hearing, even with hearing aids)
☐	Degenerative disc disease (back disease, spinal stenosis or severe chronic back pain)
☐	Obesity

8. Please enter your height and weight below:

Height: _____feet _____ inches OR _____ metres _____ cm
Weight: _____kg OR _____lbs

Thank you for your time.

Appendix 8: BUCS cut-off scores (based on 5th percentile and smoothed across age groups)

		Cut off points (impairment=less than given scores, unless specified)		
		≤64 (N=34)	65 - 74 (N=33)	≥75 (N=33)
LANGUAGE				
speech	Instruction comprehension	3	3	3
	Picture naming	11	11	10
	Sentence construction	8	8	6
reading	Nonwords – accuracy	5	4	4
	Nonwords – time*	>14 sec	>14 sec	>23 sec
	Sentence – accuracy	42	42	41
	Sentence – time*	>23 sec	>23 sec	>23 sec
writing	Words + nonword	3	3	3
NUMBER				
reading	Total	8	8	8
writing	Total	5	5	3
calculation	Total	2	2	2
PRAXIS				
visuo-constructive	Figure copy	42	41	37
limb	Multi-step	11	10	10
	Gesture production	10	9	9
	Gesture recognition	5	5	4
	Imitation	9	9	9
LTM				
orientation	Personal	8	8	8
	Time and space (MC)	6	6	6
episodic	Story - free recall 1	6	6	3
	Story – recognition 1	13	13	11
	Story – free recall 2	8	6	4
	Story – recognition 2	13	13	12
	Story – decay	>1	>1	>1
	Task – recognition	9	9	8
ATTENTION				
spatial	Apple cancellation -total	42	42	42
	Apple asymmetry - full	< -2 or >2	<-2 or >3	<-2 or >3
	Apple asymmetry - incomplete	<-1 or >1	<-1 or >1	<-1 or >1
	Left visual neglect	4	4	4
	Right visual neglect	4	4	4
	Left visual bilateral	8	7	7
	Right visual bilateral	8	8	8
	Left tactile neglect	4	4	4
	Right tactile neglect	4	4	4
	Left tactile bilateral	7	7	7
	Right tactile bilateral	8	8	7
	Auditory – WM1- practice	>1	>1	>1
	Auditory – WM2 – recall	3	3	2
	Auditory – accuracy	51	50	46
control	Auditory – sustained attention	>1	>1	>2
	B'ham – accuracy & rule	accuracy <6 or rule <1	accuracy <5 or rule <1	accuracy<4 or rule <1

* 2SD are used

Appendix 9: Invitation to Participate

Trust Letter Headed paper

Date: _ _ / _ _ / _ _ _ _

PRIVATE & CONFIDENTIAL

Dear _

Invitation to Participate in a Research Study

You are being invited to take part in a research study investigating whether or not people have a reduced quality of life and/or residual functional problems that adversely influence day to day living, after being diagnosed with a TIA (mini-stroke). Being invited to take part does not mean that you have anything wrong with you. You may have been chosen to form part of a comparison group because you have never suffered a TIA. If you do decide to take part you would be asked to complete a series of questionnaires and return them by post in a pre-paid envelope. You would also be invited to take part in a face-to-face assessment with a member of the research team. The assessment would include a series of simple tasks to measure your communication, memory, perception and attention skills. If you have difficulty understanding English, you would be entitled to ask a friend or relative to help you.
We have enclosed a lot of information about the study. If you need help to understand this information, or if you have any further questions, please get in touch with the study team who will do their best to assist you. You may wish to ask a friend or relative to help with translation if English is not your first language. Contact details for the study team are given on the participant information sheet.

After reading the study information sheet, if you decide that you are happy to take part in this study, please complete the enclosed consent form and baseline questionnaire, and return them to Nicola Brittle at the University of Birmingham in the enclosed **FREEPOST** envelope.

Thank you in anticipation.

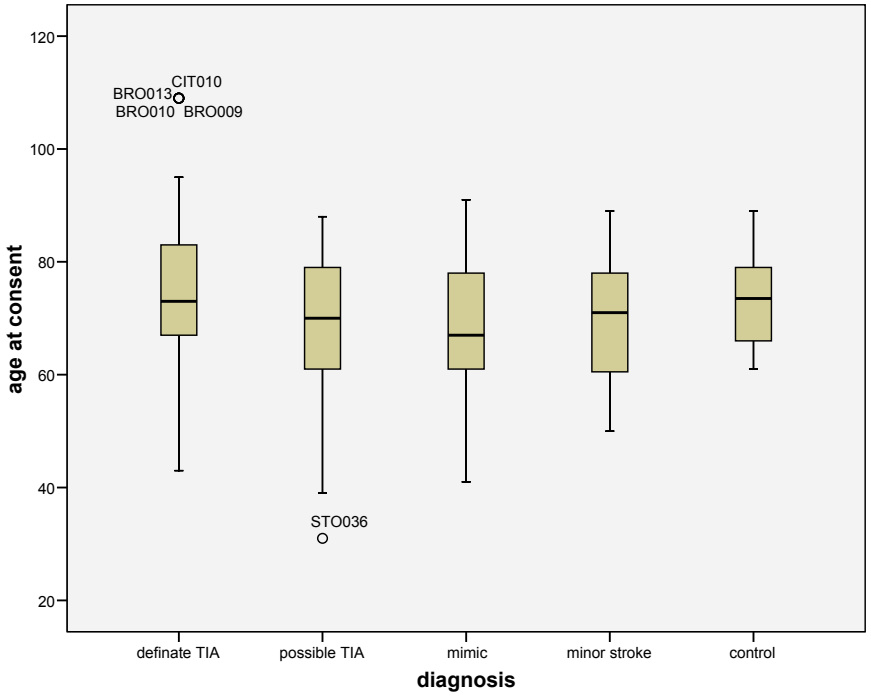
Yours sincerely

Nicola Brittle
Study coordinator

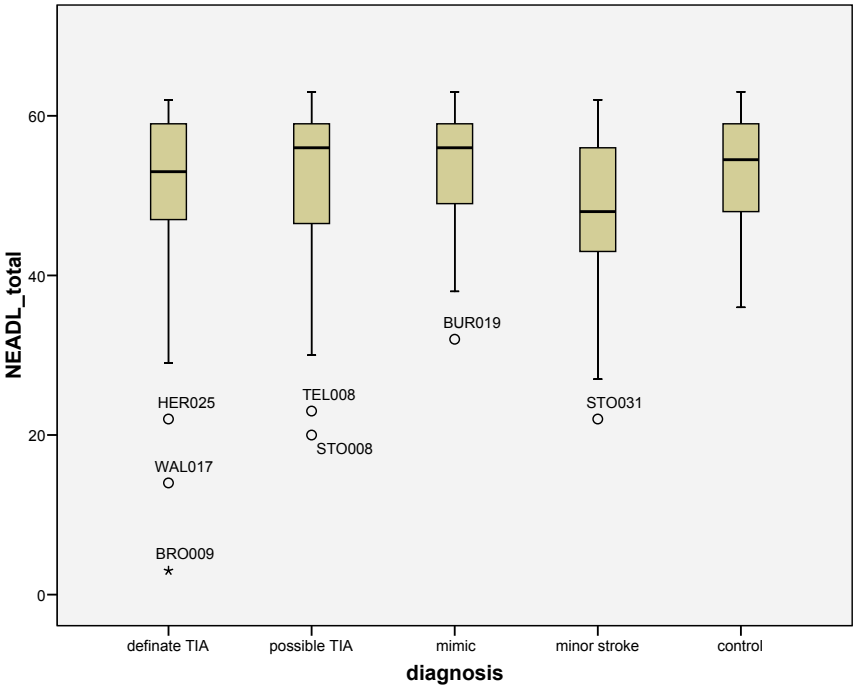
Appendix 10: Graphical representation of demographic and outcome data

Scale variables

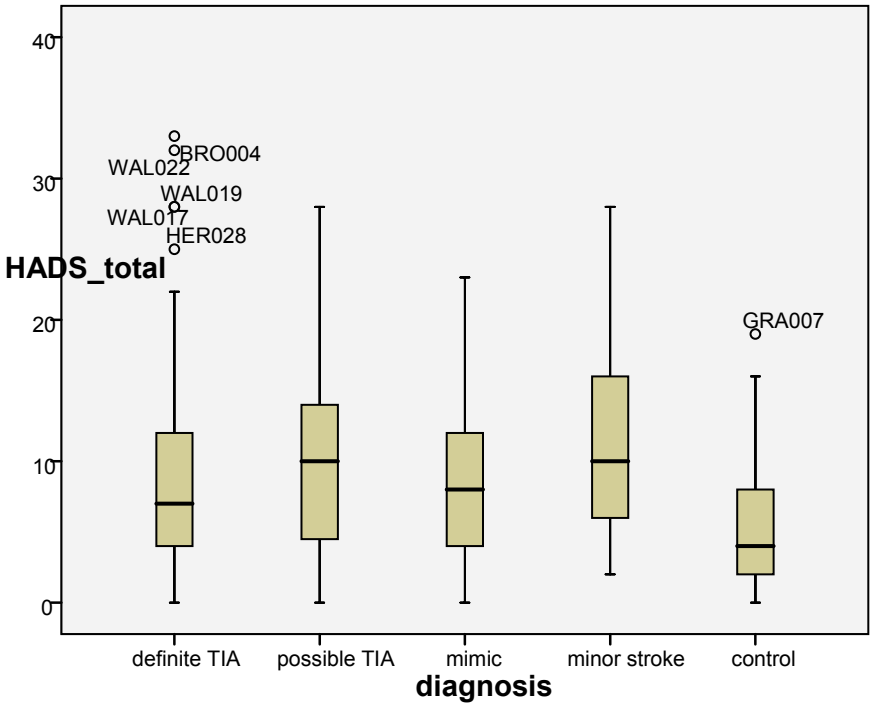
Age

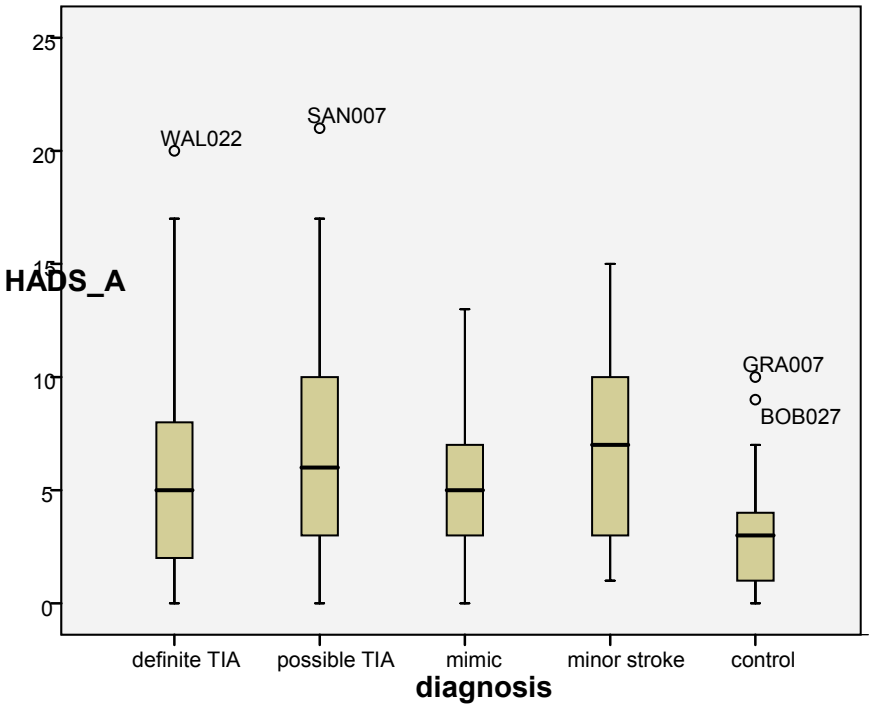


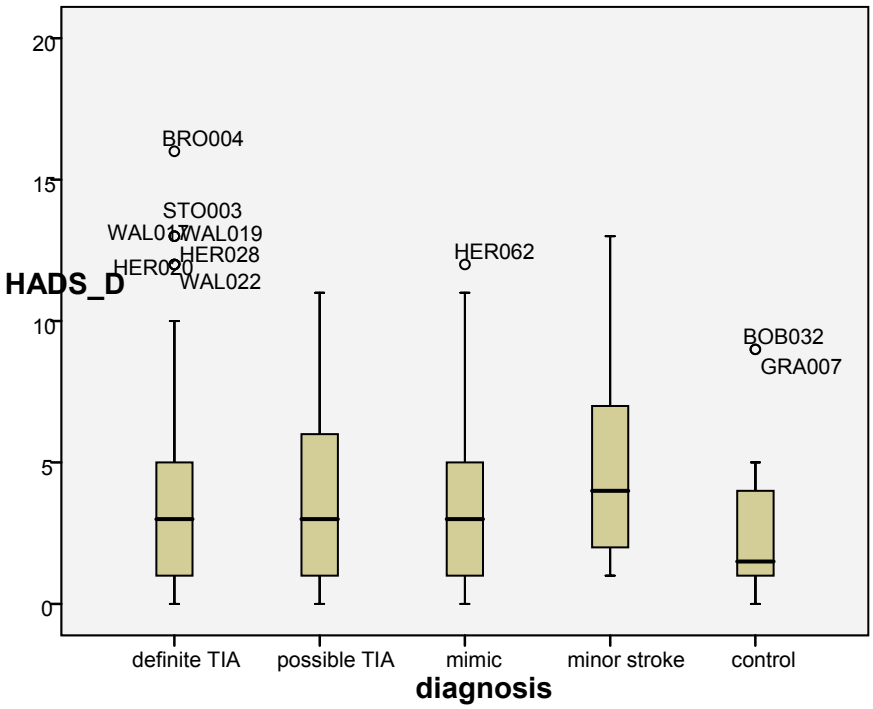
NEADL



HADS

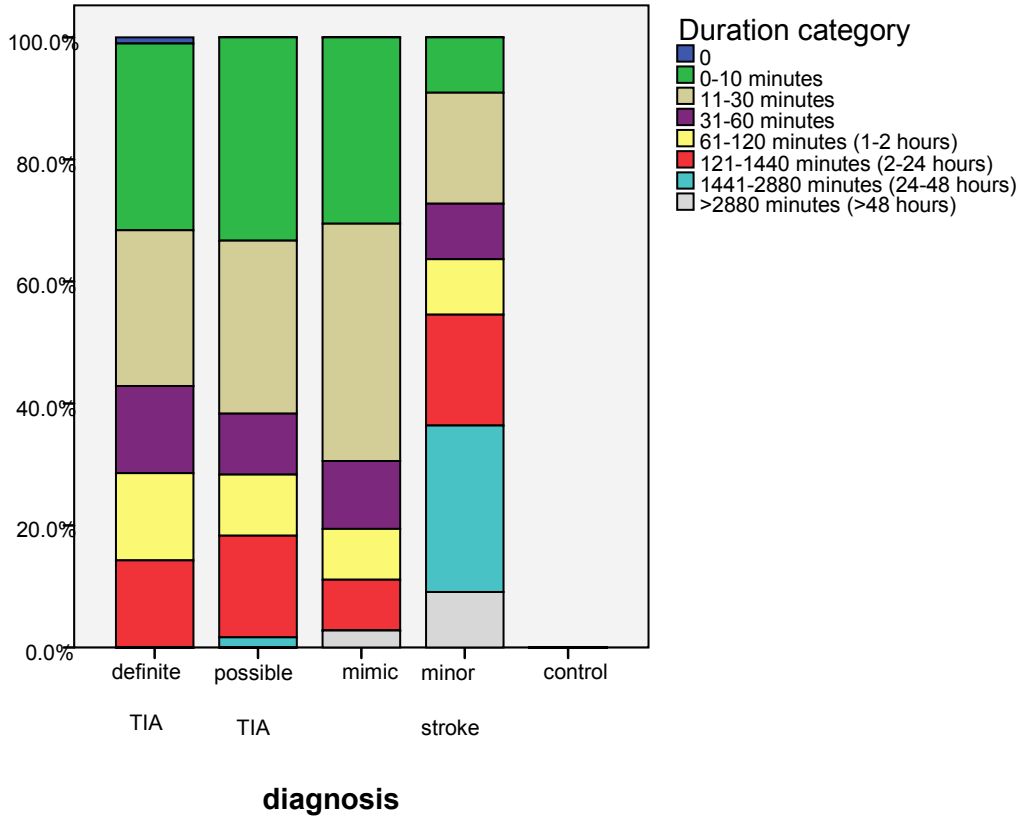

40
30
20
10
0
HADS_total
BRO004
WAL022
WAL019
WAL017
HER028
GRA007
definite TIA
possible TIA
mimic
minor stroke
control
diagnosis


25
20
15
10
5
0
HADS_A
SAN007
WAL022
GRA007
BOB027
definite TIA
possible TIA
mimic
minor stroke
control
diagnosis

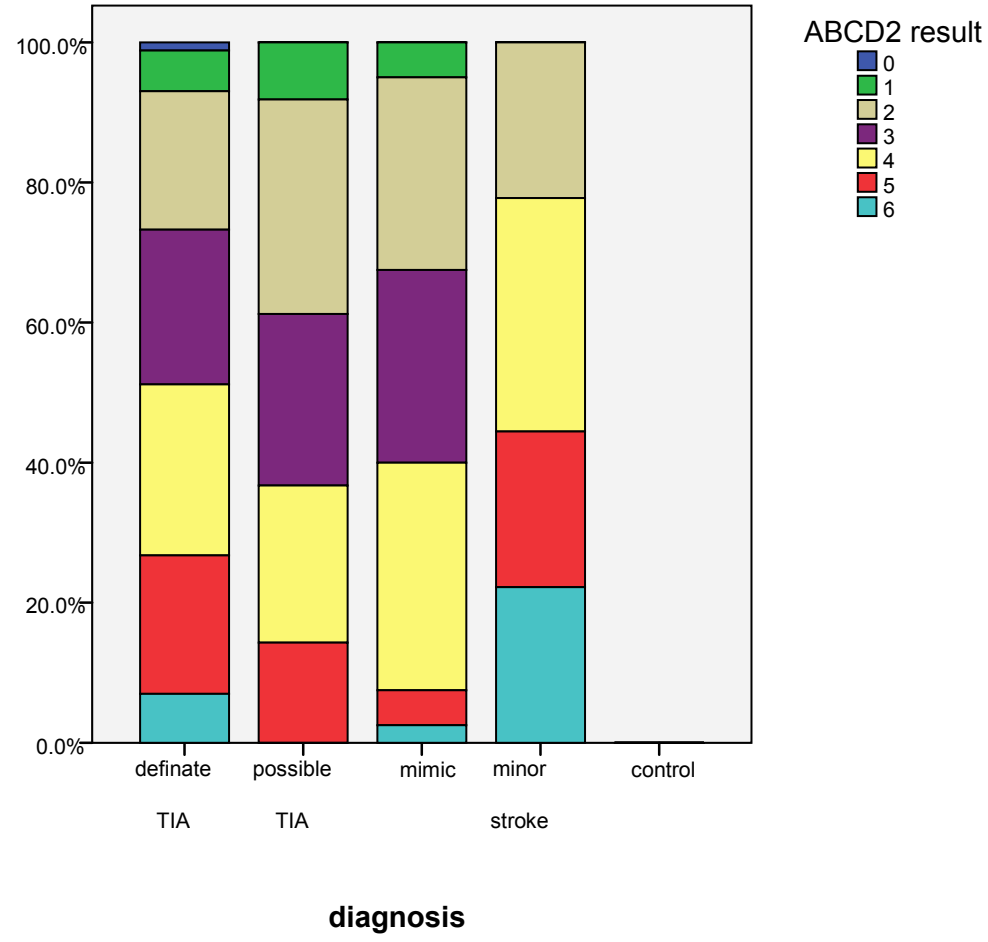

HADS_D
20
15
10
5
0
BRO004
STO003
WAL017
WAL019
HER028
HER020
WAL022
HER062
BOB032
GRA007
definite TIA
possible TIA
mimic
minor stroke
control
diagnosis

Nominal/ordinal variables

Duration of Symptoms



Stroke Risk ($ABCD^2$ score)



Appendix 11: Cohort Analyses

Nottingham Extended Activities of Daily Living

Between Groups Analysis

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	gender, stroke, age at consent, mimic, control, Poss_TIA[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: NEADL_total

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.274[a]	.075	.053	9.045

a. Predictors: (Constant), gender, stroke, age at consent, mimic, control, Poss_TIA

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1642.797	6	273.799	3.347	.003[a]
	Residual	20290.285	248	81.816		
	Total	21933.082	254			

a. Predictors: (Constant), gender, stroke, age at consent, mimic, control, Poss_TIA

b. Dependent Variable: NEADL_total

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	61.033	4.008		15.228	.000	53.139	68.927
	Poss_TIA	-.018	1.432	-.001	-.013	.990	-2.839	2.803
	mimic	1.442	1.697	.057	.850	.396	-1.901	4.785
	stroke	-5.045	2.327	-.139	-2.168	.031	-9.628	-.463
	control	2.139	1.927	.074	1.110	.268	-1.656	5.933
	age at consent	-.166	.050	-.203	-3.286	.001	-.265	-.066
	gender	1.882	1.175	.101	1.602	.110	-.432	4.196

a. Dependent Variable: NEADL_total

Hospital Anxiety and Depression Scale: Total score

Between Groups Analysis

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	gender, age at consent, stroke, mimic, control, Poss_TIA [a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_total

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.285[a]	.081	.059	6.343

a. Predictors: (Constant), gender, age at consent, stroke, mimic, control, Poss_TIA

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	882.167	6	147.028	3.654	.002[a]
	Residual	9977.974	248	40.234		
	Total	10860.141	254			

a. Predictors: (Constant), gender, age at consent, stroke, mimic, control, Poss_TIA

b. Dependent Variable: HADS_total

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	7.638	2.811		2.717	.007	2.102	13.174
	Poss_TIA	.624	1.003	.043	.622	.534	-1.351	2.600
	mimic	-.595	1.188	-.034	-.501	.617	-2.936	1.745
	stroke	2.080	1.672	.079	1.244	.215	-1.213	5.372
	control	-2.895	1.349	-.143	-2.147	.033	-5.551	-.239
	age at consent	-.025	.035	-.043	-.699	.485	-.094	.045
	gender	2.318	.824	.176	2.812	.005	.695	3.941

a. Dependent Variable: HADS_total

Hospital Anxiety and Depression Scale: Anxiety sub-score

Between Groups Analysis

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	gender, age at consent, stroke, mimic, control, Poss_TIA [a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_A

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.376[a]	.141	.120	3.941

a. Predictors: (Constant), gender, age at consent, stroke, mimic, control, Poss_TIA

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	632.735	6	105.456	6.791	.000[a]
	Residual	3850.850	248	15.528		
	Total	4483.584	254			

a. Predictors: (Constant), gender, age at consent, stroke, mimic, control, Poss_TIA

b. Dependent Variable: HADS_A

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	6.515	1.746		3.731	.000	3.076	9.955
	Poss_TIA	.699	.623	.075	1.122	.263	-.528	1.927
	mimic	-.159	.738	-.014	-.215	.830	-1.613	1.295
	stroke	1.141	1.039	.068	1.099	.273	-.904	3.187
	control	-1.543	.838	-.119	-1.841	.067	-3.193	.107
	age at consent	-.059	.022	-.160	-2.680	.008	-.102	-.016
	gender	2.154	.512	.255	4.207	.000	1.146	3.163

a. Dependent Variable: HADS_A

Hospital Anxiety and Depression Scale: Depression sub-score

Between Groups Analysis

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	gender, age at consent, stroke, mimic, control, Poss_TIA [a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_D

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.209[a]	.044	.021	3.094

a. Predictors: (Constant), gender, age at consent, stroke, mimic, control, Poss_TIA

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	108.519	6	18.086	1.890	.083[a]
	Residual	2373.583	248	9.571		
	Total	2482.102	254			

a. Predictors: (Constant), gender, age at consent, stroke, mimic, control, Poss_TIA

b. Dependent Variable: HADS_D

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	1.123	1.371		.819	.414	-1.578	3.823
	Poss_TIA	-.075	.489	-.011	-.153	.878	-1.039	.888
	mimic	-.436	.580	-.051	-.753	.452	-1.578	.705
	stroke	.938	.815	.075	1.151	.251	-.668	2.544
	control	-1.353	.658	-.140	-2.056	.041	-2.648	-.057
	age at consent	.034	.017	.125	1.980	.049	.000	.068
	gender	.164	.402	.026	.408	.684	-.628	.956

a. Dependent Variable: HADS_D

Interaction effects: The effect of cognitive impairment on NEADL score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	number_impaired, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: NEADL_total

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.333[a]	.111	.030	9.906

a. Predictors: (Constant), number_impaired, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	404.246	3	134.749	1.373	.268[a]
	Residual	3238.565	33	98.138		
	Total	3642.811	36			

a. Predictors: (Constant), number_impaired, gender, age at consent

b. Dependent Variable: NEADL_total

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	51.309	12.218		4.199	.000	26.451	76.167
	age at consent	-.075	.154	-.081	-.486	.630	-.388	.238
	gender	.898	3.388	.044	.265	.793	-5.994	7.790
	number_impaired	1.715	.932	.307	1.841	.075	-.180	3.611

a. Dependent Variable: NEADL_total

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of cognitive impairment on HADS-Total score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	number_impaired, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_total

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.464[a]	.215	.146	7.003

a. Predictors: (Constant), number_impaired, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	458.079	3	152.693	3.113	.039[a]
	Residual	1667.632	34	49.048		
	Total	2125.711	37			

a. Predictors: (Constant), number_impaired, gender, age at consent

b. Dependent Variable: HADS_total

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	2.664	8.636		.309	.760	-14.886	20.215
	age at consent	-.016	.108	-.022	-.146	.885	-.235	.204
	gender	3.496	2.378	.225	1.470	.151	-1.337	8.328
	number_impaired	1.596	.653	.379	2.446	.020	.270	2.922

a. Dependent Variable: HADS_total

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of cognitive impairment on HADS-Anxiety score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	number_impaired, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_A

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.483[a]	.233	.166	3.879

a. Predictors: (Constant), number_impaired, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	155.681	3	51.894	3.449	.027[a]
	Residual	511.583	34	15.047		
	Total	667.263	37			

a. Predictors: (Constant), number_impaired, gender, age at consent

b. Dependent Variable: HADS_A

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	6.094	4.783		1.274	.211	-3.627	15.815
	age at consent	-.064	.060	-.162	-1.063	.295	-.185	.058
	gender	1.789	1.317	.206	1.358	.183	-.888	4.465
	number_impaired	.865	.361	.366	2.394	.022	.131	1.600

a. Dependent Variable: HADS_A

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of cognitive impairment on HADS-Depression score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	number_impaired, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_D

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.451[a]	.203	.133	3.447

a. Predictors: (Constant), number_impaired, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	102.945	3	34.315	2.888	.050[a]
	Residual	403.924	34	11.880		
	Total	506.868	37			

a. Predictors: (Constant), number_impaired, gender, age at consent

b. Dependent Variable: HADS_D

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-3.430	4.250		-.807	.425	-12.067	5.208
	age at consent	.048	.053	.140	.900	.374	-.060	.156
	gender	1.707	1.170	.225	1.459	.154	-.671	4.085
	number_impaired	.731	.321	.355	2.276	.029	.078	1.383

a. Dependent Variable: HADS_D

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of ABCD^2 score on NEADL score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	ABCD2_result, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: NEADL_total

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.342[a]	.117	.077	9.687

a. Predictors: (Constant), ABCD2_result, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	832.115	3	277.372	2.956	.039[a]
	Residual	6287.603	67	93.845		
	Total	7119.718	70			

a. Predictors: (Constant), ABCD2_result, gender, age at consent

b. Dependent Variable: NEADL_total

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	67.764	8.067		8.400	.000	51.662	83.867
	age at consent	-.141	.111	-.159	-1.273	.208	-.363	.080
	gender	.093	2.396	.005	.039	.969	-4.690	4.876
	ABCD2_result	-1.777	.908	-.249	-1.958	.054	-3.589	.035

a. Dependent Variable: NEADL_total

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of ABCD^2 on HADS-Total score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	ABCD2_result, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_total

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.181[a]	.033	-.010	6.916

a. Predictors: (Constant), ABCD2_result, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	110.176	3	36.725	.768	.516[a]
	Residual	3252.269	68	47.827		
	Total	3362.444	71			

a. Predictors: (Constant), ABCD2_result, gender, age at consent

b. Dependent Variable: HADS_total

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	7.375	5.754		1.282	.204	-4.106	18.857
	age at consent	-.026	.079	-.043	-.327	.744	-.184	.132
	gender	2.414	1.705	.174	1.416	.161	-.987	5.815
	ABCD2_result	-.055	.646	-.011	-.086	.932	-1.345	1.234

a. Dependent Variable: HADS_total

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of ABCD^2 score on HADS-Anxiety score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	ABCD2_result, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_A

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.268[a]	.072	.031	3.957

a. Predictors: (Constant), ABCD2_result, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	82.270	3	27.423	1.751	.165[a]
	Residual	1064.841	68	15.659		
	Total	1147.111	71			

a. Predictors: (Constant), ABCD2_result, gender, age at consent

b. Dependent Variable: HADS_A

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	8.508	3.292		2.584	.012	1.938	15.077
	age at consent	-.073	.045	-.206	-1.613	.111	-.163	.017
	gender	1.413	.975	.174	1.448	.152	-.534	3.359
	ABCD2_result	-.028	.370	-.010	-.076	.939	-.766	.709

a. Dependent Variable: HADS_A

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of ABCD^2 score on HADS-Depression score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	ABCD2_result, gender, age at consent[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_D

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.218[a]	.048	.006	3.383

a. Predictors: (Constant), ABCD2_result, gender, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	39.004	3	13.001	1.136	.341[a]
	Residual	778.107	68	11.443		
	Total	817.111	71			

a. Predictors: (Constant), ABCD2_result, gender, age at consent

b. Dependent Variable: HADS_D

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	-1.132	2.814		-.402	.689	-6.748	4.483
	age at consent	.047	.039	.157	1.217	.228	-.030	.124
	gender	1.001	.834	.147	1.201	.234	-.662	2.665
	ABCD2_result	-.027	.316	-.011	-.086	.932	-.658	.603

a. Dependent Variable: HADS_D

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of NEADL score HADS-Total score

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_total

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.368[a]	.135	.111	6.173

a. Predictors: (Constant), control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA

ANOVA [b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1468.488	7	209.784	5.505	.000[a]
	Residual	9374.729	246	38.109		
	Total	10843.217	253			

a. Predictors: (Constant), control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA

b. Dependent Variable: HADS_total

Coefficients [a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	18.151	3.818		4.754	.000	10.631	25.671
	age at consent	-.051	.035	-.090	-1.464	.144	-.121	.018
	gender	2.590	.807	.197	3.209	.002	1.000	4.180
	NEADL_total	-.173	.044	-.242	-3.950	.000	-.259	-.087
	Poss_TIA	.601	.978	.041	.615	.539	-1.325	2.527
	mimic	-.375	1.160	-.021	-.324	.746	-2.660	1.909
	stroke	1.367	1.637	.052	.835	.405	-1.858	4.592
	control	-2.575	1.318	-.127	-1.954	.052	-5.171	.021

a. Dependent Variable: HADS_total

Interaction effects: The effect of HADS-Total score on NEADL score

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	HADS_total, mimic, age at consent, stroke, gender, control, Poss_TIA [a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: NEADL_total

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.345[a]	.119	.094	8.732

a. Predictors: (Constant), HADS_total, mimic, age at consent, stroke, gender, control, Poss_TIA

ANOVA [b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	2539.838	7	362.834	4.758	.000[a]
	Residual	18757.488	246	76.250		
	Total	21297.327	253			

a. Predictors: (Constant), HADS_total, mimic, age at consent, stroke, gender, control, Poss_TIA

b. Dependent Variable: NEADL_total

Coefficients [a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	63.566	3.927		16.188	.000	55.831	71.300
	age at consent	-.169	.049	-.210	-3.466	.001	-.265	-.073
	gender	2.506	1.154	.136	2.171	.031	.232	4.780
	Poss_TIA	.219	1.384	.011	.159	.874	-2.506	2.945
	mimic	1.229	1.639	.049	.750	.454	-2.000	4.458
	stroke	-3.260	2.310	-.089	-1.411	.159	-7.809	1.289
	control	1.069	1.878	.038	.569	.570	-2.630	4.767
	HADS_total	-.345	.087	-.246	-3.950	.000	-.518	-.173

a. Dependent Variable: NEADL_total

Interaction effects: The effect of NEADL score on HADS-Anxiety score

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_A

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.411[a]	.169	.145	3.890

a. Predictors: (Constant), control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA

ANOVA [b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	755.215	7	107.888	7.131	.000[a]
	Residual	3721.966	246	15.130		
	Total	4477.181	253			

a. Predictors: (Constant), control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA

b. Dependent Variable: HADS_A

Coefficients [a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	11.397	2.406		4.738	.000	6.659	16.136
	age at consent	-.071	.022	-.194	-3.224	.001	-.115	-.028
	gender	2.285	.509	.270	4.492	.000	1.283	3.286
	NEADL_total	-.080	.028	-.175	-2.910	.004	-.134	-.026
	Poss_TIA	.693	.616	.074	1.125	.262	-.520	1.906
	mimic	-.052	.731	-.005	-.071	.944	-1.491	1.388
	stroke	.815	1.032	.049	.790	.430	-1.217	2.847
	control	-1.387	.831	-.107	-1.670	.096	-3.023	.249

a. Dependent Variable: HADS_A

Interaction effects: The effect of NEADL score on HADS-Depression score

Variables Entered/Removed [b]

Model	Variables Entered	Variables Removed	Method
1	control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: HADS_D

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.337[a]	.113	.088	2.990

a. Predictors: (Constant), control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA

ANOVA [b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	281.046	7	40.149	4.492	.000[a]
	Residual	2198.548	246	8.937		
	Total	2479.594	253			

a. Predictors: (Constant), control, NEADL_total, stroke, gender, age at consent, mimic, Poss_TIA

b. Dependent Variable: HADS_D

Coefficients [a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	6.753	1.849		3.653	.000	3.112	10.395
	age at consent	.020	.017	.073	1.172	.242	-.014	.053
	gender	.305	.391	.049	.781	.436	-.465	1.075
	NEADL_total	-.092	.021	-.271	-4.369	.000	-.134	-.051
	Poss_TIA	-.092	.473	-.013	-.194	.846	-1.025	.840
	mimic	-.324	.562	-.038	-.576	.565	-1.430	.783
	stroke	.552	.793	.044	.696	.487	-1.010	2.113
	control	-1.188	.638	-.123	-1.861	.064	-2.445	.069

a. Dependent Variable: HADS_D

Interaction effects: The effect of ABCD^2 score on BUCS score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	gender, age at consent, stroke_risk[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: number_impaired

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.429[a]	.184	.103	2.016

a. Predictors: (Constant), gender, age at consent, stroke_ risk

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	27.542	3	9.181	2.258	.102[a]
	Residual	121.987	30	4.066		
	Total	149.529	33			

a. Predictors: (Constant), gender, age at consent, stroke_risk

b. Dependent Variable: number_impaired

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	6.928	2.675		2.590	.015	1.465	12.391
	stroke_risk	1.303	.726	.306	1.794	.083	-.180	2.786
	age at consent	-.072	.034	-.352	-2.114	.043	-.142	-.002
	gender	-.165	.719	-.039	-.230	.820	-1.635	1.304

a. Dependent Variable: number_impaired

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of NEADL score on BUCS score

Variables Entered/Removed [b,c]

Model	Variables Entered	Variables Removed	Method
1	gender, NEADL_total, age at consent [a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: number_impaired

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.345[a]	.119	.039	1.762

a. Predictors: (Constant), gender, NEADL_total, age at consent

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	13.835	3	4.612	1.485	.237[a]
	Residual	102.489	33	3.106		
	Total	116.324	36			

a. Predictors: (Constant), gender, NEADL_total, age at consent

b. Dependent Variable: number_impaired

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	.008	2.692		.003	.998	-5.470	5.485
	NEADL_total	.054	.029	.304	1.841	.075	-.006	.114
	age at consent	-.017	.027	-.105	-.634	.531	-.073	.038
	gender	.291	.601	.080	.485	.631	-.932	1.514

a. Dependent Variable: number_impaired

b. Selecting only cases for which TIA = 1

Interaction effects: The effect of HADS score on BUCS score

Variables Entered/Removed[b,c]

Model	Variables Entered	Variables Removed	Method
1	gender, age at consent, HADS_total[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: number_impaired

c. Models are based only on cases for which TIA = 1

Model Summary

Model	R TIA = 1 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.426[a]	.182	.109	1.697

a. Predictors: (Constant), gender, age at consent, HADS_total

ANOVA[b,c]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	21.750	3	7.250	2.516	.075[a]
	Residual	97.961	34	2.881		
	Total	119.711	37			

a. Predictors: (Constant), gender, age at consent, HADS_total

b. Dependent Variable: number_impaired

c. Selecting only cases for which TIA = 1

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	2.451	2.053		1.194	.241	-1.722	6.624
	HADS_total	.094	.038	.395	2.446	.020	.016	.172
	age at consent	-.021	.026	-.128	-.817	.420	-.074	.032
	gender	.049	.594	.013	.082	.935	-1.159	1.257

a. Dependent Variable: number_impaired

b. Selecting only cases for which TIA = 1