Missed opportunities for primary prevention of stroke and transient ischaemic attack (TIA) and residual impairments after TIA

by

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Abstract

The research investigated: (i) potential missed opportunities for primary prevention of stroke and transient ischaemic attack (TIA) with pharmacotherapy through a retrospective case series analysis and (ii) fatigue, psychological and cognitive impairment following TIA through a systematic review and retrospective cohort study. The case series and cohort studies used electronic primary care medical records from The Health Improvement Network (THIN).

The case series analysis found preventative drugs were under prescribed to people with clinical indications for these drugs prior to stroke or TIA. There were potential missed opportunities for prevention in 49% (7,836/16,028) of people with stroke or TIA who were eligible for lipid lowering drugs, 52% (1,647/3,194) for anticoagulant drugs and 25% (1,740/7,008) for antihypertensive drugs. Improving prescription of these drugs has the potential to reduce the incidence and subsequent burden of stroke and TIA.

The systematic review revealed there were few high quality studies investigating residual impairments in people with TIA and minor stroke; however, there was limited evidence to suggest a relatively high prevalence of cognitive impairment and depression post-TIA and minor stroke. The retrospective cohort study found that TIA patients were significantly more likely to consult in primary care for fatigue, psychological and cognitive impairment compared to matched controls. This association remained when adjusted for the potential confounding variables and the presence of the impairment prior to TIA. These findings suggest that impairments exist after initial symptoms of TIA have resolved and challenge the

‘transient’ characterisation of TIA. Residual impairments should be considered by primary care clinicians when treating patients following TIA.

Dedication

To my loving family and wonderful friends.

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Contributorship statement

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Doctor Ronan Ryan provided guidance for design and analysis of The Health Improvement Network (THIN) database studies and extracted the data from THIN for Chapters 3-5 and 8-9. Professor KK Cheng contributed to the interpretation of findings and write up of the manuscripts in Chapters 4-5 and Professor David Fitzmaurice gave subject specific advice for Chapter 5. Ben Fletcher was the second reviewer for the systematic review and provided feedback on the manuscripts in Chapters 6 and 7. Professor Cath Sackley was involved in the concept and design of the systematic review and provided feedback on the manuscripts in Chapters 6 and 7.

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List of abbreviations

A	**ABCD2**	Age, Blood pressure, Clinical features, Duration of symptoms, Diabetes
	AF	Atrial Fibrillation
	AHA/ASA	American Heart Association/American Stroke Association Stroke
	AHD	Additional Health Data
	AMR	Acceptable Mortality Reporting
B	**BDI**	Beck Depression Inventory
	BP	Blood Pressure
	BMI	Body Mass Index
	BNF	British National Formulary
C	**CENTRAL**	Cochrane Central Register of Controlled Trials
	CDSR	Cochrane Database of Systematic Reviews
	CHD	Coronary Heart Disease
	CHF	Congestive Heart Failure
	CI	Confidence Intervals
	CINAHL	Cumulative Index to Nursing and Allied Health Literature
	CKD	Chronic Kidney Disease
	CPCI	Conference Proceedings Citation Index
	CPRD	Clinical Practice Research Datalink
	COM-B	Capability, Opportunity and Motivation- Behaviour
	COPD	Chronic Obstructive Pulmonary Disease
	CRD	Centre for Reviews and Dissemination
	CT	Computed Tomographic
	CVD	Cardiovascular Disease
D	**DALYs**	Disability-Adjusted Life-Years
	DARE	Database of Abstracts of Reviews of Effects
	DSM	Diagnostic and Statistical Manual of Mental Disorders
E	**ECG**	Electrocardiogram
	EMIS	Educational Management Information System
	ESRC	Economic and Social Research Council
F	**FAI**	Fatigue Assessment Instrument
	FAST	Face Arms Speech Test
	FSS	Fatigue Severity Scale
G	**GP(s)**	General Practitioner(s)

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H	**HADS**	Hospital Anxiety and Depression Scale
	HDL	High-Density Lipoprotein
	HR	Hazard Ratio
	HRSD	Hamilton Rating Scale for Depression
I	**ICD**	International Classification of Diseases
	IQR	International Quartile Range
	IMS	Intercontinental Marketing Services
	INPS	In Practice Systems
	INR	International Normalisation Ratio
	ISOQOL	International Society for Quality of Life Research
K	**K-M**	Kaplan-Meier
L	**LDL**	Low-Density Lipoprotein
M	**MMSE**	Mini-Mental State Examination
	MoCA	Montreal Cognitive Assessment
	MRC	Medical Research Council
	MREC	Multicentre Research Ethics Committee
	MRI	Magnetic Resonance Imaging
N	**NAPCRG**	North American Primary Care Research Group
	NHS	National Health Service
	NICE	National Institute for Health and Care Excellence
	NIHR	National Institute for Health Research
	NIHSS	National Institute of Health Stroke Scale
	NR	Not Reported
O	**OR**	Odds Ratio
P	**PAD**	Peripheral Arterial Disease
	PHCRC	Primary Health Care Research Conference
	PHQ	Patient Health Questionnaire
	PPI	Patient Public Involvement
	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
	PROSPERO	Prospective Registering of Systematic Reviews
	PTSD	Post-Traumatic Stress Disorder
	PVI	Postcode Variable Indicators
Q	**QOF**	Quality and Outcomes Framework
	QoL	Quality of Life
R	**R and D**	Research and Development
	ROSIER	Recognition of Stroke in the Emergency Room

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S	**SAPC**	Society of Academic Primary Care
	SD	Standard Deviation
	SCI	Science Citation Index
	SPCR	School for Primary Care Research
	SRC	Scientific Review Committee
	STROBE	Strengthening the Reporting of Observational studies in Epidemiology
T	**TDQ**	Taiwanese Depression Questionnaire
	THIN	The Health Improvement Network
	TIA	Transient Ischaemic Attack
U	**UK**	United Kingdom
	USA	United States of America
V	**VROPSOM**	Dutch version of the Depression Adjective Check Lists
W	**WHO**	World Health Organisation
Y	**YLL**	Years of Life Lost
	YOB	Year of Birth

Thesis format

This thesis is presented in accordance with the Alternative Format Thesis Guidelines (https://intranet.birmingham.ac.uk/as/studentservices/graduateschool/documents/public/rsa/alternative-format-thesis-guidelines.pdf). As such, the pages of the publications themselves will not be included in the pagination sequence of the submission. Referencing and numbering of tables and figures will be self-contained within each chapter. The incorporation of publication-style chapters will inevitably lead to some duplication since each publication-style chapter will have self-contained components that will overlap with parts of the other sections of the thesis.

Please note, my surname changed during the duration of the PhD and, therefore, manuscripts are authored under Turner or Moran in different chapters.

Chapter 1: Background

Background

The research within this thesis focuses on stroke and transient ischaemic attack (TIA); the studies investigate missed opportunities for primary prevention of these conditions and residual impairments after TIA. This chapter provides a general background and justification for the research.

Definition of stroke, minor stroke and TIA

Stroke, minor stroke and TIA are conditions caused by restricted blood supply to the brain;[1-3] definitions are summarised in Table 1.

Stroke

Broadly, stroke refers to an episode of neurological dysfunction, with evidence of permanent brain infarction, caused by focal cerebral, spinal or retinal infarction (ischaemic stroke) or bleeding into the subarachnoid or intracerebral space (haemorrhagic stroke).[3] Symptoms of stroke are diverse and dependant on the type of stroke and area of the brain affected, but typically include disturbances in limb functioning, speech, vision or balance.[4] The 'Act F.A.S.T' (Facial weakness; Arm weakness; Speech problems; Time to call 999) media campaign, launched in England in 2009, has been successful in improving identification of symptoms and emergency admissions.[5] Diagnosis of stroke is facilitated by brain scans to determine the type of stroke (ischaemic or haemorrhagic), the location and severity.[6] The National Institute of Health Stroke Scale (NIHSS) quantifies stroke severity through scoring consciousness, eye movement, vision, facial paralysis, leg and arm motor drift, coordination, sensory loss, language, speech and attention (Table 2).[7]

Table 1: Definitions of stroke, minor stroke and transient ischaemic attack (TIA).

Diagnosis	Definition	Symptoms	Permanent brain infarction?
Stroke	Disruption of blood supply to the brain usually caused by a blood clot (ischaemic stroke) or burst blood vessel (haemorrhagic stroke)	Long-lasting and disabling	Yes
Minor stroke	Disruption of blood supply to the brain with short-term functional recovery	Mild and non-disabling	Yes
TIA	Transient disruption of blood supply to the brain caused by a temporary blood clot	Short-lasting, usually less than one hour	No

Table 2: Tests for recognition of stroke and TIA; stroke risk; and stroke severity.

Recognition of symptoms of stroke and TIA		
FAST	Face: Has their face fallen on one side?	
	Arm weakness: Can they raise both arms and keep them there?	
	Speech: Is speech slurred?	
ROSIER	Has there been loss of consciousness or syncope?	Y (-1 point)
	Has there been seizure activity?	Y (-1 point)
	Asymmetric facial weakness:	Y (1 point)
	Asymmetric arm weakness:	Y (1 point)
	Asymmetric leg weakness:	Y (1 point)
	Speech disturbance:	Y (1 point)
	Visual field defect:	Y (1 point)
Stroke risk in AF patients		
CHADS2	Congestive heart failure:	Y (1 point)
	Hypertension:	Y (1 point)
	Age ≥ 75:	Y (1 point)
	Diabetes mellitus:	Y (1 point)
	Stroke or TIA symptoms previously:	Y (2 points)
CHA_2DS_2-VASc	Congestive heart failure:	Y (1 point)
	Hypertension:	Y (1 point)
	Age ≥ 75:	Y (2 points)
	Diabetes mellitus:	Y (1 point)
	Stroke or TIA symptoms previously:	Y (2 points)
	Vascular disease:	Y (1 point)
	Age 65 to 74 years:	Y (1 point)
	Sex (female):	Y (1 point)
Stroke risk in all patients		
ABCD[2]	Age ≥60 years:	Y (1 point)
	Blood pressure >140/90 mmHg:	Y (1 point)
	Clinical features: Unilateral weakness:	Y (2 points)
	Speech disturbance without weakness:	Y (1 point)
	Other:	Y (0 points)
	Duration: > 60 mins:	Y (2 points)
	10 – 60 mins:	Y (1 point)
	< 10 mins:	Y (0 points)
	Diabetes:	Y (1 point)

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Table 2 continued from previous page

Stroke severity	
NIHSS	Level of Consciousness
	Ask month and age
	'Blink eyes' and 'squeeze hands'
	Test horizontal extraocular movements
	Test visual fields
	Test facial palsy
	Test left arm motor drift
	Test right arm motor drift
	Test left leg motor drift
	Test right leg motor drift
	Test limb ataxia
	Test sensation
	Test language/aphasia
	Test dysarthria
	Test extinction/inattention

FAST: Face Arms Speech Test; NIHSS: National Institute of Health Stroke Scale

Minor stroke

Minor stroke is also known as 'mild stroke' or 'non-disabling stroke'; however, in contrast to stroke and TIA, there is no formal definition. Fisher et al (2010) proposed the definition to be: "all stroke patients with baseline NIHSS ≥3 or all stroke patients with a score 0 or 1 on every baseline NIHSS score item, except level of consciousness items, which must be 0";[2] however, these are not consistently used. Broadly, minor stroke refers to an episode of neurological dysfunction with evidence of acute infarction whereby symptoms are non-disabling.[2] Therefore, minor stroke is differentiated from TIA by presence of brain infarction and from stroke by severity of symptoms and short-term recovery.

Transient Ischaemic Attack (TIA)

TIA is also known as 'mini-stroke' and was originally defined as an episode of neurological dysfunction with presumed vascular origin and symptoms lasting for less than 24 hours.[8] Therefore, duration of symptoms differentiated TIA from stroke. However, advances in brain imaging demonstrated that permanent brain infarction could result from short-lasting symptoms which, therefore, would not be a transient event.[9] Furthermore, the time-base classification of TIA may promote delays in treatment because clinicians could decide to wait 24 hours see if symptoms resolve.[1] In 2002, a tissue-based definition of TIA was proposed: "a TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour and without evidence of acute infarction".[10] More recently, the American Heart Association/American Stroke Association (AHA/ASA) updated the tissue-based definition to remove the reference to time (symptoms typically lasting less than one hour) and defined TIA as: "a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction".[1]

The tissue-based definition differentiates TIA from stroke and minor stroke based on presence of permanent brain infarction; however, diagnosis requires routine brain imaging. Furthermore, the new definition has not been universally adopted and important organisations, such as the National Institute for Health and Care Excellence (NICE)[6] and the World Health Organisation (WHO),[11] still use the 24 hour criteria. Symptoms of TIA are similar to those of stroke; however, non-focal neurological symptoms have also been reported such as disconnection with surroundings, lack of awareness of deficit, visual displacement and impaired articulation.[12] Use of brain imaging to diagnose TIA is not used routinely and diagnosis is predominantly based on clinical history.[6]

Incidence and prevalence

Stroke

In the United Kingdom (UK), approximately 110,000 people have a first stroke per year, of which 98,000 are ischaemic strokes.[13] The age-standardised incidence rate is estimated to be 115 per 100,000 person-years. Incidence has decreased from 142 per 100,000 person-years in 1990;[14] the greatest reduction in incidence is in people aged 70 years and over.[15] Approximately 1.1 million people have had a stroke in the UK[13] and the age-adjusted prevalence is estimated to be 591 per 100,000.[14] In contrast to incidence, prevalence has increased (age-standardised prevalence was 507 per 100,000 in 1990).[14,15]

From a global perspective, the number of first strokes per year is estimated to be 16.9 million, of which, 11.6 million are ischaemic strokes.[16] In 2010, the worldwide age-adjusted incidence rate was 258 per 100,000 person-years, which had non-significantly increased

from 1990 (251 per 100,000 person-years).[14] In terms of absolute numbers, there was a considerable increase in incident strokes, with a global increase of 68% between 1990 and 2010.[14] The global prevalence of stroke is estimated to be 33 million people and age-adjusted prevalence 502 per 100,000 people.[14] Absolute numbers of people surviving stroke increased by 84% between 1990 and 2010[14] and age-adjusted prevalence rates also increased significantly during this period.[14]

Minor stroke

The incidence and prevalence of minor stroke is not well documented and the lack of a clear definition hinders this. However, NICE estimates that 25% of strokes are minor strokes.[17]

TIA

In the UK, approximately 46,000 people have a first TIA per year and there are 510,000 people with prevalent TIA.[13] Both incidence and prevalence of TIA increase with age and are higher in women; however, this sex effect is likely to be a result of increased healthcare seeking behaviour in women.[13] Estimating the incidence and prevalence of TIA is complicated by the change in definition of TIA (time vs tissue based definition) and that the new proposed classification has not been university adopted. The above incidence estimates are based on data from the Oxford Vascular study[18] which used the time-based definition of TIA. Prevalence estimates are based on the National Stroke Audit which defined TIA using clinical codes (Read codes), which are used in primary care to record patients' information electronically as part of routine clinical care;[19] therefore, it is unclear how TIA was diagnosed at an individual level. Estimates of incidence and prevalence need to be considered with caution. There are no estimates of the global incidence and prevalence of TIA; however, it

has been estimated that approximately 5 million people in the United States of America (USA)[20] and 23.9 million people in China[21] have experienced a TIA.

UK and global burden

Stroke can cause huge burden in terms of death, disability and quality of life (QoL) (for patients, carers and family members) and is associated with high economic cost.[16] Post-stroke disability varies in severity and includes impairments related to: physical function (limb weakness or paralysis); speech (slurred speech and aphasia); mood (anxiety, depression, emotionalism, fatigue); cognition (impaired memory, attention, executive functioning).[22] Furthermore, stroke patients are at high risk of recurrent stroke.[23]

In the UK, strokes are attributable for 60,000 deaths and 665,000 disability-adjusted life-years (DALYs) lost per year. However, the absolute numbers and age-adjusted estimates of stroke-related deaths and DALYs lost have reduced considerable since 1990.[14] A North-South regional divide has been reported for stroke mortality in the UK with more stroke-related deaths in Scotland compared to the South of England.[13] The UK total economic cost of stroke is estimated to be £9 billion, of which, almost half is health and social care costs.[13]

Globally, stroke is a leading cause of death and disability in both developed and developing countries. The Global Burden of Disease study found stroke was the second leading cause of death[24] and third leading cause of DALYs lost[25] worldwide. The study also found that stroke burden varied between regions and countries,[14] changed over time and differed between stroke sub-types.[16] The estimated number of deaths and DALYs lost attributable to stroke in 2010 were 5.9 million and 102 million, respectively.[14] The age-adjusted mortality rate in

2010 was 88 per 100,000 person-years and DALYs lost was 1554.[14] Age-adjusted stroke-related mortality rates and DALYs lost decreased worldwide between 1990 and 2010; however, the absolute numbers of stroke-related deaths and DALYs lost increased by 26% and 12% respectively.[14] Although incidence is lower, haemorrhagic strokes cause more burden compared to ischaemic strokes. [16] For incident strokes, in 2010, there were 3 million compared to 2.8 million stroke-related deaths for haemorrhagic and ischaemic stroke, respectively, and 62.8 million compared to 39.4 million DALYs lost for haemorrhagic and ischaemic stroke, respectively.[16] There are geographical variations in the burden of stroke worldwide; most of the burden is in low- and middle-income countries including 71% of stroke related deaths and 78% of DALYs lost.[14] Stroke is often considered a disease of the elderly and there was a greater increase in mortality and DALYs lost between 1990 and 2010 in people aged 75 years and over compared to people aged less than 75 years (36% increase in mortality and 31% increase in DALYs lost in people ≥75 years compared to 16% increase in mortality and 15% increase in DALYs in people <75 years). [14] This has important implications given population ageing.[14] However, the absolute numbers of DALYs lost is considerably greater in people under 75 years compared to those 75 years and over (73 million vs 28.9 million in 2010, respectively).[14]

TIA is estimated to cost the UK economy £440 million per annum, of which, 83% are health and social care costs.[13] TIA patients are at high risk of having a full stroke; risk of stroke after TIA is reported to be 8% at one week, 12% at one month and 17% at three months.[26] After minor stroke, risk of stroke is 12% at one week, 15% at one month and 19% at three months. Although TIA and minor stroke are characterised by short-term functional recovery, there is evidence to suggest that TIA and minor stroke burden may extend beyond stroke risk and

patients may experience residual impairments. [27] One study found that 15% of TIA and minor stroke patients, who were previously not disabled, had at least slight disability at 90 days post-TIA.[27] Furthermore, anecdotally, people have reported ongoing symptoms (such as limb weakness, slurred speech, poor articulation, memory problems and fatigue), lack of confidence and emotionalism (feeling more emotional or unable to control emotions) post-TIA and minor stroke.[28]

Primary prevention of stroke and TIA

Given the society burden and potential devastating impact of stroke and TIA on patients and family members, primary prevention is usually preferable to treatment. For the context of this thesis, primary prevention was defined as interventions to prevent stroke or TIA in people with no prior history of stroke. Specifically, drug therapy interventions in primary care were investigated.

Stroke and TIA risk factors

A number of risk factors for stroke and TIA have been identified, some are modifiable and can be targeted through pharmacotherapy and lifestyle interventions and other are non-modifiable but are useful to determine a person's risk of stroke.

Modifiable risk factors

Hypertension

Hypertension (high blood pressure (BP)) has been proposed as the most important risk factor for stroke and TIA; it is attributable to over half of ischaemic strokes.[29] High BP induces stress on blood vessels which can lead to atherosclerosis (narrowing and hardening

of blood vessels). In turn, this causes a blockage which results in ischaemic stroke or TIA, or causes a blood vessel in the brain to burst which leads to bleeding and haemorrhagic stroke.[29] The global prevalence of hypertension in 2000 was 972 million and 26% of the adult population were estimated to have hypertension.[30] There is a positive and continuous relationship between increasing BP and stroke.[31,32] Hypertension is asymptomatic and influenced by lifestyle, including smoking, alcohol intake, inactivity and diet.[33] Furthermore, hypertension is more prevalent with increasing age[30] and people of South Asian and African-Caribbean ethnicities are generally at higher risk compared to white people.[34] Antihypertensive drugs have been found to reduce stroke incidence and evidence for the effectiveness of these drugs is strong.[35]

Atrial fibrillation (AF)

Atrial fibrillation (AF) is characterised by an irregular heart rhythm and associated with a five-fold increase in stroke risk.[36] Furthermore, strokes in people with AF are associated with greater mortality and disability compared to people without AF.[37] Reduced blood flow from the irregular heart rhythm increases risk of blood clots forming in the heart which can migrate to the brain and cause stroke.[38] The global prevalence of AF is 33.5 million and prevalence increases with age.[39] Independent stroke risk factors have been identified for people with AF, including older age (≥65 years), female sex, history of stroke or TIA, congestive heart failure (CHF), hypertension, vascular disease and diabetes.[40] Aspirin was found to reduce stroke risk in AF patients; however, anticoagulant drugs have now been shown to be more effective.[41] Furthermore, the reduction of stroke risk through anticoagulation with warfarin is very high[42] (particularly compared to lipid lowering and

antihypertensive drugs) and novel anticoagulant drugs are now available which are potentially safer based on current evidence.[43]

Dyslipidaemia

Dyslipidaemia, abnormal amount of lipids in the blood, is defined as high levels of total or low-density lipoprotein (LDL) cholesterol or low levels of high-density lipoprotein (HDL) cholesterol.[44] The association between cholesterol levels and stroke is complex; high levels of total cholesterol have been found to increase the risk of ischaemic stroke,[45] but protect against haemorrhagic stroke.[46] There are inconsistencies from epidemiological studies regarding the association between lipid levels and stroke risk;[47,48] however, lipid lowering drugs have been found to be effective at reducing stroke incidence.[49] In addition to lifestyle factors, particularly diet, high cholesterol can be caused by familial hypercholesterolemia, a genetic condition with a UK prevalence of 1 in 500.[50]

Other modifiable risk factors

Risk of stroke is at least doubled by smoking,[51] consuming large amounts of alcohol[52] and having diabetes.[53] Other lifestyle factors, including diet (high in saturated fat or salt), obesity and physical inactivity, contribute to increase stroke risk through raising cholesterol levels, BP and risk of diabetes.[54]

Non-modifiable risk factors

Non-modifiable risk factors for stroke and TIA are important to determine a person's risk of stroke. Age is the most important non-modifiable risk factor; the incidence and prevalence of stroke and TIA increases with age[13] and risk of stroke doubles every decade after age 55 years.[55] Male sex is considered a risk factor for stroke; men have a higher incidence of stroke

and their mean age of first stroke is approximately five years younger compared to women.[56] In the UK, people of South Asian and African-Caribbean ethnicities have been found to have increased stroke risk compared to the national average.[57] In addition, having a family history of stroke is associated with increased stoke risk.[58]

Evidence-based guidelines for the prevention of stroke and TIA

Evidence-based guidelines which identify people who are at high risk of stroke and TIA and recommend appropriate pharmacotherapy and lifestyle interventions have been developed for use in primary care. NICE guidelines relevant to the research within this thesis are discussed below and include hypertension, AF and lipid modification guidelines.[43,59,60]

Hypertension guidelines recommend that antihypertensive drug prescribing is considered in the context of cardiovascular disease (CVD) and CVD risk, not solely BP measurements.[59] Antihypertensive drugs should be prescribed to people with sustained high BP (≥160/100 mmHg) or moderately high BP (≥140/90 mmHg) and established CVD or high CVD risk.[59] Lifestyle advice regarding smoking, alcohol intake, diet and exercise should also be administered. People with sustained moderately high BP (≥140/90 mmHg) but no other risk factors should receive lifestyle advice and be reviewed annually.

AF guidelines take into consideration the independent stroke risk factors for people with AF and recommend that patients' stroke risk is estimated using a risk algorithm (Table 2).[60] The 2006 NICE AF guideline[61] recommended that patients at low risk of stroke are prescribed aspirin for stroke prevention, at moderate risk are prescribed aspirin or anticoagulant drugs and at high risk are prescribed anticoagulant drugs. However, the guideline was updated in the 2014[60] to recommend anticoagulation, using warfarin or new oral anticoagulants, in high

risk patients (defined as CHA_2DS_2-VASc score ≥2) and specifies that aspirin monotherapy should not be used for stroke prevention. Anticoagulant drugs should be considered for males with a CHA_2DS_2-VASc score of 1, but stroke prevention drugs should not be prescribed to females with a CHA_2DS_2-VASc score of 1, (one point is given for female sex) or males with a score of 0.[60]

Lipid modification guidelines recommend prescription of lipid lowering drugs based on CVD risk as opposed to blood cholesterol levels. [43] The guidelines advise that lipid lowering drugs are prescribed and lifestyle advice administered to people with existing CVD or at high risk of CVD. For calculated CVD risk, the 2008 lipid modification guidelines[62] used a threshold of a 10-year CVD risk of ≥20%; however, this was lowered to ≥10% in the updated 2014 guidelines.[43]

Potential barriers to stroke and TIA prevention in primary care

The decrease in the incidence of stroke and TIA is associated with an increase in prescribing trends of primary prevention drugs.[15] However, evidence suggests prescribing remains suboptimal and there are barriers to guideline adherence.[63-65] Cabana et al (1999) identified multiple and diverse barriers to physicians' adherence to guidelines which included factors related to physicians' knowledge of the guidelines (lack of awareness or familiarity), physicians' attitudes towards the guidelines (lack of agreement, self-belief, outcome expectancy) and external barriers (time or resource constrains, organisational barriers, patient factors).[66]

Barriers for adherence to guidelines relevant for stroke prevention have been demonstrated and impact on prevention drug prescribing. For antihypertensive prescribing, barriers

identified were: lack of agreement with guidelines;[67] accepting higher BP thresholds than guideline recommendations; belief that benefits for the patient does not outweigh the potential harms or there were side effects; and knowledge of patients' non-adherence to medication.[67,68] For anticoagulant prescribing, a systematic review reported that the main barriers were associated with clinicians' attitude towards the guidelines and external factors, including those related to patients' age, comorbidities and risk of bleeding or falls.[69] In relation to lipid modification guidelines, a qualitative study reported barriers to statin prescribing included: interpretation of risk tools, concerns about medicalisation of patients, patients' non-adherence to medication and organisational issues.[65] Studies have reported under-prescribing of stroke prevention drugs to patients with clinical indications for these drugs[63,64,70-72] and over-prescribing to patients without clinical indications.[73,74]

Management of stroke, minor stroke and TIA

Treatment pathways are summarised in Figure 1. Rapid response to stroke and TIA reduces death, disability and recurrent events.[75] Therefore, fast diagnosis and referral to specialist stroke services is essential. Recognition of stroke or TIA symptoms are important; the Face Arms and Speech Test (FAST)[76] is a validated tool which can be used by members of the public or healthcare professionals and the Recognition of Stroke in the Emergency Room (ROSIER) score[77] is a more detailed tool used in emergency departments (Table 2). People with suspect TIA and stroke should have blood sugar checked by first responders to exclude hypoglycaemia, which can cause stroke and TIA-like symptoms, and be transferred to a specialist stroke unit within one hour of symptoms onset.[6] The pathways for management of stroke and TIA are differentiated by whether symptoms have resolved at the time of assessment and there is not a distinct pathway for the management of minor stroke.[6]

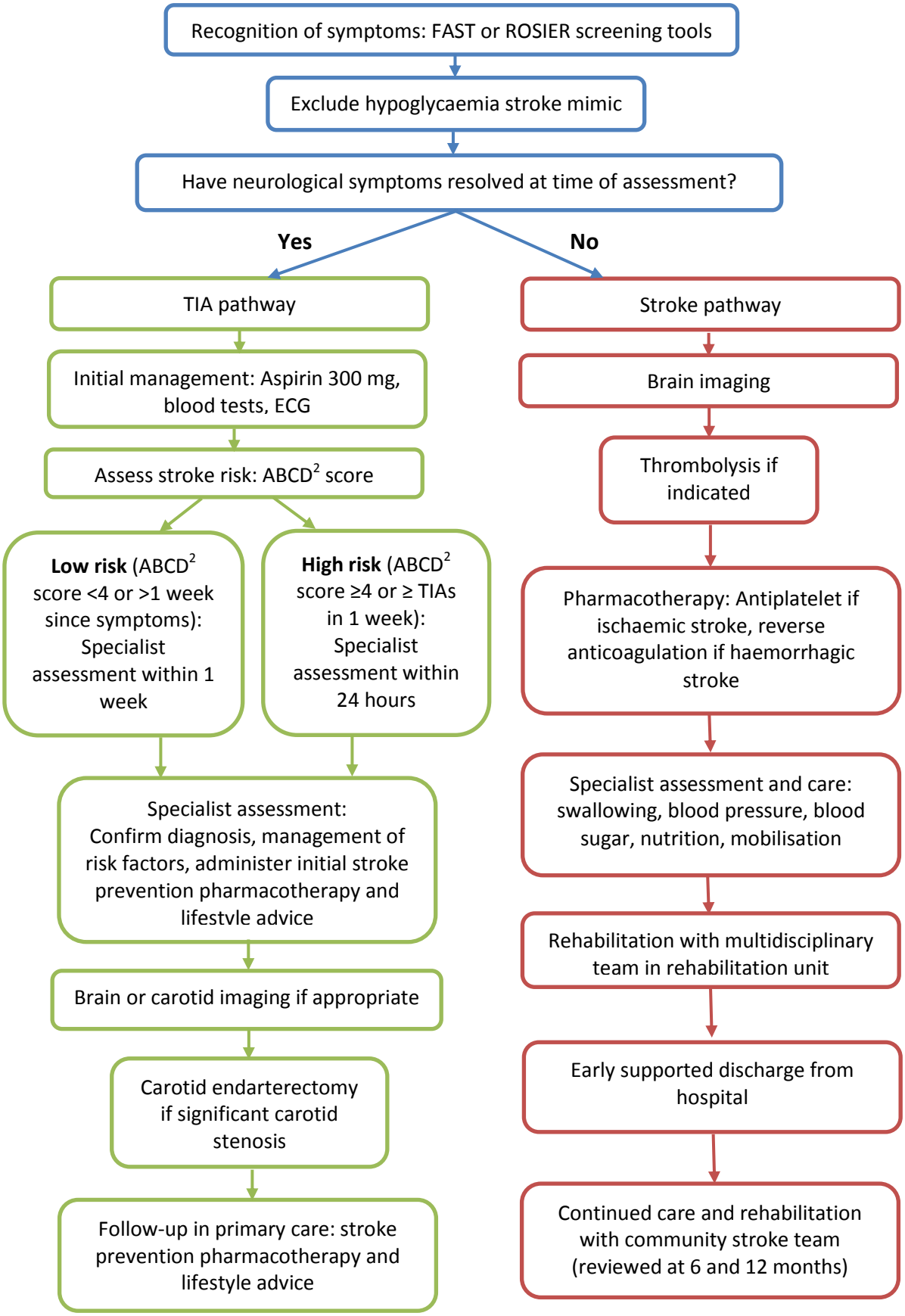

Figure 1: Summary of treatment pathways for stroke and transient ischaemic attack (TIA). Adapted from National Institute for Health and Care Excellence (NICE) pathways.[79]

Stroke

If neurological symptoms persist, a patient is considered to have a stroke during the initial assessment.[6] Brain imaging should be performed within one hour if indicated (such as known bleeding tendency or thrombolysis indicated) or 24 hours if no indications.[6] For ischaemic strokes, thrombolysis with alteplase should be administered within four and a half hours, if indicated from the brain imaging.[75] Acute treatment in the specialist stroke unit comprises of antiplatelet therapy for ischaemic stroke and reversal of anticoagulation for haemorrhagic stroke if indicated. Further specialist assessments and care includes: electrocardiogram (ECG), early mobilisation, assessment of swallowing function, continence assessment, nutritional supplements, BP and blood sugar control, surgery for intracerebral haemorrhage (if deemed appropriate) and anticoagulant and statin therapy.[78]

Following acute treatment, stroke patients are assessed to determine the extent of impairments and disability and may be transferred to a rehabilitation unit.[78] Stroke can cause a wide range of impairments which vary in severity and can affect cognition, emotion, speech, function, vision, hearing and balance.[78] Patients should be screened and goals set by a multidisciplinary rehabilitation team including: clinicians, nurses, physiotherapists, occupational therapists, speech and language therapists and social workers.[6] Before hospital discharge, an early support discharge plan is developed whereby patients' health and social care needs are assessed, including support and training requirements for carers and family members.[6] Following discharge, rehabilitation is continued in primary care and with community stroke teams. A patient tailored health and social care plan is developed to support patients and carers, including return to work, and is reviewed at six months and then annually.[6]

TIA

According to the NICE guidelines, a diagnosis of TIA should be considered if neurological symptoms resolved within a few hours. [6] Initial management comprises of administration of aspirin (300 mg) and/or modified-release dipyridamole to prevent occlusive vascular events; blood tests, including fasting blood glucose and lipids, platelets and renal function; and an ECG test to exclude AF.[76] A validated tool should be used to assess stroke risk, such as the $ABCD^2$ score (Age, Blood pressure, Clinical features of TIA, Duration of symptoms, Diabetes).[80] People should be considered at high risk of stroke if they have an $ABCD^2$ score ≥4 or present with two or more TIAs in one week.[76] High risk patients receive specialist assessment within 24 hours.[76] People with an $ABCD^2$ score <4 or who present more than a week after symptoms have resolved should be considered at low risk of stroke and receive specialist assessed within one week.[76] Specialist assessment should confirm the diagnosis, assess risk factors, administer initial pharmacotherapy and lifestyle advice and, if appropriate, refer for brain and carotid imaging. People should undergo brain imaging if the vascular territory or pathology is uncertain or haemorrhage needs to be excluded.[6] Carotid imaging should be completed within one week if carotid endarterectomy is considered. If carotid imaging shows evidence of significant carotid stenosis, carotid endarterectomy should be performed within two weeks.[6] People with a confirmed diagnosis of TIA are followed-up at one month in primary or secondary care and then annually in primary care.[81] Follow-up comprises of review of drug therapy and lifestyle advice for stroke and TIA prevention.[81]

Justification for research

Missed opportunities for primary stroke and TIA prevention

The burden of stroke and TIA to patients and society is substantial;[16] therefore, primary prevention is important to reduce their incidence and subsequent burden. Hypertension, AF and dyslipidaemia are important modifiable risk factors for stroke and TIA. There is a strong evidence-base for the effectiveness of primary prevention drugs which target these risk factors and reduce stroke incidence; comprehensive primary care guidelines identify people at high stroke risk and are eligible for prevention drugs.[43,59,60] There is evidence of improvement in the prescribing of primary prevention drugs between 1999 and 2008;[15] however, literature suggests that prescribing remains suboptimal.[63,64,70-72] Therefore, it is important to quantify missed opportunities for prevention prior to stroke or TIA to determine if primary prevention in primary care is inadequate.

Residual impairments after TIA

The care pathway for TIA patients is focused on prevention of subsequent TIA or stroke. Symptoms of TIA are short-lasting; however, there is anecdotal evidence to suggest that these patients may experience ongoing impairments.[28] If TIA causes ongoing impairments, these impairments may impact on patients' health and wellbeing. Therefore, it is important to understand the holistic consequences of TIA to ensure patents receive adequate health care.

Aims

The research within this thesis aimed to determine: (i) the extent to which people that had a stroke or TIA had prior missed opportunities for prevention with pharmacotherapy and (ii) if TIA patients experience ongoing residual impairments after initial symptoms have resolved.

Objectives

1. To quantify missed opportunities for primary stroke and TIA prevention with lipid lowering, anticoagulant and antihypertensive drugs through analysis of electronic primary care records.
2. To identify patient characteristics associated with missed opportunities for primary prevention of stroke and TIA.
3. To establish the prevalence of fatigue, cognitive and psychological impairment post-TIA and minor stroke through a systematic review of the literature.
4. To investigate if TIA is associated with consultation for fatigue, psychological or cognitive impairment in primary care in an age and gender matched population from an electronic primary care database.

References

1. Easton JD, Saver JL, Albers GW, et al. Definition and Evaluation of Transient Ischemic Attack: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease: The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke.* 2009;40(6):2276-2293.
2. Fischer U, Baumgartner A, Arnold M, et al. What Is a Minor Stroke? *Stroke.* 2010;41(4):661-666.
3. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st Century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2013;44(7):2064-2089.
4. Stroke Association. What are the symptoms of stroke? https://www.stroke.org.uk/what-stroke/what-happens-when-you-have-stroke/what-are-symptoms-stroke. Accessed October, 2015.
5. Flynn D, Ford GA, Rodgers H, Price C, Steen N, Thomson RG. A time series evaluation of the FAST national stroke awareness campaign in England. *PLoS ONE.* 2014;9(8):e104289.
6. National Institute for Health and Clinical Excellence (NICE). Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE Clinical Guideline 68. 2008.
7. National Institute of Health Stroke Scale (NIHSS). http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf. Accessed October, 2015.
8. National Institute of Neurological and Communicative Disorders and Stroke. A classification and outline of cerebrovascular diseases. II. *Stroke.* 1975;6(5):564-616.
9. Kidwell CS, Alger JR, Di Salle F, et al. Diffusion MRI in patients with transient ischemic attacks. *Stroke.* 1999;30(6):1174-1180.
10. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack--proposal for a new definition. *The New England Journal of Medicine.* 2002;347(21):1713-1716.
11. World Health Organisation (WHO). The WHO Family of International Classifications. http://apps.who.int/classifications/en/. Accessed October, 2015.
12. Kirkpatrick S, Locock L, Giles MF, Lasserson DS. Non-focal neurological symptoms associated with classical presentations of transient ischaemic attack: qualitative analysis of interviews with patients. *PLoS ONE.* 2013;8(6):e66351.
13. Scarborough P, Peto V, Bhatnagar P, et al. Stroke statistics. British Heart Foundation and Stroke Association: London; 2009.
14. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet.* 2014;383(9913):245-255.
15. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database. *BMJ Open.* 2011;1(2):e000269.
16. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet Global Health.* 2013;1(5):e259-e281.
17. National Institute for Health and Clinical Excellence (NICE). Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)- Costing report, in NICE Clinical Guideline 68. 2008:1-38.

18. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *The Lancet.* 2005;366(9499):1773-1783.
19. Hippisley-Cox J, Pringle M, Ryan R. *Stroke: prevalence, incidence and care in general practices 2002 to 2004. Final report to the National Stroke Audit Team. Royal College of Physicians: London* 2004.
20. Johnston SC, Fayad PB, Gorelick PB, et al. Prevalence and knowledge of transient ischemic attack among US adults. *Neurology.* 2003;60(9):1429-1434.
21. Wang Y, Zhao X, Jiang Y, et al. Prevalence, knowledge, and treatment of transient ischemic attacks in China. *Neurology.* 2015;84(23):2354-2361.
22. Stroke Association. State of the nation: stroke statistics. 2015; https://www.stroke.org.uk/sites/default/files/stroke_statistics_2015.pdf. Accessed October, 2015.
23. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke.* 1994;25(2):333-337.
24. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet.* 2012;380(9859):2095-2128.
25. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet.* 2012;380(9859):2197-2223.
26. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ (Clinical Research Ed.).* 2004;328(7435):326.
27. Coutts SB, Modi J, Patel SK, et al. What causes disability after transient ischemic attack and minor stroke?: Results from the CT and MRI in the Triage of TIA and minor Cerebrovascular Events to Identify High Risk Patients (CATCH) Study. *Stroke.* 2012;43(11):3018-3022.
28. Residual symptoms after transient ischaemic attack (TIA). http://www.healthtalk.org/peoples-experiences/nerves-brain/tia-and-minor-stroke/residual-symptoms-after-transient-ischaemic-attack-tia. Accessed October, 2015.
29. Lawes CMM, Hoorn SV, Rodgers A. Global burden of blood-pressure-related disease, 2001. *The Lancet.* 2008;371(9623):1513-1518.
30. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *The Lancet.* 2005;365(9455):217-223.
31. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet.* 2002;360(9349):1903-1913.
32. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1: Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *The Lancet.* 1990;335(8692):765-774.
33. Beilin LJ, Puddey IB, Burke V. Lifestyle and hypertension. *American Journal of Hypertension.* 1999;12(9):934-945.
34. Brown MJ. Hypertension and ethnic group. *BMJ (Clinical Research Ed.).* 2006;332(7545):833-836.
35. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* 2003;289(19):2534-2544.
36. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983-988.

37. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke.* 1996;27(10):1760-1764.
38. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. *Stroke.* 2001;32(3):803-808.
39. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation.* 2014;129(8):837-847.
40. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: The framingham heart study. *JAMA.* 1994;271(11):840-844.
41. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *The Lancet.* 2007;370(9586):493-503.
42. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2005(3):Cd001927.
43. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline 181. National Clinical Guideline Centre; 2014.
44. Fodor G. Primary prevention of CVD: treating dyslipidaemia. Systematic review 215 *BMJ Clinical Evidence.* 2008: Pii0215
45. Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *International Journal of Epidemiology.* 2003;32(4):563-572.
46. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke.* 2013;44(7):1833-1839.
47. The Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. *The Lancet.* 1995;346(8991-8992):1647-1653.
48. Zhang X, Patel A, Horibe H, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *International Journal of Epidemiology.* 2003;32(4):563-572.
49. Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke.* 2004;35(12):2902-2909.
50. National Institute for Health and Care Excellence (NICE). Identification and management of familial hypercholesterolaemia. Clinical guideline 71. National Clinical Guideline Centre; 2008.
51. Thun MJ, Carter BD, Feskanich D, et al. 50-Year Trends in Smoking-Related Mortality in the United States. *The New England Journal of Medicine.* 2013;368(4):351-364.
52. Guiraud V, Amor MB, Mas JL, Touze E. Triggers of ischemic stroke: a systematic review. *Stroke.* 2010;41(11):2669-2677.
53. Banerjee C, Moon YP, Paik MC, et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke.* 2012;43(5):1212-1217.
54. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2014;45(12):3754-3832.
55. Hollander M, Koudstaal P, Bots M, Grobbee D, Hofman A, Breteler M. Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. *Journal of Neurology, Neurosurgery and Psychiatry.* 2003;74(3):317-321.
56. Appelros P, Stegmayr B, Terént A. Sex Differences in Stroke Epidemiology: A Systematic Review. *Stroke.* 2009;40(4):1082-1090.

57. Chaturvedi N. Ethnic differences in cardiovascalr disease. *Heart.* 2003;89(6):681-686.
58. Liao D, Myers R, Hunt S, et al. Familial history of stroke and stroke risk: rhe family heart study. *Stroke.* 1997;28(10):1908-1912.
59. National Institute for Health and Clinical Excellence (NICE). Hypertension: the clinical management of primary hypertension in adults. Clinical Guideline 127. National Clinical Guideline Centre; 2011.
60. National Institute for Health and Clinical Excellence (NICE). Atrial fibrillation: the management of atrial fibrillation. Clinical Guideline 180. National Clinical Guideline Centre; 2014.
61. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: national clinical guideline for management in primary and secondary care. Clinical Guideline 36. National Clinical Guideline Centre; 2006.
62. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. Clinical Guideline 67. National Clinical Guideline Centre; 2008.
63. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *The American Journal of Medicine.* 2010;123(7):638-645.e634.
64. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2010;17(5):530-540.
65. Kedward J, Dakin L. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *The British Journal of General Practice.* 2003;53(494):684-689.
66. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA.* 1999;282(15):1458-1465.
67. Lin ND, Martins SB, Chan AS, et al. Identifying barriers to hypertension guideline adherence using clinician feedback at the point of care. *AMIA Annual Symposium Proceedings.* 2006:494-498.
68. Midlov P, Ekesbo R, Johansson L, et al. Barriers to adherence to hypertension guidelines among GPs in southern Sweden: a survey. *Scandinavian Journal of Primary Health care.* 2008;26(3):154-159.
69. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. *Age and Ageing.* 2011;40(6):675-683.
70. Missault L, Witters N, Imschoot J. High cardiovascular risk and poor adherence to guidelines in 11 069 patients of middle age and older in primary care centres. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2010;17(5):593-598.
71. Palm F, Kleemann T, Dos Santos M, et al. Stroke due to atrial fibrillation in a population-based stroke registry (Ludwigshafen Stroke Study) CHADS2, CHA2DS2-VASc score, underuse of oral anticoagulation, and implications for preventive measures. *European Journal of Neurology.* 2013;20(1):117-123.
72. Partington SL, Abid S, Teo K, Oczkowski W, O'Donnell MJ. Pre-admission warfarin use in patients with acute ischemic stroke and atrial fibrillation: The appropriate use and barriers to oral anticoagulant therapy. *Thrombosis Research.* 2007;120(5):663-669.
73. Lip GY, Rushton-Smith SK, Goldhaber SZ, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. *Circulation. Cardiovascular Quality and Outcomes.* 2015;8(2 Suppl 1):S12-20.

74. Wu J, Zhu S, Yao GL, Mohammed MA, Marshall T. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in UK general practice: a national retrospective cohort study. *PLoS ONE.* 2013;8(7):e67611.
75. Deparment of Health. National Stroke Strategy. 2007; http://clahrc-gm.nihr.ac.uk/cms/wp-content/uploads/DoH-National-Stroke-Strategy-2007.pdf. Accessed October, 2015.
76. Tyrrell P, Swain S, Rudd A. Diagnosis and initial management of transient ischaemic attack. Royal College of Physicians; 2010.
77. Nor AM, Davis J, Sen B, et al. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. *The Lancet Neurology.* 2005;4(11):727-734.
78. Intercollegiate Stroke Working Party. National clinical guideline for stroke. Fourth ed. London: Royal College of Physicians; 2012.
79. National Institute for Health and Care Excellence (NICE). NICE pathways: stroke overview. file:///C:/Users/gxt513/Downloads/stroke-stroke-overview.pdf. Accessed October, 2015.
80. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *The Lancet.* 2007;369(9558):283-292.
81. National Institute for Health and Care Excellence (NICE). Follow up after TIA. http://cks.nice.org.uk/stroke-and-tia#!scenariorecommendation:11. Accessed October, 2015.

Chapter 2: General methods

General methods

This thesis is comprised of three studies: a case series analysis, a systematic review and a retrospective cohort study. The case series analysis and retrospective cohort study used electronic primary care medical records extracted from The Health Improvement Network (THIN). This chapter provides a general overview of the methods used and justifies the approach taken. Detailed protocols are presented in Chapters 3, 6 and 8.

Primary care database studies

Two studies (Chapters 3-5 and 8-9) used anonymised electronic primary care medical records extracted from the THIN database. The first investigated missed opportunities for primary prevention of stroke and TIA (case series analysis). The second explored if TIA was associated with consultation for fatigue, psychological or cognitive impairment in primary care (retrospective cohort study). The full protocols for these studies are presented in Chapters 3 and 8.

The Health Improvement Network (THIN) database

THIN is a database that contains anonymised electronic patient records from over 580 general practices from the UK.[1] The THIN database covers approximately 6% of the UK population and includes data on 12 million patients, of which, 3.6 million are active and the remainder are former (left the practice) or deceased patients.[1] Data can be extracted from THIN and used for epidemiological research.[2]

Data collection and extraction

The data collection process is summarised in Figure 1. General practitioners (GPs) record clinically relevant information from consultations using Vision patient records software as part of routine clinical care.[2] Additional administrative data and lab results are also recorded in Vision and demographic data (such as age and sex) are collected when a patient joins the general practice. [2] Anonymised data is collected from contributing general practices through software developed by In Practice Systems (INPS).[2] General practices receive financial incentives to contribute data to THIN.[3] A full collection of retrospective data is completed when a general practice first joins THIN and subsequent data are automatically downloaded on a monthly basis. Intercontinental Marketing Services (IMS) Health, the company which owns THIN, combines data from different general practices within THIN, completes quality checks and provides access to the data for research.[4] The University of Birmingham holds a sub-licence for THIN whereby the entire database is accessible and updated three times a year.[5] Study specific data required for each of the two THIN database studies were extracted by Doctor Ronan Ryan.

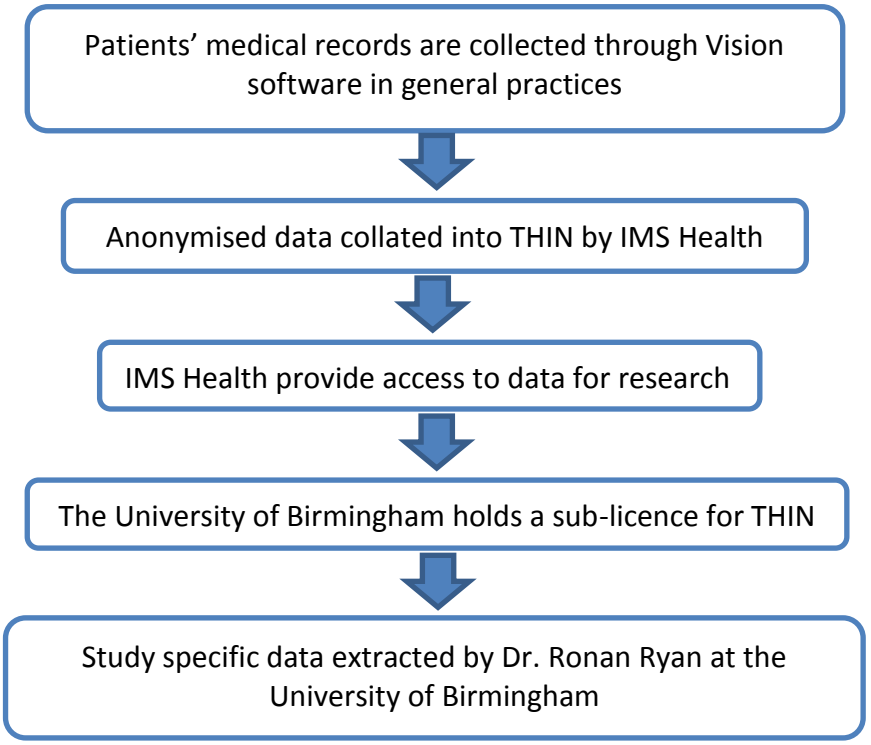

Figure 1: Summary of how data is collected for The Health Improvement Network (THIN) from general practices and made available for research.

Structure of the THIN database

The structure of the THIN database is summarised in Figure 2. Data is organised by general practice then patient and linked by practice ID and patient ID. There are practice files, four main files (patient, therapy, medical and additional health data (AHD) files) and three linked files (postcode variable indicators (PVI), staff and consult files), which are described below.

Practice file

The practice file is a separate file for each general practice which includes date of computerisation, acceptable mortality reporting (AMR) date (when the practice mortality rate is similar to the UK mortality rate),[6] date of last data collection and country. This file is linked to the four main files below.

Main files

1. **Patient file:** Demographic information (including sex and year of birth) and registration information (such as registration date and date patient left the practice).
2. **Therapy file:** Data on prescriptions (including strength and formulation) which is automatically recorded when a GP or nurse issues a prescription.
3. **Medical file:** Diagnoses and symptoms which are recorded at consultations and information provided from secondary care discharge notes.
4. **AHD file:** Other information including lifestyle factors (such as smoking and alcohol), information for preventive healthcare (such as height, weight and cholesterol) and lab test results.

Linked files

1. **PVI file:** Socioeconomic and environmental data at an area level to maintain anonymity (linked to the patient file).
2. **Staff file:** Data on the sex and roles of general practice staff (linked to the therapy, medical and AHD files).
3. **Consult file:** Information on consultations including date, time and duration (linked to the therapy, medical and AHD files).

Data within THIN are presented in the form of coded information, with the exception of free text.[7] Clinical data, including diagnoses, procedures, investigations, signs and symptoms, are coded using Read codes (version 2).[8] Read codes are hierarchical, organised in chapters and categories, and comprise of seven characters (e.g. G64z200: left sided cerebral infarction). Read codes for diagnoses also map to International Classification of Diseases-9 (ICD-9) codes.[8] Additional clinical information, such as clinical measurements, are coded using AHD codes. The therapy file contains drug codes which correspond to specific drug formulations and British National Formulary (BNF) codes which are based on BNF chapters.[9] Anonymised free text comments are contained in the medical and AHD files.[7]

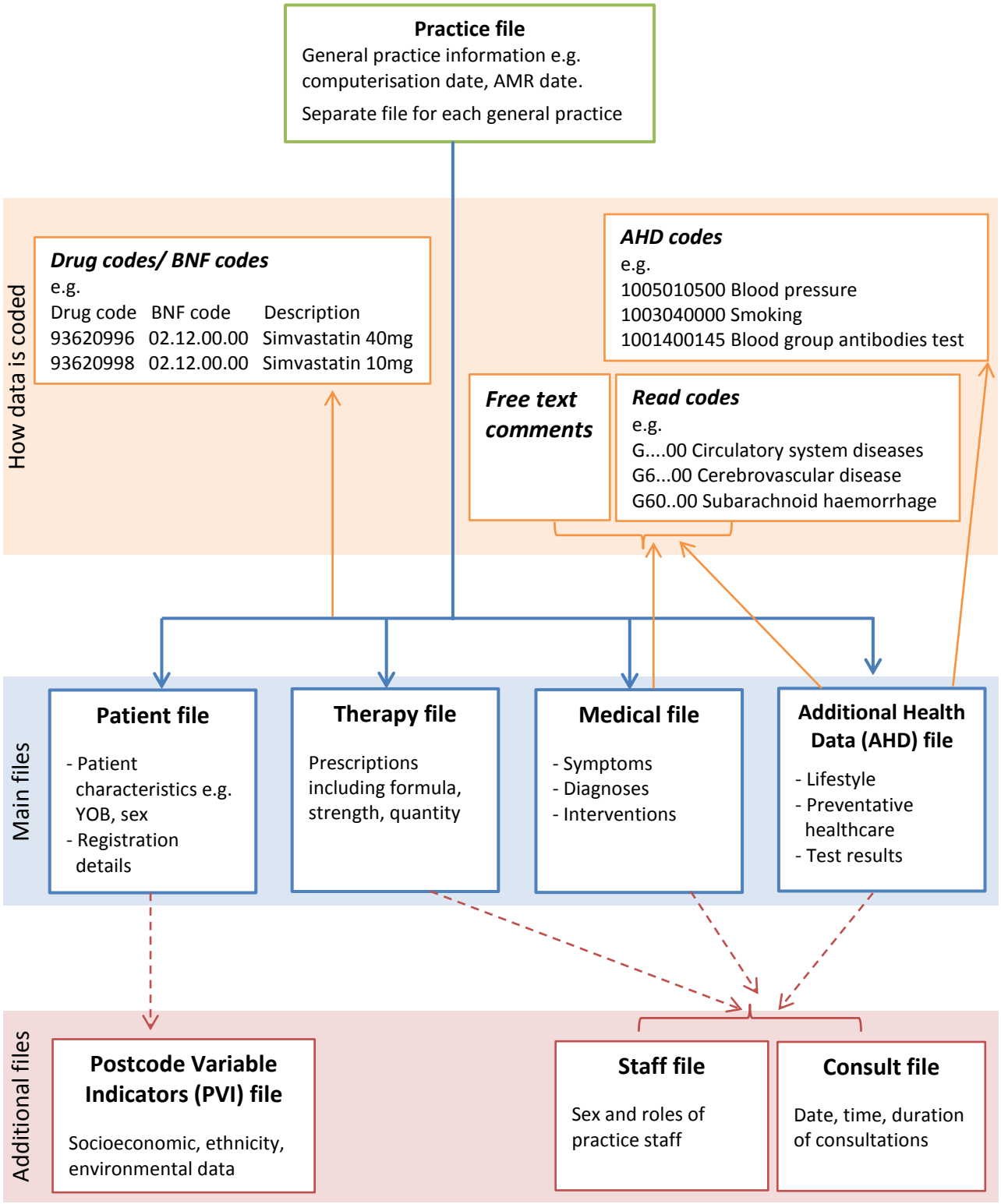

Figure 2: Structure of The Health Improvement Network (THIN) database.

AHD: Additional Health Data; AMR: Acceptable Mortality Rate; BNF: British National Formulary; PVI: Postcode Variable Indicators; YOB: Year of Birth

Defining variables

Prior to data extraction, comprehensive lists of Read and drug codes were developed which defined the population, outcomes, exposures and variables for each study. The Read and drug codes which define these can affect results or interpretation of a study; therefore, it is important that comprehensive search strategies are employed to identify all relevant codes and there is transparency in the reporting of codes. Read code and drug code dictionaries detail the individual codes and corresponding description.[7] A systematic approach was used to identify all relevant Read codes which comprised of: (i) identifying Quality and Outcomes Framework (QOF) Read codes (GPs are incentivised to use QOF Read codes), (ii) searching the Read code dictionary for key words, (iii) conducting hierarchical searches of Read codes identified in the first two steps, (iv) reviewing the literature and (v) consulting a clinician (Professor Tom Marshall). Drug codes were identified through searching the drug code dictionary for relevant BNF chapters. Drug codes corresponding to relevant BNF chapters were reviewed for relevance and checked by clinician Professor Tom Marshall. The selection of AHD codes was more straightforward as individual clinical measurements, such as BP, are identified using a single AHD code.[7] Free text was not used for either of the THIN database studies within this thesis.

Ethical approval

Research which involves National Health Service (NHS) patients requires Research Ethics Committee approval; data collection for THIN was approved by the South East Multicentre Research Ethics Committee (MREC) in 2003.[3] Individual studies using THIN data do not require separate ethical approval if only anonymised THIN data is used. However, these studies must be reviewed by an independent Scientific Review Committee (SRC) to ensure

data is analysed and interpreted appropriately.[10] The two studies within this thesis that used THIN data received SRC approval in May 2013 (reference: 13-023) and February 2014 (reference: 14-008, Appendix 1.2 and 6.2). THIN studies that use non-anonymised patient data, such as patient questionnaires, require additional MREC and local Research and Development (R and D) approval;[10] however, this was not required for the studies within this thesis.

Strengths

One of the main strengths is that the THIN database is representative of usual primary care practice because data are routinely collected and, therefore, non-interventional. The database has geographical spread across the UK, allowing regional sub-analyses, and is broadly representative of the UK population.[11] Over 580 general practices contribute data to THIN; therefore, large sample sizes can be obtained from this database.[1] The data are continuously updated and the database at the University of Birmingham is updated three times a year. Therefore, current data was extracted for each study. Consultations for an individual patient are linked which allows knowledge of patients' medical history and follow-up over time. Furthermore, the data includes people who are often excluded from research, such as pregnant women or the very elderly.

The THIN database contains rich clinical and prescribing data. Vision software is used to print prescriptions and these are automatically retained in the patients' electronic record; therefore, prescribing data is comprehensive and accurate.[2] The quality of clinical data is improved by validation checks within Vision which prevent implausible values being entered, such as height,[7] and the UK pay-for-performance scheme, QOF, which incentivises the

recording and management of patients with common chronic comorbidities.[12] Furthermore, quality checks of THIN data are completed by IMS Health and AMR dates calculated which identify when the practice mortality rate is similar to UK mortality rate.[4] THIN data is amenable to epidemiological study designs and case patients and controls can be extracted from the same source population. A major advantage of the database is the accessibility and relatively minimal time and cost required compared to traditional prospective epidemiological studies that recruit patients. It would not have been feasible to complete the two studies presented in this thesis within the time and financial constraints of the PhD if patients had been prospectively recruited and followed-up.

Limitations

The THIN database has limitations which have implications for research. Importantly, accuracy of the research is dependent on quality of the data recorded by GPs. A key characteristic of electronic primary care patient records is that they are routinely collected for clinical management, not for research purposes. Therefore, GPs may not record information that is not considered important for patients' health care but may be important for research. There is a hierarchy of data accuracy in THIN and, while prescribing and demographic (age and sex) data are comprehensive,[2] lifestyle, socio-economic data and over the counter medication is less accurate and ethnicity is poorly recorded.[7] Furthermore, prescription of a medication does not necessarily mean that it was collected or the drugs were taken by the patient; however, does reflect the behaviour of the GP.

The introduction of QOF improved recording of common long term conditions;[12] however, other conditions not included in QOF may be underreported. QOF was introduced in 2004;

therefore, recoding of QOF conditions before 2004 may be less reliable. Furthermore, changes in QOF may affect the recording of different conditions and associated clinical variables over time.[13] Consideration of QOF changes must be taken into account when looking at time trends. QOF incentives may also introduce a bias in the recording of clinical variables which are incentivised under QOF.[12] Disease severity may not be recorded within primary care databases like THIN if this information is not present in the Read codes.[8] This had implications for the studies within this thesis because minor stroke could not be distinguished from full stroke. In addition, it is not always possible to differentiate between subtypes of stroke (such as ischaemic or haemorrhagic stroke). There will inevitably be missing and incomplete data within general practices and data are not always missing at random.[14] It is possible to infer diagnoses from other data recorded, such as depression from antidepressant drug prescriptions, but this is not feasible for many diagnoses.

General practices are likely to vary in the information they record and how information is coded.[15] Furthermore, data entry is subject to human error and data which requires manual input, such as information from hospital letters, may be less accurate or missing.[16] There are some validation checks within Vision and implausible values can be excluded from the analysis;[7] however, values which are incorrect but plausible are difficult to identify. Furthermore, there is only information available for people who are registered in primary care and timing of data collection can be sporadic, as opposed to planned follow-up time points in a prospective cohort study. Finally, although the size of the THIN database is a major advantage, this may also create a problem of having too much power which may cause statistical significance in all analyses. Therefore, clinical significance should be considered when interpreting results.

Alternative methods and primary care databases

An alternative method to the use of a primary care database for epidemiological studies is to recruit participants to an observational study, such as a prospective cohort study. The advantage of this method is that there is greater control over the data collected and the timing of collection, which may allow more accurate measurement, as opposed to reliance on what information is routinely collected during consultations. In addition, outcomes measured may be more representative of community incidence rather than being reliant on patients consulting in primary care; however, this depends on sampling strategies. The main limitations of conducting a prospective observational study are the high cost and length of follow-up required; two full prospective observational studies would not have been feasible within the time and financial constraints of this PhD. It would also not have been achievable to recruit a large, UK wide sample size which was obtained by use of THIN data. In addition to time and financial burden, prospective observational studies also impose burden on participants. Other methodological limitations of observational studies include those related to recruitment, retention and introduction of bias.[17]

The aims of the thesis could have been explored using qualitative studies. The advantage of qualitative research is that 'why' questions can be asked, such as why clinicians do not prescribe prevention medication to eligible patients. This method also allows context to be explored, such as how residual impairments post-TIA impact on people's lives. However, the objectives of the thesis (such as, quantifying missed opportunities for stroke and TIA prevention and investigating the association between TIA and residual impairments) could not be delivered through qualitative methods.

In addition to THIN, there are other UK primary care databases including Clinical Practice Research Datalink (CPRD; formerly GPRD)[18] and QResearch[19]. CPRD collects primary care data through Vision and Educational Management Information System (EMIS) software and there is an approximate 50% overlap between the general practices which contribute data to THIN and CPRD.[18] In addition, CPRD has links to secondary care data.[18] QResearch also contains electronic primary care patient records and collects data using EMIS software.[19] The THIN database was chosen for the research conducted within this thesis because of accessibility to the data through the sub-licence at the University of Birmingham.

Systematic review

A systematic review, which investigated fatigue, psychological and cognitive impairment after TIA and minor stroke, was completed to identify and synthesise existing literature.

Scoping search

Prior to the systematic review, a scoping search was completed to: (i) determine if there were any existing reviews related to the topic; (ii) obtain an insight into the extent and quality of existing literature; and (iii) inform the search strategy and inclusion criteria for the systematic review.

The scoping searches found one unpublished systematic review which explored functional, emotional and cognitive outcomes after TIA (Brittle 2012).[20] The review included cohort and case-control studies, between 1991 and 2012, which compared TIA patients with no history of stroke to controls free of stroke and TIA. The outcomes were measures of cognition, emotion or physical function. Twelve studies met the inclusion criteria: nine measured

cognition, four depression, two QoL and one activities of daily living. The studies were heterogeneous in the study designs, populations recruited, outcome measures and statistical analyses. Furthermore, the strength of evidence was judged as low or medium in seven out of 12 of studies. Significant differences between TIA patients and controls were reported in five out nine studies which measured cognition, two out of four studies which measured depression and the two studies which measured QoL. A non-significant difference was reported by the study that measured activities of daily living. The main limitations of the review were that non-English papers were excluded and there was a lack of clarity for the outcomes reported. It was unclear how the outcome measures for TIA patients and controls were compared (for example, were difference in mean or total scores compared) and summary measures were not reported for the outcomes. Furthermore, it was unclear if functional, emotional and cognitive outcomes were clinically relevant, which is often identified by a pre-defined cut-off score on validated measurement tools.

The findings of the Brittle (2012)[20] systematic review demonstrated there were few high quality studies which measured residual impairments after TIA. However, further scoping searches found studies relevant to the aims of this thesis which had not met the eligibility criteria for the Brittle (2012)[20] systematic review. Therefore, there was a need to complete a broader systematic review of the literature which was not restricted by study design or English language and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[21] Furthermore, minor stroke patients should be included because, by definition, these strokes are non-disabling[22] and, therefore, follow-up care is likely to focus on secondary stroke prevention similar to TIA patients.[23] To obtain a comprehensive understanding of the literature, inclusion criteria for

my systematic review were kept broad in terms of study design and publication status. Based on scoping searches and anecdotal evidence, the residual impairments included were: fatigue, anxiety, depression, post-traumatic stress disorder (PTSD) and cognitive impairment. Frequency of these impairments post-TIA and minor stroke was selected as the primary outcome to determine the prevalence of impairments post-TIA and minor stroke. The full protocol for the systematic review is presented in chapter 6.

Strengths and limitations

Systematic reviews are generally considered the highest level of information in evidence hierarchies for health care research and the gold standard to synthesise existing evidence.[24] The strengths of conducting a systematic review are that a clearly formulated research question is answered through methods that adhere to a pre-defined protocol, which is explicit and reproducible. A comprehensive and systematic search aims to identify all relevant studies, regardless of publication status, using pre-defined inclusion criteria.[25] The reporting of study characteristics and findings is systematic and transparent. If appropriate, quantitative data can be pooled using statistical techniques in a meta-analysis. Furthermore, quality of the studies and generalisability and reliability of findings are assessed. However, systematic reviews are very time consuming and, despite best efforts, some studies may be missed. Furthermore, the strength of evidence for the findings of the review is dependent on the quality of the studies included.

Alternative methods

Other methods which could have been used to synthesise literature instead of a systematic review include a literature review or rapid review and are discussed below.

Literature review

A literature review attempts to summarise evidence and usually covers a general topic or broad question rather than a focused research question. The methods are not usually described explicitly or pre-specified. Searches of the literature may or may not be systematic, but are limited and usually restricted to published studies. Inclusion criteria and excluded studies are not reported or justified. The included studies are generally not critically appraised and results are synthesised narratively. The advantage of a literature review is that less time and resources are required compared to a systematic review. However, bias may be introduced (for example, publication or authors' bias), it is unlikely that all relevant literature is included and findings may not be reproducible.

Rapid review

Rapid reviews can be a quick and efficient method of evidence synthesis.[26] Specific research questions are answered but these may be broader than those of a systematic review. Systematic review methods are usually employed; however, not as robustly as a systematic review, for example, fewer electronic databases searched. The definition and methodology of rapid reviews are not standardised and vary in which components of a systematic review are included (searching, screening, quality assessment, data extraction, synthesis methods, report structure and number of reviewers).[27] Synthesis of results are usually narrative. The advantage of a rapid review is that less time and resources are required compared to a

systematic review. Rapid reviews are valuable when rapid decision making is required and are often used in commissioning. However, caution is required when interpreting findings because they are not as evidence-based as those of a systematic review.

References

1. Intercontinental Marketing Services (IMS) Health. The Health Improvement Network (THIN) statistics. http://www.csdmruk.imshealth.com/our-data/statistics.shtml. Accessed October, 2015.
2. In Practice Systems (INPS). Vision Software. http://www.inps.co.uk/vision/health-improvement-network-thin. Accessed October, 2015.
3. CSD Helath Research. The Health Improvement Network (THIN) website. http://www.thin-uk.net. Accessed October, 2015.
4. IMS Health. Data collection for The Health Improvement Network (THIN). http://csdmruk.cegedim.com/our-data/data-collection.shtml. Accessed October, 2015.
5. The University of Birmingham: Medical and Dental Sciences. The Health Improvement Network (THIN) database. http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PCCS/THIN/index.aspx. Accessed October, 2015.
6. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiology and Drug Safety.* 2009;18(1):76-83.
7. CSD Medical Research. THIN data guide for researchers. 2014;v2.7:1-114.
8. Health and Social Care Information Centre (HSCIC). Read codes. http://systems.hscic.gov.uk/data/uktc/readcodes. Accessed October, 2015.
9. British National Formulary (BNF). (Accessed October, 2015, at http://www.bnf.org/bnf/index.htm.)
10. IMS Health. THIN database ethics. http://csdmruk.cegedim.com/our-data/ethics.shtml. Accessed October, 2015.
11. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in Primary Care.* 2011;19(4):251-255.
12. Health and Social Care Information Centre (HSCIC). Quality and Outcomes Framework (QOF). http://www.hscic.gov.uk/qof. Accessed October, 2015.
13. Welch C. Longitudinal Recording of Health Indicators. 2012; https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/mi/recording_in_thin/long_record. Accessed October, 2015.
14. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiology and Drug Safety.* 2010;19(6):618-626.
15. Gray J, Orr D, Majeed A. Use of Read codes in diabetes management in a south London primary care group: implications for establishing disease registers. *BMJ (Clinical Research Ed.).* 2003;326(7399):1130.
16. Shephard E, Stapley S, Hamilton W. The use of electronic databases in primary care research. *Family Practice.* 2011;28(4):352-354.
17. Delgado-Rodríguez M, Llorca J. Bias. *Journal of Epidemiology and Community Health.* 2004;58(8):635-641.
18. Clinical Practice Research Datalink (CPRD). http://www.cprd.com/intro.asp. Accessed October, 2015.
19. QResearch. http://www.qresearch.org/SitePages/Home.aspx. Accessed October, 2015.
20. Brittle NG. *Functional, cognitive and emotional outcomes after transient ischaemic attack: a systematic review and controlled cohort study* [M. Phil.]: Primary Care Clinical Sciences, University of Birmingham; 2012.

21. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. http://www.prisma-statement.org/. Accessed October, 2015.
22. Fischer U, Baumgartner A, Arnold M, et al. What is a minor stroke? *Stroke.* 2010;41(4):661-666.
23. National Institute for Health and Clinical Excellence (NICE). Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE guideline 68. 2008.
24. Mulrow CD. Rationale for systematic reviews. *BMJ (Clinical Research Ed.).* 1994;309(6954):597-599.
25. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. *The Cochrane Collaboration* 2011.
26. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. *Systematic Reviews.* 2012;1:10.
27. Harker J, Kleijnen J. What is a rapid review? A methodological exploration of rapid reviews in Health Technology Assessments. *International Journal of Evidence-Based Healthcare.* 2012;10(4):397-410.

Chapter 3: Missed opportunities for prevention of stroke and TIA: Protocol

Retrospective case review of missed opportunities for primary prevention of stroke and TIA in primary care: protocol paper

The absolute numbers of first strokes and stroke-related deaths and disability has increased worldwide.[1] Primary prevention of stroke and TIA is important to reduce the incidence and subsequent burden of these conditions. Lipid lowering, anticoagulant and antihypertensive drugs are effective at reducing incidence of stroke and TIA;[2-5] however, may be underused in primary care.[6-8] The extent of missed opportunities for primary prevention prior to stroke or TIA in the UK is unknown. This chapter presents the protocol for a study which aims to quantify the proportion of strokes and TIAs with prior missed opportunities for prevention with lipid lowering, anticoagulant and antihypertensive drugs. The protocol describes the use of primary care electronic medical records extracted from the THIN database to conduct a retrospective analysis to identify people who had stroke and TIA prevention drugs clinically indicated at the time of their stroke or TIA but were not prescribed them. The findings of this study are presented in Chapter 4 (missed opportunities for lipid lowering drugs) and Chapter 5 (missed opportunities for anticoagulant and antihypertensive drugs). Multiple missed opportunities for prevention with all three drugs are presented in Chapter 5.

References

1. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet Global Health.* 2013;1(5):e259-e281.
2. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2005(3):Cd001927.
3. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2007(3):Cd006186.
4. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* 2003;289(19):2534-2544.
5. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane Database of Systematic Reviews.* 2013;1:Cd004816.
6. Missault L, Witters N, Imschoot J. High cardiovascular risk and poor adherence to guidelines in 11 069 patients of middle age and older in primary care centres. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2010;17(5):593-598.
7. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *The American Journal of Medicine.* 2010;123(7):638-645.e634.
8. Roccatagliata D, Avanzini F, Monesi L, et al. Is global cardiovascular risk considered in current practice? Treatment and control of hypertension, hyperlipidemia, and diabetes according to patients' risk level. *Vascular Health and Risk Management.* 2006;2(4):507-514.

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Retrospective case review of missed opportunities for primary prevention of stroke and TIA in primary care: protocol paper

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ABSTRACT

Introduction: Stroke is a major health problem and transient ischaemic attack (TIA) is an important risk factor for stroke. Primary prevention of stroke and TIA will have the greatest impact on reducing the burden of these conditions. Evidence-based guidelines for stroke/TIA prevention identify individuals eligible for preventative interventions in primary care. This study will investigate: (1) the proportion of strokes/TIAs with prior missed opportunities for prevention in primary care; (2) the influence of patient characteristics on missed prevention opportunities and (3) how the proportion of missed prevention opportunities has changed over time.

Methods and analysis: A retrospective case review will identify first-ever stroke and patients with TIA between 2000 and 2013 using anonymised electronic medical records extracted from the health improvement network (THIN) database. Four categories of missed opportunities for stroke/TIA prevention will be sought: untreated high blood pressure in patients eligible for treatment (either blood pressure ≥160/100 or ≥140/90 mm Hg in patients at high cardiovascular disease (CVD) risk); patients with atrial fibrillation with high stroke risk and no anticoagulant therapy; no lipid modifying drug therapy prescribed in patients at high CVD risk or with familial hypercholesterolaemia. The proportion of patients with each missed opportunity and multiple missed opportunities will be calculated. Mixed effect logistic regression will model the relationship between demographic and patient characteristics and missed opportunities for care; practice will be included as a random effect.

Ethics and dissemination: THIN data collection was approved by the NHS South East Multi-centre Research Ethics Committee (MREC) in 2003. This study was approved by the independent scientific review committee in May 2013. Dissemination of findings has the potential to change practice, improve the quality of care provided to patients and ultimately reduce the incidence of strokes and TIAs. Findings will be published in a peer-reviewed journal and disseminated at national and international conferences.

INTRODUCTION

Stroke is one of the leading causes of mortality and disability in the UK.[1] Transient ischaemic attack (TIA) is characterised by transient stroke-like symptoms and is an important risk factor for stroke. Given there are approximately 110 000 first strokes and 46 000 first TIAs a year reported in the UK,[1 2] primary prevention is important to reduce the burden of stroke and TIA.[3]

Understanding risk factors for stroke and TIA is important to identify people at high risk and implement preventative intervention. Hypertension is arguably the most well-documented risk factor; a positive and continuous relationship has been shown between increasing blood pressure and stroke.[4 5] Atrial fibrillation is associated with a fivefold increase in stroke risk.[6] In addition, evidence suggests strokes in patients with atrial fibrillation are associated with greater disability and higher mortality rates.[6] Cholesterol has been identified as risk factor for stroke; however, the relationship is not well characterised and is likely to be complex. Epidemiological studies have observed an association between lipid levels and stroke[7] but findings are inconsistent across studies.[8] On the other hand, a systematic review of 26 studies found a 20% reduction in strokes with statin therapy compared with placebo or usual care.[9] Other conditions found to increase stroke risk include diabetes and cardiovascular disease (CVD).[10] In addition, lifestyle factors related to diet, obesity, physical inactivity, smoking and alcohol intake have been identified as risk factors for stroke and, moreover, have been shown to interact with other risk factors to exacerbate the risk. For example, obesity is associated with hypertension and high cholesterol.[11]

Age is an important risk factor; incidence and prevalence of stroke and TIA increases with age[2] and stroke risk doubles every decade over 55 years.[12] Male sex has also been identified as a risk factor with men having a higher incidence of stroke compared with women.[13] Although the mechanism is not fully understood, increased stroke

incidence has been observed in south Asian and Afro-Caribbean ethnic groups.[14]

A person's stroke and CVD risk is determined by the combination of different risk factors. Multivariable CVD risk equations have been developed to identify high-risk patients and express risk as a probability over a period of time.[15] Multiple risk equations exist, although they differ slightly in the risk factors included, the majority include age, sex, blood pressure, cholesterol, smoking and diabetes.[16] Patients with atrial fibrillation stroke risk is increased by independent risk factors.[17] Stroke risk algorithms for these patients include the risk factors: age, congestive heart failure, hypertension, diabetes and previous stroke or TIA.[6]

Primary care offers the best opportunity to identify people at high risk of stroke and TIA and administer preventative action. Studies have shown that pharmacological treatments reduce risk by a constant proportion.[18] Evidence-based guidelines relevant to stroke prevention have been developed for hypertension, atrial fibrillation and lipid modification. Hypertension guidelines advise antihypertensive drug therapy is initiated in people with sustained blood pressure ≥160/100 mm Hg or a lower threshold of ≥140/90 mm Hg for people with established CVD, diabetes or an estimated CVD risk of ≥20% over 10 years.[19] Atrial fibrillation guidelines recommend patients' stroke risk is assessed using an algorithm and high-risk patients should be prescribed anticoagulant therapy.[6] Lipid modification guidelines advise lipid lowering drug therapy should be initiated in people considered high risk as opposed to measuring blood cholesterol levels. Guidelines regard high risk as people with established CVD, diabetes or an estimated CVD risk of ≥20% over 10 years and endorse prescription of statins.[16]

Despite the extensive evidence-based guidelines to reduce stroke risk, patients who present at hospital with first stroke have been found to have multiple untreated or undertreated risk factors.[20] Furthermore, it has been found that some general practitioners (GPs) accept higher blood pressure thresholds than recommended by the guidelines[21] and overestimate the proportion of their patients with controlled blood pressure.[22] Existing studies of adherence to stroke prevention guidelines are limited as they use hypothetical questionnaires or retrospective interviews, where responses may differ from actual practice, and often focus on only one risk factor. Considering the complexity of the risk factors for first-time stroke and TIA, a large-scale UK study using real-life primary care data to examine the administration of primary prevention is an important and necessary step to reduce the burden of strokes and TIAs on the National Health Service (NHS) and society.

AIMS

The study aims to investigate: (1) the proportion of first strokes and TIAs with prior missed opportunities for prevention in primary care; (2) the influence of patient characteristics on missed prevention opportunities and (3) how proportions of missed prevention opportunities have changed over time.

METHODS AND ANALYSIS

Study design

A retrospective case review of patients with a first-ever stroke or TIA.

Data source

Relevant data will be extracted from the health improvement network (THIN), a large database of anonymised UK electronic primary care records. Data are comprised of over 500 general practices, include 11.9 million patients and cover 6% of the UK population.[23] The information recorded within THIN is comprehensive and includes demographics, diagnoses, prescriptions, additional health information (eg, lifestyle factors), socioeconomic data and free-text comments. Data are coded using drug codes which correspond to British National Formulary (BNF) chapters[24] and Read codes (V.2).[25] THIN data collection was approved by the NHS South East Multi-centre Research Ethics Committee (MREC) in 2003.[26]

Population

Patients with stroke and TIA between 2000 and 2013 will be identified and relevant data extracted from the THIN database. This study will investigate primary prevention of stroke and TIA; therefore, will comprise of patients with first-ever stroke and TIA. However, as TIA is a risk factor for stroke, patients will be categorised into three groups: stroke only, TIA only, stroke with a history of TIA. To exclude childhood stroke, only patients with a diagnosis of stroke or TIA over 18 years will be included in the study. Date of stroke or TIA will be taken as the index date, and patients must be registered for at least 1 year prior to the index date to allow sufficient time for risk factor data to be recorded. To ensure data quality, the index date must occur at least 1 year after the practice had begun using Vision software, and after the practice date of acceptable mortality recording, the year mortality rates for the practice correspond to expected regional mortality rates.[27]

Outcomes

Four missed opportunities for primary stroke and TIA prevention have been defined through consulting relevant guidelines[6 16 19] and encompass the risk factors hypertension, atrial fibrillation and dyslipidaemia. The missed opportunities will be defined as:

1. *Untreated high blood pressure*: Patients with an average of three blood pressure recordings ≥160 mm Hg for systolic or ≥100 mm Hg for diastolic but no antihypertensive medication has been prescribed.

2. *Untreated moderately high blood pressure and at high CVD risk*: Patients with an average of three blood pressure recordings ≥140 mm Hg for systolic or ≥90 mm Hg for diastolic and have a history of coronary heart disease (CHD), peripheral arterial disease (PAD), chronic kidney disease (CKD), diabetes mellitus and over 40 years or an estimated CVD risk of ≥20% over 10 years but no antihypertensive medication has been prescribed.
3. *Atrial fibrillation and at high risk of stroke with no anticoagulant therapy prescribed*: Patients with atrial fibrillation and a CHADS2 score ≥1 but no anticoagulant medication prescribed.
4. *Patients at high CVD risk or with familial hypercholesterolaemia and no lipid-modifying drug therapy prescribed*: High CVD risk will be defined as having a history of CHD, PAD, CKD, diabetes mellitus and over 40 years or an estimated CVD risk of ≥20% over 10 years.

Definition of outcomes and variables

Stroke/TIA

A comprehensive list of stroke and TIA Read codes has been developed to identify the eligible population (see online supplementary appendix 1). A systematic search strategy was conducted to ensure all relevant Read codes were included:

1. Quality Outcomes Framework (QOF)[28] stroke and TIA Read codes were reviewed for relevance to the study's eligibility criteria. To capture first stroke and TIA, Read codes relating to history of stroke or TIA were removed.
2. To identify additional Read codes not included in QOF, we conducted a hierarchy screening of QOF stroke and TIA Read codes and key word searches using STATA V.12 (College Station, Texas, USA).
3. Literature was searched for additional Read codes and a clinician was consulted.

Missed opportunities variables

To identify patients with blood pressure ≥160/100 or ≥140/90 mm Hg, the average of the three most recent systolic and diastolic blood pressure recordings within 3 years prior to the index date will be used. Diagnoses of atrial fibrillation, CHD, CKD, diabetes mellitus and PAD will be identified using QOF Read codes (V.27).[28] In addition, where present, Read codes indicating history of diagnosis will be used. Similarly, where available, we have identified 'resolved' Read codes (eg, 212H.00 diabetes resolved), which will be used to indicate if the condition resolved before the index date (see online supplementary appendix 2). Familial hypercholesterolaemia is poorly coded in primary care but is associated with total cholesterol of ≥9 mmol/L.[29] Therefore, in addition to Read codes for familial hypercholesterolaemia, total cholesterol of ≥9 mmol/L (most recent record prior to index date) will be used to indicate familial hypercholesterolaemia.

A missed opportunity will be identified if a patient was eligible for primary prevention drug therapy but was not on relevant treatment at the time of stroke or TIA. To determine if patients were on antihypertensive, anticoagulant or lipid-modifying drug therapies before their stroke or TIA, the most recent prescriptions for these drugs prior to the index date will be extracted. Prescriptions will be identified using drug codes corresponding to relevant BNF chapters (V.67) and relevant Read codes (eg, 66Q..11, anticoagulant monitoring; see online supplementary appendix 3). In primary care, 90 days is the maximum prescribing length for any treatment. Therefore, a missed opportunity will be recorded when patients were eligible for treatment but their most recent prescription was over 90 days from the index date and consequently were not on treatment at the time of stroke or TIA. However, prescribing anticoagulant therapy usually involves referral to an anticoagulant clinic; to account for this, an additional lag period of 30 days will be allowed for anticoagulant prescribing (ie, 120 days from the index date). The length of the lag period was determined though consultation with eight practising GPs.

The Framingham risk equation will be used to calculate CVD risk over 10 years (table 1). This risk equation was chosen as it can be incorporated within Vision, the electronic system used by general practices that contribute to the THIN database. In addition, it was the risk score recommended by the guidelines during the majority of the study period[16] and the equation is freely available. For consistency, the Framingham CVD risk will be calculated at the index date for all eligible patients and in accordance with Vision calculations.[30] As recommended by the guidelines, the Framingham CVD risk will be adjusted for South Asian ethnicity and family history of premature CHD.[16] The CHADS2 score will be used to determine stroke risk for patients with atrial

Table 1 Variables required for the Framingham cardiovascular disease risk equation

Variable	Criteria	Default value
Age*	30–74	†
Sex	Male/female	†
Systolic blood pressure	Most recent record prior to index date	†
Total cholesterol	Most recent record prior to index date	6.0
HDL cholesterol	Most recent record prior to index date	Female: 1.4 Male: 1.15
Smoking	Yes/no	
Diabetes mellitus	Yes/no	
ECG-LVH	Yes/no	

*Age at index date.
†Mandatory field.
HDL, high-density lipoprotein; LVH, left ventricular hypertrophy.

fibrillation (table 2). Similar to the Framingham risk equation, CHADS2 will be used because it can be incorporated within Vision and it will be calculated at the index date in compliance with Vision calculations.

Predictor variables

Sociodemographic variables will be extracted including Townsend deprivation quintiles,[31] urban rural scores,[31] strategic health authority[32] and ethnicity. Comorbidities will be identified and defined by QOF Read codes (QOF business rules V.27; see online supplementary appendix 2).[33] To document patients' contact with primary care before their stroke or TIA, the number of consultations in the year prior to the index date and length of registration will be extracted for each patient. In addition, Read codes indicating exceptions for initiating stroke prevention drug therapy will be extracted including white coat hypertension and contraindications to prescribing antihypertensive, anticoagulant or lipid-modifying drugs (eg, 8I3N.00, hypertension treatment refused; see online supplementary appendix 4).

Predictor variables encompassing modifiable and non-modifiable risk factors for stroke and TIA will be extracted. Non-modifiable risk factors include sex and age at index date, whereas modifiable risk factors relate to lifestyle: body mass index (BMI), smoking and alcohol intake. GPs initiating lifestyle interventions has been reported to delay initiation of antihypertensive drug therapy by up to 12 months;[21] therefore, we have also identified Read codes indicating lifestyle interventions related to smoking, alcohol intake, diet, exercise and weight (see online supplementary appendix 5).

Quality checks, missing data and extreme values

Absence of a diagnosis code will be taken to indicate the diagnosis is not present. For categorical variables (eg, smoking status), a separate 'missing' category will be created. Extreme values for blood pressure, total and high-density lipoprotein cholesterol, height and BMI will be identified using the ranges seen in the Health Survey for England statistics as a guide[34] and excluded. Incidence of stroke and TIA diagnoses will be investigated over time to check for indication of unusual variation which might indicate incorrect clinical coding. If appropriate, a cut-off date will be introduced for quality of reporting.

Table 2 Variables required for the CHADS2 stroke risk equation for patients with atrial fibrillation

	Variable	Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S2	Prior stroke or TIA	2

TIA, transient ischaemic attack.

Analysis

The primary analysis will calculate the proportion of strokes and TIAs with missed opportunities for primary prevention drug therapy. Proportions will be calculated for each missed opportunity: untreated high blood pressure; untreated moderately high blood pressure and high CVD risk; atrial fibrillation and high risk of stroke with no anticoagulant therapy prescribed; high CVD risk or with familial hypercholesterolaemia and no lipid-modifying drug therapy prescribed. In addition, the proportion of patients with two, three or four missed opportunities will be calculated.

Secondary analysis will comprise of multivariable logistic regression modelling to predict the effect of demographic and patient characteristics on missed opportunities. The logistic regression model will be mixed effect and include practice as a random effect. Year of stroke will be included to investigate how missed opportunities have changed over time. We aim to develop a model that fits the data well, is biologically meaningful and can be meaningfully interpreted. To achieve this, explanatory variables will be entered into the logistic regression model which have been prespecified and informed through literature searches and clinical input (table 3). There is compelling evidence from the literature that age and sex are important predictors of non-adherence to guidelines in primary care;[21 35 36] therefore, these variables will be included in the model regardless of statistical contribution. Although the other prespecified variables have been informed through the literature and clinical advice, the evidence is limited; for that reason, a backwards elimination approach will be adopted to inform model selection. Backwards elimination will be used as it is favourable over forwards or stepwise selection.[37] Traditionally, a p value of >0.1–0.2 is used as a criteria to eliminate variables. However, our sample size is expected to be large and consequently we will use a p-to-eliminate value of >0.05. Exploratory analysis will be conducted to explore the relationship of the effect of consultation frequency in the year prior to the index date and duration of registration on missed opportunities for stroke and TIA prevention.

DISCUSSION

This study will quantify the proportion of patients in whom opportunities to prevent strokes and TIAs were missed. In addition, it will identify the risk factors with the highest proportion of untreated patients. The results of the regression model will be important to provide insight into patient characteristics that predict missed prevention opportunities. Dissemination of these findings to GPs will raise awareness of patients who are vulnerable to not being prescribed relevant stroke and TIA prevention pharmacotherapy when eligible. Furthermore, the findings have the potential to change practice and improve patient care.

The strength of this study is that data are available from over 500 general practices and reflect actual practice.

Table 3 Explanatory variables for logistic regression modelling

Variable	Categories
Age	5 year age bands
Sex	Male, female
Townsend deprivation quintiles	1, 2, 3, 4 ,5, Missing
Urban/rural score	Urban, rural, missing
Strategic health authority	East of England, East Midlands, London, North East, North West, South Central, South East Coast, South West, West Midlands, Yorkshire and the Humber
Country	England, Northern Ireland, Scotland, Wales
BMI	Healthy, overweight, obese, missing
Smoking status	Current smoker, ex-smoker, non-smoker, missing
Alcohol intake	High, moderate, low, never, missing
Comorbidities: asthma/atrial fibrillation/cancer/CHD/CKD/ COPD/dementia/depression/diabetes mellitus/epilepsy/heart failure/hypertension/hypothyroidism/learning disabilities/ mental health/osteoporosis/palliative care/rheumatoid arthritis	Individually entered: yes/no Number of comorbidities
Lifestyle intervention	Yes/no
Year of stroke	Year
GP practice	Random effect

BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GP, general practitioner.

However, the data will be extracted from routinely collected electronic medical records and, therefore, does not capture the decision-making process which occurs during a consultation. For instance, patients' preferences and GPs knowledge of patient's adherence to medication.[38] Although our study will include comorbidities in the regression model and report Read codes which indicate contraindications for medications, there may be other legitimate reasons for not prescribing stroke prevention drug therapy and patients might decline antihypertensive, anticoagulant or lipid-lowering drug therapy. Inevitably, there will be missing data and errors in data entry; however, this is expected to be a small proportion of the population and we will exclude extreme values and incorporate missing data as a category in the analysis. The use of QOF Read codes to identify comorbidities is likely to result in missing diagnoses that have been recorded using alternative Read codes. However, the use of QOF Read codes provides a consistent method to identify diagnoses and, since being introduced, GPs are incentivised to use QOF Read codes.

In conclusion, this study will offer an insight into whether stroke and TIA risk factors are being managed adequately in UK primary care. Primary prevention of stroke and TIA is important to reduce the burden of these conditions on the NHS and society. If optimal rates of prevention are not being delivered in primary care, dissemination of our findings will be important and further research should be conducted to identify barriers to guideline adherence and intervention(s) to overcome these.

ETHICS AND DISSEMINATION

Individual studies using THIN data do not require separate ethical approval but must be approved by the independent Scientific Review Committee (SRC). The findings will be disseminated through publication in a peer-reviewed journal and presented at national and international conferences.

Contributors GMM led the design of the study as doctoral research supervised by TM, MC and MGF. GMM drafted the manuscript. TM, MC and MGF provided feedback on the manuscript and all authors approved the final version.

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Competing interests None.

Ethics approval This study was approved by the SRC on 31 May 2013 (reference number: 13-023)

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Scarborough P, Peto V, Bhatnagar P, *et al*. *Stroke statistics*. London: British Heart Foundation and Stroke Association, 2009.
2. Townsend N, Wickramasinghe K, Bhatnagar P, *et al*. *Coronary heart disease statistics 2012 edition*. London: British Heart Foundation, 2012.
3. The Lancet Editorial. Stroke-prevention is better than cure. *Lancet* 2007;369:247.
4. Lewington S, Clarke R, Qizilbash N, *et al*. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.
5. MacMahon S, Peto R, Cutler J, *et al*. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765–74.
6. National Collaborating Centre for Chronic Conditions. *Atrial fibrillation: national clinical guideline for management in primary and secondary care*. London: Royal College of Physicians, 2006.

7. Zhang X, Patel A, Horibe H, *et al*. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol* 2003;32:563–72.
8. The Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. *Lancet* 1995;346:1647–53.
9. Amarenco P, Labreuche J, Lavallee P, *et al*. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;35:2902–9.
10. Goldstein LB, Bushnell CD, Adams RJ, *et al*. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:517–84.
11. Brown CD, Higgins M, Donato KA, *et al*. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res* 2000;8:605–19.
12. Hollander M, Koudstaal PJ, Bots ML, *et al*. Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. *J Neurol Neurosurg Psychiatry* 2003;74:317–21.
13. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic review. *Stroke* 2009;40:1082–90.
14. Tillin T, Hughes A, Mayet J, *et al*. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited)—a prospective population-based study. *J Am Coll Cardiol* 2013;61:1777–86.
15. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;91 (Suppl V):1–52.
16. National Institute for Health and Clinical Excellence. *Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67*. National Collaborating Centre for Primary Care, 2008.
17. The Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;69:549–54.
18. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423–7.
19. National Institute for Health and Clinical Excellence. *Hypertension: the clinical management of primary hypertension in adults. Clinical Guideline 127*. National Clinical Guideline Centre, 2011.
20. Guptha SH, Shibu P, Owusu-Agyei P. Stroke prevention: missed opportunities. *Lancet* 369:904–5.
21. Midlov P, Ekesbo R, Johansson L, *et al*. Barriers to adherence to hypertension guidelines among GPs in southern Sweden: a survey. *Scand J Prim Health Care* 2008;26:154–9.
22. Steinman MA, Fischer MA, Shlipak MG, *et al*. Clinician awareness of adherence to hypertension guidelines. *Am J Med* 2004;117:747–54.
23. CSD Medical Research UK. CSD Medical Research UK [cited September 2014]. http://csdmruk.cegedim.com/index.html
24. British National Formulary (BNF). British National Formulary (BNF) 67 2014. http://www.bnf.org/bnf/index.htm
25. Health and Social Care Information Centre. Read Codes 2014 [cited September 2014]. http://systems.hscic.gov.uk/data/uktc/readcodes
26. CDS Health Research. The Health Improvement Network Ethics [cited September 2014]. http://www.thin-uk.com/mrec.htm
27. Maguire A, Blak B, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf* 2009;18:76–83.
28. Health and Social Care Information Centre. Quality and Outcomes Framework (QOF) 2014 [cited September 2014]. http://www.hscic.gov.uk/qof
29. Koivisto PV, Koivisto UM, Miettinen TA, *et al*. Diagnosis of heterozygous familial hypercholesterolemia. DNA analysis complements clinical examination and analysis of serum lipid levels. *Arterioscler Thromb Vasc Biol* 1992;12:584–92.
30. In Practice Systems Ltd. CVD/Stroke Risk Calculators within Vision 2012 [cited September 2014]. http://www.inps.co.uk/my-vision/user-guides-downloads/user-guides/releases/vision-releases
31. CSD Medical Research UK. THIN Data Guide for Researchers. 2013; Vol 2.6.
32. Public Health England. Strategic Health Authorities in England 2014 [cited September 2014]. http://www.swpho.nhs.uk/default.aspx?RID=27853
33. Primary Care Commissioning. QOF business rules v27 2013 [cited September 2014]. http://www.pcc-cic.org.uk/article/qof-business-rules-v27
34. Health Survey for England. Health Survey for England (HSE)—2012 adult trend tables 2012 [cited September 2014]. http://www.hscic.gov.uk/pubs/hse10trends
35. Ramsay SE, Whincup PH, Wannamethee SG, *et al*. Missed opportunities for secondary prevention of cerebrovascular disease in elderly British men from 1999 to 2005: a population-based study. *J Public Health* 2007;29:251–7.
36. McKinlay JB, Link CL, Freund KM, *et al*. Sources of variation in physician adherence with clinical guidelines: results from a factorial experiment. *J Gen Intern Med* 2007;22:289–6.
37. Mantel N. Why stepdown procedures in variable selection. *Technometrics* 1970;12:621–5.
38. Cabana MD, Rand CS, Powe NR, *et al*. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458–65.

Appendices for Chapter 3

Chapter 4: Missed opportunities for prevention of stroke and TIA: Results

Part One: Lipid lowering drugs

Missed opportunities for prevention of stroke or TIA with lipid lowering drugs

Dyslipidaemia is an important modifiable risk factor for stroke and TIA,[1] but can be targeted through intervention with lipid lowering drugs to reduce the incidence of stroke and TIA.[2] This chapter presents the findings of the retrospective analysis of primary care electronic medical records described in Chapter 3 for the lipid lowering drugs analysis. The aims were to determine: (i) the proportion of strokes and TIAs with prior missed opportunities for prevention with lipid lowering drugs; (ii) the relationship between patient and demographic characteristics and the probability of having a missed opportunity; and (iii) how the proportion of missed opportunities for prevention with lipid lowering drugs has changed over time.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. *Global burden of disease and risk factors.* Washington (DC): World Bank; 2006.
2. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane Database of Systematic Reviews.* 2013;1:Cd004816.

Dissemination

Year	Conference	Location	Oral/Poster
2015	College of Medical and Dental Sciences Festival of Graduate Research	Birmingham, UK	Oral presentation ***Awarded best abstract from the School of Health and Population Sciences**
	Society of Academic Primary Care (SAPC) South West Regional Conference	Birmingham, UK	Oral presentation
	North American Primary Care Research Group (NAPCRG) Annual Meeting	Cancun, Mexico	Distinguished paper oral presentation ***Abstract ranked in top 5 out of 350**
2014	NAPCRG Annual Meeting	New York, USA	Poster
	National Institute for Health Research (NIHR) School for Primary Care Research (SPCR) Showcase	Oxford, UK	Poster
	NIHR SPCR Annual Trainees Meeting	Oxford, UK	Poster

This chapter is formatted in the style of an original article for the Journal of the American Medical Association (JAMA). The paper is currently under review in a peer-reviewed journal.

Missed opportunities for prevention of stroke or TIA with lipid lowering drugs

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Abstract

Importance

There are estimated to be 16.9 million strokes annually worldwide, making it a leading cause of death and disability. Lipid lowering therapy in eligible patients can prevent strokes, but these drugs may be underused. The scale of missed opportunities for prevention with lipid lowering drugs prior to stroke is unknown.

Objective

To determine the proportion of patients with a missed opportunity for prevention with lipid lowering drugs prior to a stroke or TIA.

Design

Analysis of anonymised electronic primary care records from the United Kingdom (UK) between 2009 and 2013.

Setting

556 general practices in the UK providing data to The Health Improvement Network (THIN), a primary care database which includes 3.6 million current patients and 8.8 million former or deceased patients and covers approximately 6% of the UK population.

Participants

29,043 patients with a diagnosis of first-stroke and/or TIA between 1st January 2009 and 31st December 2013 who were aged ≥18 years at the time of the event.

Main outcome

The proportion of strokes/TIAs with a prior missed opportunity for prevention with lipid lowering drugs. A missed opportunity was when lipid lowering drugs were clinically indicated but not prescribed at the time of stroke/TIA.

Results

Of the 29,043 stroke/TIA patients included, 16,028 of these were eligible for lipid lowering drugs. However, 49% (7,836/16,028) of eligible patients were not prescribed lipid lowering drugs at the time of stroke/TIA.

Conclusions and relevance

Almost half of eligible patients were not prescribed lipid lowering drugs prior to stroke/TIA in this population where coverage of primary care is nearly complete. Extrapolating our results to the UK stroke incidence in people ≥35 years, we estimate that at least 9,300 first strokes could potentially be prevented annually by prescribing all eligible patients lipid lowering drugs. Improving prescription of these drugs is important to reduce the burden of stroke/TIA.

Introduction

Stroke is a leading cause of death and disability worldwide with an estimated annual incidence of 16.9 million first-strokes and 6 million stroke-related deaths.[1] Although the age-standardised incidence rates have decreased over the past two decades, the absolute numbers of strokes and stroke-related deaths and disability have increased due to the ageing population.[1] Transient ischaemic attack (TIA) is an important risk factor for stroke.[2] Primary prevention through targeted intervention of modifiable risk factors[3-5] can reduce the global burden of stroke and TIA.

Dyslipidaemia is one of the leading contributors to stroke and TIA worldwide[6] and lipid lowering drugs significantly reduce stroke incidence.[7,8] Evidence-based guidelines recommend lipid lowering drugs for people with existing cardiovascular disease (CVD) or those at high CVD risk.[4,9,10]

Despite evidence-based guidelines, research suggests that prescribing of primary prevention lipid lowering drugs is suboptimal in primary care;[11-13] however, there is no quantitative estimate of the size of missed opportunities prior to stroke or TIA. Our objectives were to determine in a large database covering approximately 6% of the United Kingdom (UK) population: (i) the proportion of patients with a missed opportunity for lipid lowering drug prevention therapy prior to a stroke or TIA; (ii) the relationship between patient/demographic characteristics and the probability of a stroke or TIA patient having a prior missed opportunity; and (iii) how the proportion of missed opportunities for prevention with lipid lowering drugs has changed over time.

Methods

The full protocol for this study has been published elsewhere,[14] methods are summarised in brief below.

Study design and data source

The study analysed routine electronic primary care medical records from The Health Improvement Network (THIN) database.[15] This is a large database of anonymised UK electronic primary care records extracted from general practices using Vision patient records software. The database covers approximately 6% of the UK population, including 3.6 million current patients and 8.8 million former or deceased patients.[16] Analysis of the THIN database has ethical approval from the National Health Service (NHS) South-East Multi-centre Research Ethics Committee subject to independent scientific review.[17] This study was approved by a Scientific Review Committee (SRC) (reference: 13-023).

Population

The study population comprised of patients with a diagnosis of first-stroke and/or TIA between 1st January 2009 and 31st December 2013 who were aged 18 years and over at the time of the event. Patients were categorised with a diagnosis of: (i) stroke only, (ii) TIA only, or (iii) stroke with previous TIA. The date of first stroke or TIA was taken as the index date. To ensure data quality and that important patient outcomes were being recorded consistently, the index dates had to occur at least one year after the practice began using Vision patient record software and after the practice date of acceptable mortality recording.[18] Only patients registered at a practice for at least one year were included to allow sufficient time for risk factor data to be recorded.

Outcomes

Patients were categorised as eligible or ineligible for lipid lowering drugs using the most recent risk factor data prior to their stroke or TIA. A missed opportunity for prevention was recorded when eligible patients had not received a prescription for lipid lowering drugs up to 90 days before their stroke or TIA (the usual maximum prescription length in the UK) or had no clinical code indicating the patient was on lipid lowering drugs. Patients were eligible for lipid lowering medication if they had a history of coronary heart disease (CHD); chronic kidney disease (CKD); peripheral arterial disease (PAD); TIA (in stroke patients with prior TIA); diabetes mellitus and aged over 40 years; a 10-year CVD risk of ≥20% estimated by the adjusted Framingham risk equation; or familial hypercholesterolemia. These eligibility criteria were based on UK national guidelines used during the study period.[19,20] A sensitivity analysis explored the effect of using the QRISK2-2014 equation instead of the Framingham equation to reflect updated recommendations of the 2014 UK guidlines.[4] Familial hypercholesterolemia was defined as having a clinical code for the diagnosis or total cholesterol of ≥9mmol/L.[21]

Definition of outcomes and variables

A comprehensive list of clinical codes (Read codes)[22] for stroke and TIA was used to identify the study cohort. Comorbidities were defined by the standard list of clinical codes used to identify chronic diseases for the UK chronic disease monitoring programme (Quality and Outcomes Framework (QOF) business rules version 27[23]) and, where present, 'history of' or 'resolved' clinical codes were extracted. Patients with a clinical code indicating history of stroke or TIA recorded before a clinical code for stroke or TIA were excluded as their true index date could not be identified. Socio-demographic and patient characteristics were also

extracted.[14] Drug prescriptions corresponding to British National Formulary (BNF) chapter 2.12 (v67)[24] for lipid lowering drugs and clinical codes indicating that the patient was on lipid lowering drugs were extracted to identify treated patients.

Quality checks, missing data and extreme values

Absence of a clinical code for an individual diagnosis prior to the index date was taken to indicate the diagnosis was not present at the index date. Missing data were not imputed; however, a separate 'missing' category was created for categorical predictor variables if there was no value recorded prior to the index date because patients with variables recorded systematically differ from those with missing data.[25] Clinically implausible values were excluded for blood pressure, height, weight, body mass index (BMI), total cholesterol, and high density lipoprotein (HDL) cholesterol based on pre-specified cut-off values (eTable 1 in the Supplement). If no clinically plausible values were recorded at any time prior to the index date, the variable was categorised as missing. Data were initially extracted between 2000 and 2013; however, crude incidence of recorded stroke and TIA before 2008 was less than 15% of recorded stroke and TIA incidence after 2009 (eFigure 1 in the Supplement). After 2009, recorded incidence was more stable; therefore, only strokes and TIAs which occurred from the 1st January 2009 were included.

Analysis

All analysis was conducted using STATA version 12 (StataCorp, College Station, Texas). Patients were categorised as having a stroke, TIA, or stroke with previous TIA. The proportion of patients with a missed opportunity for lipid lowering drug therapy was calculated for each group and the difference between groups tested using Pearson's Chi

squared. The relationship between patient/demographic characteristics (eTable 2 in the Supplement) and having a missed opportunity was evaluated using mixed-effects logistic regression, with general practice as a random effect and odds ratio (OR) reported. Age and sex were forced into the model because they were pre-identified as important predictors of undertreatment.[26-28] Year of stroke/TIA was included as a covariate in the regression model to investigate change over time. Backwards elimination with a p-to-eliminate value of >0.05 was used to select variables to be included in the final model. Exploratory analyses were conducted (see the online Supplement).

Results

During the study period, 29,043 stroke and TIA patients met the inclusion criteria; of these, 55% (16,028/29,043) were eligible for lipid modification therapy at the time of their stroke or TIA. Their median age was 75 years (IQR 67,83) and 56% were male (Table 1). Fifty-three percent of patients had experienced a stroke, 32% a TIA, and 15% a stroke with previous TIA. Only 5% (869/16,028) of patients eligible for lipid lowering drugs had a clinical code indicating these drugs were declined, contraindicated or there was an adverse reaction.

Table 1: Descriptive characteristics of patients eligible (n=16,028) and ineligible (n=13,015) for lipid lowering prevention drugs prior to stroke or transient ischaemic attack (TIA).

		Eligible Patients Frequency (%)	Ineligible Patients Frequency (%)
Total		16,028 (100)	13,015 (100)
Age (years)	<45	115 (0.7)	997 (7.7)
	45-49	221 (1.4)	723 (5.6)
	50-54	494 (3.0)	919 (7.0)
	55-59	811 (5.1)	954 (7.3)
	60-64	1,489 (9.3)	1,097 (8.4)
	65-69	2,049 (12.8)	1,193 (9.2)
	70-74	2,638 (16.5)	1,083 (8.3)
	75-79	2,329 (14.5)	2,069 (15.9)
	80-84	2,514 (15.7)	1,791 (13.8)
	85-89	2,068 (12.9)	1,293 (9.9)
	90-94	1,012 (6.3)	665 (5.1)
	≥95	288 (1.8)	231 (1.8)
Sex	Male	8,941 (55.8)	5,263 (40.4)
	Female	7,087 (44.2)	7,752 (59.6)
BMI	Healthy (18.5-25.9 kg/m^2)	4,655 (29.1)	4,548 (34.9)
	Underweight (<18.5 kg/m^2)	339 (2.1)	373 (2.9)
	Overweight (26-30 kg/m^2)	5,995 (37.4)	4,293 (33.0)
	Obese (>30 kg/m^2)	4,172 (26.0)	2,442 (18.8)
	Missing	867 (5.4)	1,359 (10.4)
Smoking status	Non	3,927 (24.5)	2,410 (18.5)
	Ex	7,910 (49.0)	7,180 (55.2)
	Current	3,716 (23.3)	2,521 (19.4)
	Missing	475 (3.2)	904 (6.9)
Rurality	Urban	5,997 (37.4)	4,881 (37.5)
	Rural	10,021 (62.5)	8,128 (62.5)
	Missing	10 (0.1)	6 (0.0)
Deprivation	1 (least deprived)	3,709 (23.2)	3,242 (24.9)
	2	3,497 (21.8)	3,085 (23.7)
	3	3,210 (20.0)	2,685 (20.6)
	4	3,047 (19.0)	2,201 (16.9)
	5 (most deprived)	2,187 (13.6)	1,486 (11.4)
	Missing	378 (2.4)	316 (2.5)

Continued on next page

Table 1 continued from previous page

		Eligible Patients	Ineligible Patients
Comorbidity	Atrial fibrillation	2,392 (14.9)	1,152 (8.9)
	Asthma	1,724 (10.8)	1,338 (10.3)
	Cancer	1,911 (11.9)	1,328 (10.2)
	CHD	5,543 (34.6)	0 (0.0)
	CKD	5,774 (36.0)	0 (0.0)
	COPD	1,470 (9.2)	728 (5.6)
	Dementia	737 (4.6)	533 (4.1)
	Depression	3,420 (21.3)	2,754 (21.2)
	Diabetes	4,486 (28.0)	26 (0.2)
	Epilepsy	287 (1.8)	327 (2.5)
	Familial hypercholesterolemia	95 (0.6)	0 (0.0)
	Heart failure	1,338 (8.3)	287 (2.2)
	Hypertension	9,666 (60.3)	4,980 (38.3)
	Hypothyroidism	1,724 (10.8)	1,166 (9.0)
	Learning disability	54 (0.3)	76 (0.6)
	Osteoporosis	1,265 (7.9)	1,053 (8.1)
	PAD	1,431 (8.9)	0 (0.0)
	Palliative care	223 (1.4)	136 (1.0)
	Psychosis	262 (1.6)	177 (1.4)
	Rheumatoid arthritis	394 (2.5)	261 (2.0)
CVD Risk	≥20% over 10 years	3,902 (24.3)	0 (0.0)

BMI: Body Mass Index, CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, CVD: Cardiovascular Disease, PAD: Peripheral Artery Disease

Proportion of missed opportunities

The proportion of stroke and TIA patients with a missed opportunity for lipid lowering drug prevention therapy was 49% (7,836/16,028). There were statistically significant differences (p=<0.01) in the proportions of missed opportunities in patients with stroke (51%), TIA (46%), and stroke with previous TIA (50%) (Table 2).

Table 2: Proportion of stroke and transient ischaemic attack (TIA) patients with a missed opportunity for prevention with lipid lowering drugs.

Diagnosis	Missed opportunities Frequency (%)
Stroke only (n=8,464)	4,276 (50.5)
TIA only (n=5,212)	2,387 (45.8)
Stroke with previous TIA (n=2,352)	1,173 (49.9)
Total (n=16,028)	7,836 (48.9)

Demographic and patient characteristics associated with having a missed opportunity

The results of the multivariable logistic regression model are presented in Table 3. With age 75-79 years (median age) as the reference category, there was a J-shaped relationship between age and proportion of missed opportunities, which were markedly more frequent in both older and younger age groups (Figure 1). Sex was not significantly associated with having a missed opportunity but remained in the model as pre-specified.

The odds of having a missed opportunity were more than halved in stroke and TIA patients with a diagnosis of CHD or diabetes and significantly reduced in patients with a diagnosis of PAD, CKD, or hypertension. Stroke and TIA patients receiving palliative care had more than twice the odds of having a missed opportunity. With healthy BMI (18.5-25.9 kg/m^2) as the reference category, both BMI <18.5 kg/m^2 (underweight) and missing BMI were associated with increased odds of having a missed opportunity, whereas BMI 26-30 kg/m^2 (overweight) and BMI >30 kg/m^2 (obese) were associated with decreased odds. Being a current smoker and having no record of smoking status were associated with increased odds of having a missed opportunity. There was no association between area deprivation score and the odds of having a missed opportunity; however, there were statistically significant regional differences with stroke and TIA patients in Wales and Northern Ireland less likely to have a missed opportunity (West Midlands region of England as reference). Administration of lifestyle interventions for smoking or weight was associated with reduced odds of having a missed opportunity. There was no statistically significant change in the proportion of missed opportunities between 2009 and 2013, and the remaining predictor variables were non-significant and excluded from the model (eTable 2 in the Supplement). Results for exploratory analyses are presented in the online Supplement.

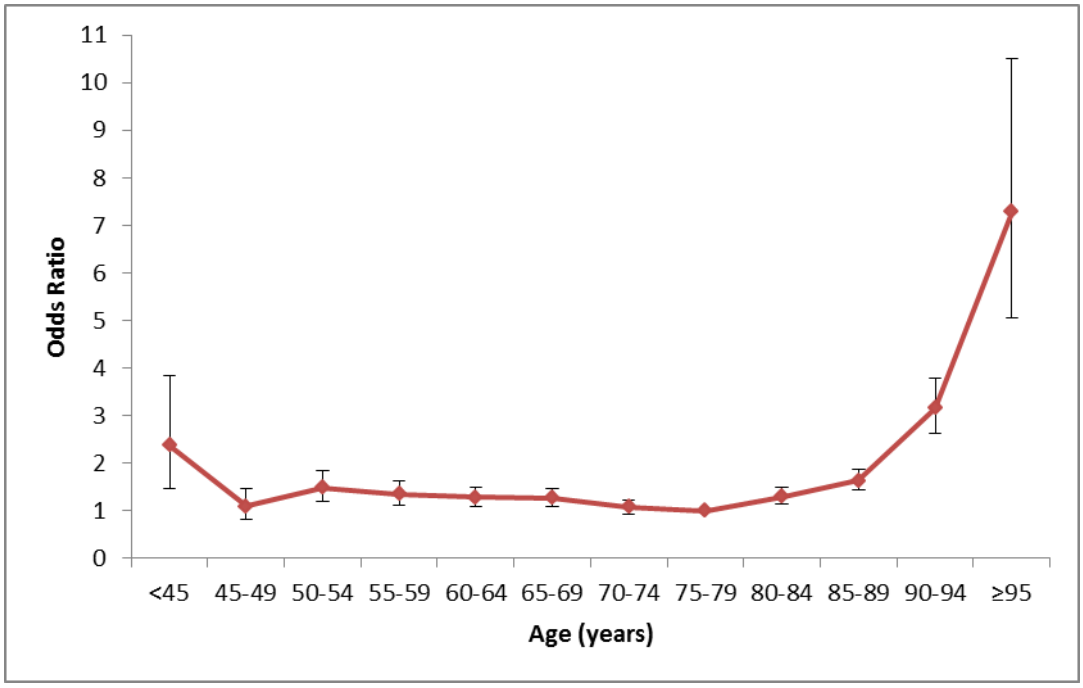

Figure 1: Adjusted odds ratios for effect of age on having a missed opportunity for prescription of lipid lowering drugs, in eligible patients, prior to stroke or transient ischaemic attack (TIA), with age 75-79 years as the reference category.

Table 3: Adjusted* odds ratios for effects of patient and demographic characteristics on having a missed opportunity for prescription of lipid lowering drugs, in eligible patients, prior to stroke or transient ischaemic attack (TIA).

		Odds Ratio	95% CI	P value
Age (years)	<45	2.34	1.46, 3.74	<0.01
	45-49	1.11	0.83, 1.47	0.48
	50-54	1.50	1.21, 1.86	<0.01
	55-59	1.36	1.13, 1.64	<0.01
	60-64	1.28	1.10, 1.50	<0.01
	65-69	1.27	1.10, 1.47	<0.01
	70-74	1.08	0.94, 1.24	0.26
	75-79	1.00		
	80-84	1.30	1.13, 1.48	<0.01
	85-89	1.63	1.42, 1.86	<0.01
	90-94	3.14	2.61, 3.78	<0.01
	≥95	7.11	4.93, 10.26	<0.01
Sex	Male	1.00		
	Female	0.96	0.89, 1.04	0.28
Comorbidity	CHD	0.21	0.19, 0.22	<0.01
	CKD	0.86	0.79, 0.94	<0.01
	PAD	0.52	0.45, 0.60	<0.01
	Diabetes	0.31	0.28, 0.33	<0.01
	Hypertension	0.69	0.64, 0.75	<0.01
	Palliative care	2.48	1.83, 3.34	<0.01
BMI	Healthy (18.5-25.9 kg/m^2)	1.00		
	Underweight (<18.5 kg/m^2)	1.93	1.45, 2.57	<0.01
	Overweight (26-30 kg/m^2)	0.89	0.81, 0.97	0.01
	Obese (>30 kg/m^2)	0.79	0.72, 0.88	<0.01
	Missing	1.58	1.32, 1.88	<0.01
Smoking	Non-smoker	1.00		
	Current	1.40	1.21, 1.61	<0.01
	Ex	1.08	0.98, 1.19	0.12
	Missing	1.65	1.31, 2.07	<0.01
Region	West Midlands	1.00		
	Yorkshire & Humber	0.95	0.72, 1.25	0.72
	North West	0.85	0.70, 1.05	0.13
	East Midlands	1.01	0.81, 1.25	0.93
	North East	0.85	0.65, 1.13	0.26

Continued on next page

Table 3 continued from previous page

		Odds Ratio	95% CI	P value
Region	East of England	0.94	0.75, 1.18	0.59
	London	0.84	0.70, 1.02	0.07
	South East Coast	0.87	0.73, 1.05	0.16
	South Central	1.01	0.86, 1.20	0.87
	South West	1.00	0.96, 1.18	0.96
	Northern Ireland	0.72	0.59, 0.88	<0.01
	Scotland	0.92	0.78, 1.09	0.34
	Wales	0.72	0.59, 0.89	<0.01
	Missing	0.80	0.47, 1.37	0.42
Lifestyle intervention	Smoking	0.76	0.68, 0.84	<0.01
	Weight	0.78	0.67, 0.91	<0.01

*Each odds ratio is adjusted for the other variables in the table.

BMI: Body Mass Index, CHD: Coronary Heart Disease, CI: Confidence Intervals, CKD: Chronic Kidney Disease, PAD: Peripheral Artery Disease

Discussion

Half of eligible patients were not prescribed lipid lowering drugs prior to first-stroke or TIA. There was no association between missed opportunities for prevention with lipid lowering drugs and sex, but there was a J-shaped relationship with age. Missed opportunities were more common in people who were underweight, smokers, were receiving palliative care or lived in Wales or Northern Ireland (compared to the West Midlands in England). In contrast, missed opportunities were less common in people who were overweight or obese or had a diagnosis of CHD, CKD, diabetes, PAD or hypertension. There was no change in the proportion of missed opportunities between 2009 and 2013.

Stroke is a global issue; the most recent Global Burden of Disease study[29] found stroke was the third leading cause of years of life lost (YLL) worldwide. Furthermore, the absolute number of first-strokes, stroke related deaths and disability-adjusted life-years (DALYs) has increased worldwide over the last two decades.[30] Primary prevention of stroke and TIA is, therefore, important to reduce the burden of these conditions. We extrapolated our findings using estimates of UK population,[31] stroke incidence[32] and relative risk reduction of statins[8] to determine the potential impact of improving prescribing of lipid lowering drugs on stroke prevention in the UK. We estimate that in people aged 35 years and over, approximately 9,300 strokes could be prevented in the UK each year by prescribing lipid lowering drugs to all eligible patients (eTable 5 in the Supplement). Lipid lowering drugs are often more commonly associated with CHD prevention; however, these estimates demonstrate the potential impact of improving prescription of lipid lowering drugs in the context of stroke prevention. UK primary care aims to provide universal access, free at the point of delivery and, in international comparisons, financial barriers to care are very low.[33] Missed

opportunities are likely to be lower in such a system compared to countries with restricted access or barriers to primary health care. Stroke incidence rates and burden are higher in low- and middle-income countries compared to high-income countries,[34] which may reflect disparities in prevention therapy. Therefore, the potential of improving the prescribing of stroke prevention drugs is likely to be even greater in these countries compared to the UK.

We found that a diagnosis of CHD, CKD, PAD, diabetes, or hypertension was associated with reduced odds of having a missed opportunity. In the UK, there are incentives to include such patients on a chronic disease register which might promote better management in terms of stroke prevention. Furthermore, exploratory analysis found patients with high CVD risk but without comorbid CVD had a 3-fold increase in odds of having a missed opportunity (see the online Supplement). This suggests that inclusion on a disease register was more strongly associated with lipid lowering drug prescribing rather than calculated CVD risk. Underweight patients were also less likely to be treated, whereas, overweight, or obese patients were more likely. This finding is more consistent with lay epidemiology (the concept of lay perception of health risk) than clinical epidemiology.[35]

Lipid lowering drugs are second to antihypertensive drugs as the most common drugs prescribed for CVD prevention;[36] in 2013 there were 78.8 million prescriptions for lipid lowering drugs in the UK.[37] Statin drugs account for the majority of lipid lowering drugs prescribed[38] and prescription of statins has increased over the past decade.[39] Despite this, there is controversy regarding administration of statins for primary stroke prevention. Fears about side effects and polypharmacy, particularly in the elderly, have been highlighted as reasons for GPs not prescribing statins.[40] Medicalisation of “healthy” patients and concerns

that pharmacotherapy would discourage patients from participating in lifestyle interventions have also been identified as barriers for GPs prescribing statins.[41] In addition, there is a lack of evidence for the benefits of statin prescribing in the very elderly.[42] However, statins have been found to be effective at reducing incidence of stroke[8] and statin-induced side effects are likely to be less frequent than originally thought.[43] The most recent updated lipid guideline recommendations[4,10] increase the number of people eligible for statin drug therapy, which has further fuelled concerns regarding medicalisation of the population. On the other hand, Wu et al (2013) found that over half of their sample who were prescribed lipid lowering drugs were ineligible.[44] Therefore, improving lipid lowering drug prescribing in eligible people may reduce the number of unnecessary prescriptions without substantially increasing the number of people taking lipid lowering drugs.

The strengths of this study are that the dataset is representative of UK general practice and the data are recent. Prescribing data are comprehensively recorded and the sample size is very large. Stroke and the main comorbidities are likely to be accurately recorded as they are clinically significant and, in the UK, GPs are incentivised to keep a register of patients with these conditions; however, TIA may be misclassified.[45] Furthermore, restricting the definition of comorbidities to QOF clinical codes may result in diagnoses being missed if they were recorded using alternative clinical codes. Patients with a clinical code indicating lipid lowering drugs were declined, contraindicated, or there was an adverse reaction were not excluded from the analysis; however, we reported this descriptively. The Framingham equation was used in our primary analysis because this was in use during the early part of the period of interest. In more recent years the Framingham equation has been superseded by QRISK2; therefore, in a sensitivity analysis we explored impact of using QRISK2-2014 over

the Framingham equation to calculate 10-year CVD risk. In addition to non-prescribing, patients' non-adherence to prevention drugs is an important consideration in the context of stroke prevention. A limitation of the dataset is that information on adherence is not available and prescription of lipid lowering drugs may not reflect patients' medication taking behaviour.

Future research could go beyond stroke and investigate missed opportunities for CVD prevention. Additional research should also investigate ineligible patients prescribed lipid lowering drugs to identify the patient/demographic characteristics associated with unnecessary prescribing. Furthermore, we found that inclusion on a disease register with active monitoring of performance was associated with greatly improved prevention. Therefore, the effects of creating a register of high CVD risk patients for primary prevention should be investigated.

In conclusion, almost half of eligible patients were not prescribed lipid lowering drugs for primary prevention prior to stroke or TIA. Furthermore, the proportion of missed opportunities is likely to increase following the updated UK guideline recommendations where the threshold for lipid lowering therapy was reduced from a 10-year CVD risk of 20% to 10%.[4,10] Substantial numbers of strokes and TIAs could potentially be prevented through improving prescription of lipid lowering drug in primary care.

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Authors' contributions

GMT, TM, MC, MGF, and RR contributed to the study conception and design. GMT conducted the analysis and GMT, TM, MC, MGF, RR, and KC were involved in the interpretation of results. GMT drafted the manuscript and TM, MC, MGF, RR, and KC provided feedback. All authors read and approved the final manuscript.

Declaration of interests

Ms. Turner reports grants from NIHR SPCR, during the conduct of the study. Dr. Calvert reports grants from the European Society Cardiology and personal fees from Astellas, outside the submitted work. Dr. Cheng reports grants from Pfizer China, outside the submitted work. Dr. Feltham, Dr. Ryan, and Dr. Marshall have nothing to disclose.

References

1. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet Global Health* 2013;1:e259-e81.
2. Sacco RL. Risk factors for TIA and TIA as a risk factor for stroke. *Neurology* 2004;62:S7-S11.
3. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: national clinical guideline for management in primary and secondary care. London: Royal College of Physicians; 2006.
4. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline 181. National Clinical Guideline Centre; 2014.
5. National Institute for Health and Clinical Excellence (NICE). Hypertension: the clinical management of primary hypertension in adults. Clinical Guideline 127. National Clinical Guideline Centre; 2011.
6. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global burden of disease and risk factors: Washington (DC): World Bank; 2006.
7. Wang W and Zhang B. Statins for the prevention of stroke: a meta-analysis of randomized controlled trials. *PLoS ONE* 2014;9:e92388.
8. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane Database of Systematic Reviews.* 2013;1:CD004816.
9. Reiner Z, Catapano AL, DeBacker G, et al. ESC/EAS Guidelines for the management of dyslipidaemias. *European Heart Journal* 2011;32:1769–818.
10. Stone NJ, Robinson J, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2014;63:(25)2889–934
11. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. *European Journal of Cardiovascular Prevention and Rehabilitation* 2010;17:530-40.
12. Missault L, Witters N, Imschoot J. High cardiovascular risk and poor adherence to guidelines in 11 069 patients of middle age and older in primary care centres. *European Journal of Cardiovascular Prevention and Rehabilitation* 2010;17:593-8.
13. Roccatagliata D, Avanzini F, Monesi L, et al. Is global cardiovascular risk considered in current practice? Treatment and control of hypertension, hyperlipidemia, and diabetes according to patients' risk level. *Vascular Health and Risk Management* 2006;2:507-14.
14. Moran GM, Calvert M, Feltham MG, Marshall T. Retrospective case review of missed opportunities for primary prevention of stroke and TIA in primary care: protocol paper. *BMJ Open* 2014;4:e006622.
15. The Health Improvement Network (THIN). (Accessed October, 2015, at http://www.thin-uk.com/.)
16. THIN data statistics. (Accessed October, 2015, at http://csdmruk.cegedim.com/index.html.)
17. THIN database ethics. (Accessed October, 2015, at http://csdmruk.cegedim.com/our-data/ethics.shtml.)
18. Maguire A, Blak B, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiology and Drug Safety* 2009;18:76-83.

19. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. Clinical Guideline 67. National Collaborating Centre for Primary Care and Royal College of General Practitioners. 2008.
20. British Cardiac Society BHS, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;91 Suppl 5:1-52.
21. Koivisto P, Koivisto U, Miettinen T, Kontula K. Diagnosis of heterozygous familial hypercholesterolemia. DNA analysis complements clinical examination and analysis of serum lipid levels. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1992;12:584-92.
22. Read codes. (Accessed October, 2015, at http://systems.hscic.gov.uk/data/uktc/readcodes/index_html.)
23. Quality and Outcomes Framework (QOF). (Accessed October, 2015, at http://www.hscic.gov.uk/qof.)
24. British National Formulary (BNF). (Accessed October, 2015, at http://www.bnf.org/bnf/index.htm.)
25. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiology and Drug Safety* 2010;19:618-26.
26. McKinlay JB, Link CL, Freund KM, Marceau LD, O'Donnell AB, Lutfey KL. Sources of variation in physician adherence with clinical guidelines: results from a factorial experiment. *Journal of General Internal Medicine* 2007;22:289-96.
27. Midlov P, Ekesbo R, Johansson L, et al. Barriers to adherence to hypertension guidelines among GPs in southern Sweden: a survey. *Scandinavian Journal of Primary Health Care* 2008;26:154-9.
28. Ramsay SE, Whincup PH, Wannamethee SG, et al. Missed opportunities for secondary prevention of cerebrovascular disease in elderly British men from 1999 to 2005: a population-based study. *Journal of Public Health* 2007;29:251-7.
29. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2015;385:117-71.
30. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study. *The Lancet* 2010;383:245-55.
31. Office for National Statistics (ONS) Population Estimates. (Accessed October, 2015, at http://data.london.gov.uk/dataset/office-national-statistics-ons-population-estimates-borough.)
32. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *The Lancet* 2005;366:1773-83.
33. Davis K, Ballreich J. Equitable access to care-how the United States ranks internationally. *The New England Journal of Medicine* 2014;371:1567-70.
34. Bennett DA, Krishnamurthi RV, Barker-Collo S, et al. The global burden of ischemic stroke: findings of the GBD 2010 study. *Global Heart* 2014;9:107-12.
35. Davison C, Davey-Smith G, Frankel S. Lay epidemiology and the prevention paradox: the implications of coronary candidacy for health education. *Sociology of Health and Illness* 1991;13:1-19.

36. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003–2012. *National Center for Health Statistics Data Brief* 2014;177:1-7.
37. Townsend N, Williams J, Bhatnagar P, Wickramasinghe K, Rayner M. Cardiovascular disease statistics. British Heart Foundation: London2014.
38. Prescription Cost Analysis, England - 2013 (Accessed October, 2015, at http://www.hscic.gov.uk/catalogue/PUB13887.)
39. Health, United States, 2013: National Health and Nutrition Examination Survey. (Accessed October, 2015, at http://www.cdc.gov/nchs/hus.htm.)
40. AB E, Denig P, van Vliet T, Dekker J. Reasons of general practitioners for not prescribing lipid-lowering medication to patients with diabetes: a qualitative study. *BMC Family Practice* 2009;10:24.
41. Kedward J, Dakin L. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *The British Journal of General Practice* 2003;53:684-9.
42. Noaman S, Ibrahim JE, Grenfell R. Prescribing statins for cardiovascular disease prevention in the old: an absence of evidence and an absence of guidelines. *Heart Lung and Circulation* 2014;23:619-24.
43. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *European Journal of Preventive Cardiology* 2014;21:464-474
44. Wu J, Zhu S, Yao GL, Mohammed MA, Marshall T. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in UK general practice: a national retrospective cohort study. *PLoS ONE* 2013;8:e67611.
45. Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. *Stroke* 2010;41:1367-70.

Appendices for Chapter 4

Chapter 5: Missed opportunities for prevention of stroke and TIA: Results

Part Two: Anticoagulant and antihypertensive drugs

Missed opportunities for prevention of stroke or TIA with anticoagulant and antihypertensive drugs

In addition to dyslipidaemia, AF and hypertension are also important modifiable risk factors for stroke and TIA.[1,2] Similar to dyslipidaemia, these risk factors can be targeted through intervention with anticoagulant and antihypertensive drugs, respectively, to reduce the incidence of stroke and TIA.[3-5] This chapter presents the findings of the retrospective analysis of primary care electronic medical records, described in Chapter 3, for the anticoagulant and antihypertensive drug analysis. The aims were to determine: (i) the proportion of strokes and TIAs with prior missed opportunities for prevention with anticoagulant and antihypertensive drugs; (ii) the relationship between patient and demographic characteristics and the probability of having a missed opportunity; and (iii) how the proportion of missed opportunities for prevention with anticoagulant and antihypertensive drugs has changed over time. Multiple missed opportunities for prevention with all three drugs are presented at the end of the chapter (page 113).

References

1. Vokó Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JCM, Breteler MMB. J-Shaped Relation Between Blood Pressure and Stroke in Treated Hypertensives. *Hypertension*. 1999;34(6):1181-1185.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983-988.
3. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2005(3):Cd001927.
4. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews*. 2007(3):Cd006186.
5. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* 2003;289(19):2534-2544.

Dissemination

Year	Conference	Location	Oral/Poster
2015	College of Medical and Dental Sciences Festival of Graduate Research	Birmingham, UK	Oral presentation ***Awarded best abstract from the School of Health and Population Sciences**
	Society of Academic Primary Care (SAPC) South West Regional Conference	Birmingham, UK	Oral presentation
	North American Primary Care Research Group (NAPCRG) Annual Meeting	Cancun, Mexico	Distinguished paper oral presentation ***Abstract ranked in top 5 out of 350**
2014	NAPCRG Annual Meeting	New York, USA	Poster
	National Institute for Health Research (NIHR) School for Primary Care Research (SPCR) Showcase	Oxford, UK	Poster
	NIHR SPCR Annual Trainees Meeting	Oxford, UK	Poster

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Missed opportunities for prevention of stroke or TIA with anticoagulant and antihypertensive drugs

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Abstract

Background

Stroke is a leading cause of death and disability worldwide. Anticoagulant and antihypertensive drugs are effective in preventing stroke/TIA in patients with atrial fibrillation (AF) and hypertension, respectively; however, their use in primary care may be suboptimal. The objective of this study was to quantify the size of missed opportunities for prevention with these drugs prior to stroke/TIA.

Methods

Analysis of anonymised electronic primary care records from the United Kingdom (UK), extracted from The Health Improvement Network (THIN) database which covers approximately 6% of the UK population. The study included first-ever stroke/TIA patients, with a diagnosis between 2009 and 2013, aged ≥18 years. A missed opportunity for prevention was when anticoagulant or antihypertensive drugs were indicated but not prescribed at the time of stroke/TIA. The proportions and predictors of strokes/TIAs with a missed opportunity for prevention were calculated.

Results

29,043 stroke/TIA patients met the inclusion criteria; 3,194 patients were eligible for anticoagulant drugs and 7,008 for antihypertensive drugs. Missed opportunities for prevention were identified in 52% (1,647/3,194) of the patients eligible for anticoagulants and 25% (1,740/7,008) of patients eligible for antihypertensive drugs.

Conclusions

Anticoagulant and antihypertensive drugs are underused for primary prevention prior to stroke/TIA. We estimate that, in people aged >35 years, approximately 2,900 and 3,100 first strokes could potentially be prevented a year in the UK through optimal prescribing of anticoagulant and antihypertensive drugs, respectively. Improving prescription of anticoagulant and antihypertensive drugs is important to reduce the incidence and burden of stroke and TIA.

Introduction

Stroke is a leading cause of death and disability worldwide.[1] The global annual incidence of first-ever strokes is 16.9 million and the absolute number of strokes has increased over the past two decades.[2] Transient ischaemic attack (TIA) is characterised by short-lasting stroke-like symptoms and is a risk factor for stroke.[3] Targeting common modifiable risk factors is important to reduce the global burden of stroke and TIA.

Atrial fibrillation (AF) and hypertension are two of the most important risk factors for stroke and TIA and have a high global prevalence of 33.5 million[4] and 978 million[5], respectively. Absolute numbers of people with each risk factor has increased over the past two decades.[4,5] AF is associated with a five-fold increase in stroke risk and strokes in these patients are correlated with greater post-stroke disability and mortality.[6,7] Hypertension is one of the most well documented risk factors for stroke and TIA and there is a positive and continuous relationship between blood pressure (BP) and stroke.[8] Anticoagulant and antihypertensive drugs have been shown to be effective at reducing stroke incidence in patients with AF and hypertension respectively.[9-11] Evidence-based guidelines recommend prescription of anticoagulant drugs for AF patients at high stroke risk.[12,13] Antihypertensive drugs are recommended for people with stage 2 hypertension (BP ≥160/100 mmHg) or with stage 1 hypertension (BP ≥140/90 mmHg) and existing cardiovascular disease (CVD) or at high CVD risk.[14]

Despite guideline recommendations and the evidence for the effectiveness of anticoagulant and antihypertensive drugs for stroke and TIA prevention, prescription of these drugs may be suboptimal in primary care. A systematic review (1997-2008), found non-prescribing of

anticoagulant drugs ranged between 19% and 81% in patients with previous stroke or TIA (n=29 studies) and 39% to 92% in patients with a CHADS2 score ≥2 (n=9 studies).[15] Treatment of hypertension has also been found to be variable; survey data found percentages of treated hypertensive patients were 51% in England, 74% in the United States and 80% in Canada.[16] Furthermore, a systematic review identified multiple physician and patient barriers to hypertension treatment including those related to knowledge and agreement with guidelines and health system barriers, such as time and resource constraints.[17] However, there is a lack of studies which focus on primary stroke and TIA prevention and quantify missed opportunities for anticoagulant and antihypertensive drug prescribing prior to stroke or TIA using a large sample size and recent data.

Our objectives were to determine in a large database covering approximately 6% of the UK population: (i) the proportion of patients with a missed opportunity for prevention with anticoagulant and antihypertensive drugs prior to a stroke or TIA; (ii) the relationship between patient/demographic characteristics and the probability of a stroke or TIA patient having a prior missed opportunity; and (iii) how proportions of missed opportunities have changed over time.

Methods

The full protocol for this study has been published elsewhere,[18] methods are summarised in brief below.

Study design and data source

The study analysed United Kingdom (UK) primary care data from The Health Improvement Network (THIN) database.[19] This is a large database of anonymised, electronic primary care

records extracted from general practices using Vision patient records software. The database covers approximately 6% of the UK population, including 3.6 million current patients and 8.8 million former or deceased patients.[20] Analysis of the THIN database has ethical approval from the National Health Service (NHS) South-East Multi-centre Research Ethics Committee subject to independent scientific review.[21] This study was approved by a Scientific Review Committee in May 2013 (reference: 13-023).

Population

The study population comprised of patients with a diagnosis of first-stroke and/or TIA between 1st January 2009 and 31st December 2013 who were aged 18 years and over at the time of the event. Patients were categorised with a diagnosis of: (i) stroke only, (ii) TIA only, or (iii) stroke with previous TIA. The date of first stroke or TIA was taken as the index date. To ensure data quality and that important patient outcomes were being recorded consistently, the index dates had to occur least one year after the practice began using Vision patient record software and after the practice date of acceptable mortality recording.[22] Only patients registered at a practice for at least one year were included to allow sufficient time for risk factor data to be recorded.

Outcomes

Patients were categorised as eligible or ineligible for prevention drugs using the most recent risk factor data prior to their stroke or TIA. A missed opportunity for prevention was recorded when eligible patients had not received a prescription for antihypertensive drugs up to 90 days before their stroke or TIA (the usual maximum prescription length in the UK) or up to 120 days for anticoagulant drugs (to allow for referral to an anticoagulation clinic),

and had no clinical code indicating the patient was on these drugs. Patients were eligible for anticoagulant drugs if they had a diagnosis of AF and were at high risk of stroke (CHADS2 score ≥1). Patients were eligible for antihypertensive medication if they had high BP (≥160/100 mmHg) or moderately high BP (≥140/90 mmHg) with existing CVD or high risk of CVD. Patients with a clinical code to indicate a diagnosis of hypertension but whose average BP recordings were lower than these thresholds were excluded from the analysis; therefore, the analysis for antihypertensive drugs focused on uncontrolled hypertension. Exiting CVD was defined as having a history of coronary heart disease (CHD); chronic kidney disease (CKD); peripheral arterial disease (PAD); TIA (in stroke patients with prior TIA); or diabetes mellitus and aged over 40 years. High risk of CVD was defined as having a 10-year CVD risk of ≥20% estimated by the adjusted Framingham risk equation. These eligibility criteria were based on UK national guidelines used during the study period.[12,14]

Definition of outcomes and variables

A comprehensive list of clinical codes (Read codes)[23] for stroke and TIA was used to identify the study cohort. Comorbidities were defined by the standard list of clinical codes used to identify chronic diseases for the UK chronic disease monitoring programme (Quality and Outcomes Framework (QOF) business rules version 27[24]) and, where present, disease-specific 'history of' or 'resolved' clinical codes were extracted. Patients with a clinical code indicating history of stroke or TIA recorded before a clinical code for stroke or TIA were excluded as their true index date could not be identified. Socio-demographic and other non-clinical patient characteristics were also extracted.[18] Drug prescriptions corresponding to British National Formulary chapters (v67)[25] for anticoagulant and antihypertensive drugs and clinical codes indicating that the patient was on one of these drugs were extracted to

identify treated patients. Clinical codes indicating that prevention drugs were declined or contraindicated, a patient had white coat hypertension or there was an adverse reaction were also extracted.

Quality checks, missing data and extreme values

Absence of a clinical code for a comorbidity diagnosis prior to the index date was taken to indicate that the diagnosis was not present at the index date. Missing data were not imputed; however, separate 'missing' category was created for categorical predictor variables if there was no value recorded prior to the index date because patients with variables recorded systematically differ from those with missing data.[26] Clinically implausible values were excluded for BP, height, weight, body mass index (BMI), total cholesterol, and high density lipoprotein (HDL) cholesterol based on pre-specified cut-off values (Table S1 in the Supplementary Appendix). If no clinically plausible values were recorded at any time prior to the index date, the variable was categorised as missing. Data were initially extracted between 2000 and 2013; however, the number of incident stroke and TIA events before 2008 was less than 15% of recorded stroke and TIA incidence after 2009 (Figure S1 in the Supplementary Appendix). After 2009, this was more stable; therefore, only strokes and TIAs which occurred from the 1st January 2009 were included.

Analysis

All analysis was conducted using STATA version 12 (StataCorp, College Station, Texas). Patients were categorised as having a stroke, TIA, or stroke with previous TIA. The proportions of patients with a missed opportunity for stroke and TIA prevention with anticoagulant or antihypertensive drugs were calculated for each group and the difference

between groups tested using Pearson's Chi squared. The relationship between patient/demographic characteristics (Table S2 in the Supplementary Appendix) and having a missed opportunity was evaluated using mixed-effects logistic regression models, with general practice as a random effect and odds ratio (OR) reported. Age and sex were forced into the model because they were pre-identified as important predictors of undertreatment.[27-29] Year of stroke/TIA was included as a covariate in the regression model to investigate change over time. Backwards elimination with a p-to-eliminate value of >0.05 was used to select variables to be included in the final model. Exploratory analyses were conducted (see the Supplementary Appendix).

Results

During the study period, 29,043 stroke and TIA patients met the inclusion criteria; 3,194 patients were eligible for anticoagulant drugs and 7,008 for antihypertensive drugs. Of the patients eligible for antihypertensive drugs, 2,038 had high BP (≥160/100 mmHg) and 6,272 had moderately high BP (≥140/90 mmHg) with high CVD risk (groups not mutually exclusive). Descriptive characteristics of patients eligible for each prevention drug are presented in Table 1. Patients eligible for anticoagulant drugs had a median age of 82 years [IQR 77, 87] and 54% were female. For patients eligible for antihypertensive drugs, the median age was 76 years [IQR 68, 84] and 51% were female. Seven percent (244/3,194) of patients eligible for anticoagulants and 0.7% (47/7,008) of patients eligible for antihypertensive drugs had a clinical code indicating these drugs were declined, contraindicated, there was an adverse reaction, or had a record of white coat hypertension (for hypertensive patients).

Table 1: Descriptive characteristics of patients eligible and ineligible for antihypertensive and anticoagulant drugs prior to stroke or transient ischaemic attack (TIA).

		Anticoagulant drugs				Antihypertensive drugs			
		Eligible		Ineligible		Eligible		Ineligible	
		Frequency	(%)	Frequency	(%)	Frequency	(%)	Frequency	(%)
Diagnosis	Stroke only	1,881	(58.9)	14,364	(55.6)	3,843	(54.8)	12,402	(56.3)
	TIA only	958	(30.0)	9,488	(36.7)	2,253	(32.2)	8,193	(37.2)
	Stroke with previous TIA	355	(11.1)	1,997	(7.7)	912	(13.0)	1,440	(6.5)
	Total	3,194	(100.0)	25,849	(100.0)	7,008	(100.0)	22,035	(100.0)
Age (years)	<45	6	(0.2)	1,106	(4.3)	69	(1.0)	1,043	(4.7)
	45-49	9	(0.3)	935	(3.6)	109	(1.5)	835	(3.8)
	50-54	15	(0.5)	1,398	(5.4)	190	(2.7)	1,223	(5.6)
	55-59	39	(1.2)	1,726	(6.7)	311	(4.4)	1,454	(6.6)
	60-64	70	(2.2)	2,516	(9.7)	556	(7.9)	2,030	(9.2)
	65-69	170	(5.3)	3,072	(11.9)	832	(11.9)	2,410	(10.9)
	70-74	291	(9.1)	3,430	(13.3)	1,091	(15.6)	2,630	(11.9)
	75-79	604	(18.9)	3,794	(14.7)	1,133	(16.2)	3,265	(14.8)
	80-84	760	(23.8)	3,545	(13.7)	1,179	(16.8)	3,126	(14.2)
	85-89	719	(22.5)	2,642	(10.2)	974	(13.9)	2,387	(10.8)
	90-94	399	(12.5)	1,278	(4.9)	453	(6.5)	1,224	(5.6)
	≥95	112	(3.5)	407	(1.6)	111	(1.6)	408	(1.9)
Sex	Male	1,469	(46.0)	12,735	(49.3)	3,440	(49.1)	10,764	(48.8)
	Female	1,725	(54.0)	13,114	(50.7)	3,568	(50.9)	11,271	(51.2)

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Table 1 continued from previous page

		Anticoagulant drugs				Antihypertensive drugs			
		Eligible		Ineligible		Eligible		Ineligible	
BMI*	Healthy	1,108	(34.7)	8,095	(31.3)	1,953	(27.9)	7,250	(32.9)
	Underweight	98	(3.1)	614	(2.4)	135	(1.9)	577	(2.6)
	Overweight	1,141	(35.7)	9,147	(35. 4)	2,599	(37.1)	7,689	(34.9)
	Obese	651	(20.4)	5,963	(23.0)	2,010	(28.7)	4,604	(20.9)
	Missing	196	(6.1)	2,030	(7.9)	311	(4.4)	1,915	(8.7)
Smoking status	Non	886	(27.7)	5,452	(21.1)	1,626	(23.2)	4,712	(21.4)
	Ex	1,865	(58.4)	13,173	(51.0)	3,702	(52.8)	11,336	(51.4)
	Current	335	(10.5)	5,916	(22.9)	1,487	(21.2)	4,764	(21.6)
	Missing	108	(3.4)	1,308	(5.1)	193	(2.8)	1,223	(5.6)
Rurality	Urban	1,236	(38.7)	9,642	(37.3)	2,555	(36.5)	8,323	(37.8)
	Rural	1,957	(61.3)	16,192	(62.6)	4,451	(63.5)	13,698	(62.1)
	Missing	1	(0. 0)	15	(0.1)	2	(0.0)	14	(0.1)
Deprivation	1 (least deprived)	815	(25.5)	6,136	(23.7)	1,630	(23.3)	5,321	(24.1)
	2	763	(23.9)	5,819	(22.5)	1,582	(22.6)	5,000	(22.7)
	3	670	(21.0)	5,225	(20.2)	1,405	(20.0)	4,490	(20.4)
	4	528	(16.5)	4,720	(18.3)	1,323	(18.9)	3,925	(17.8)
	5 (most deprived)	347	(10.9)	3,326	(12.9)	900	(12.8)	2,773	(12.6)
	Missing	71	(2.2)	623	(2.4)	168	(2.4)	526	(2.4)
Comorbidity	AF	3,194	(100. 0)	350	(1.4)	923	(13.2)	2,621	(11.9)
	Asthma	320	(10.0)	2,742	(10.6)	736	(10.5)	2,326	(10.6)
	Cancer	420	(13.1)	2,819	(10.9)	796	(11.4)	2,443	(11.1)
	CHD	1,083	(33.9)	4,460	(17.3)	2,023	(28.9)	3,520	(16.0)

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		Anticoagulant drugs				Antihypertensive drugs			
		Eligible		Ineligible		Eligible		Ineligible	
	CKD	1,157	(36.2)	4,617	(17.9)	2,343	(33.4)	3,431	(15.6)
	COPD	309	(9.7)	1,889	(7.3)	547	(7.8)	1,651	(7.5)
	Dementia	213	(6.7)	1,057	(4.1)	226	(3.2)	1,044	(4.7)
	Depression	613	(19.2)	5,561	(21.5)	1,413	(20.2)	4,761	(21.6)
	Diabetes	658	(20.6)	3,854	(14.9)	1,796	(25.6)	2,716	(12.3)
	Epilepsy	47	(1.5)	567	(2.2)	117	(1.7)	497	(2.3)
	Heart failure	651	(20.4)	974	(3.8)	437	(6.2)	1,188	(5.4)
	Hypertension	2,297	(71.9)	12,349	(47.8)	5,241	(74.8)	9,405	(42.7)
	Hypothyroidism	440	(13.8)	2,450	(9.5)	755	(10.8)	2,135	(9.7)
	Learning disability	6	(0.2)	124	(0.5)	16	(0.2)	114	(0.5)
	Osteoporosis	372	(11.6)	1,946	(7.5)	578	(8.2)	1,740	(7.9)
	PAD	216	(6.8)	1,215	(4.7)	576	(8.2)	855	(3.9)
Comorbidity	Palliative care	52	(1.6)	307	(1.2)	67	(1.0)	292	(1.3)
	Psychosis	30	(0.9)	409	(1.6)	96	(1.4)	343	(1.6)
	Rheumatoid arthritis	80	(2.5)	575	(2.2)	170	(2.4)	485	(2.2)

*BMI: Healthy (18.5-25.9 kg/m^2), Underweight (<18.5 kg/m^2), Overweight (26-30 kg/m^2), Obese (>30 kg/m^2)

AF: Atrial Fibrillation; BMI: Body Mass Index, CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, PAD: Peripheral Artery Disease, TIA: Transient Ischaemic Attack

Proportion of missed opportunities

A missed opportunity for primary prevention was found in half of patients eligible for anticoagulant drugs (52%; 1,647/3,194) and a quarter of patients eligible for antihypertensive drugs (25%; 1,740/7,008). Of those eligible for antihypertensive drugs, there were missed opportunities in 27% (540/2,038) of patients with high BP (≥160/100 mmHg) and 24% (1,484/6,272) in patients with moderately high BP (≥140/90 mmHg) and high CVD risk (groups not mutually exclusive). There were significantly more missed opportunities for anticoagulant drug prescribing in patients with stroke only or TIA only compared to patients who had stroke with previous TIA (p=0.02; Table 2). This was not the case for antihypertensive drug prescribing (p=0.21; Table 2).

Table 2: Proportion of stroke and transient ischaemic attack (TIA) patients with a prior missed opportunity for antihypertensive or anticoagulant drug prevention therapy.

	Proportion of missed opportunities (% (frequency))	
	Anticoagulant drugs	**Antihypertensive drugs**
Stroke	52.3 (983/1,881)	25.3 (971/3,843)
TIA	52.8 (506/958)	23.6 (531/2,253)
Stroke with previous TIA	44.5 (158/355)	26.1 (238/912)
Total	51.6 (1,647/3,194)	24.8 (1,740/7,008)

Demographic and patient characteristics associated with having a missed opportunity

Anticoagulant drug prescribing

Variables associated with having a missed opportunity for anticoagulant drug prescribing are presented in Table 3. With age 75-79 years (median age of total sample) as the reference category, younger age (55-59 years) was associated with reduced odds of having a missed opportunity, whereas age over 85 years was associated with increased odds (Figure 1). A sex effect was observed with females having increased odds of having a missed opportunity compared to males. The odds of having a missed opportunity for anticoagulant drug prescribing was reduced in patients with a diagnosis of heart failure or diabetes, but increased in people with a diagnosis of dementia. With non-smoker as the reference category, current smokers and patients with a missing smoking status had increased odds of having a missed opportunity. Being underweight, overweight, obese and having a missing BMI were all associated with increased odds of having a missed opportunity compared to patients with a healthy BMI (18.5-25.9 kg/m^2). There was a marked decrease in the proportion of missed opportunities between 2009 and 2013 (Figure 2). Exploratory analyses are presented in the Supplementary Appendix.

Antihypertensive drug prescribing

Variables associated with having a missed opportunity for antihypertensive drug prescribing are presented in Table 4. With age 75-79 years as the reference category, both younger age (50-59 and 65-69 years) and very old age (≥90 years) were associated with increased the odds of having a missed opportunity (Figure 1). In contrast to anticoagulant prescribing,

female sex was associated with decreased odds of having a missed opportunity for antihypertensive prescribing. The odds of having a missed opportunity were more than halved in patients with a diagnosis of hypertension, CHD, AF, diabetes, heart failure and CKD. In addition, patients with a diagnosis of PAD, cancer, hypothyroidism, asthma and dementia had significantly reduced odds. However, dementia and multimorbidity were associated with increased odds of having a missed opportunity. Administration of lifestyle advice for weight was protective against having a missed opportunity. In comparison to anticoagulant drugs, no change in the odds of having a missed opportunity for antihypertensive drugs was observed between 2009 and 2013 (Figure 2). Exploratory analyses are presented in the Supplementary Appendix.

Table 3: Adjusted* odds ratios for effects of patient and demographic characteristics on having a missed opportunity for prescription of anticoagulant drugs, in eligible patients, prior to stroke or transient ischaemic attack (TIA).

		Odds Ratio	95% CI	P value
Age (years)	<55	0.72	0.33, 1.57	0.41
	55-59	0.36	0.17, 0.77	0.01
	60-64	1.01	0.62, 1.66	0.97
	65-69	0.98	0.68, 1.40	0.90
	70-74	0.89	0.66, 1.20	0.43
	75-79	1.00		
	80-84	1.01	0.81, 1.26	0.94
	85-89	1.27	1.02, 1.57	0.03
	90-94	1.74	1.32, 2.30	<0.01
	≥95	4.54	2.60, 7.94	<0.01
Sex	Male	1.00		
	Female	1.37	1.18, 1.58	<0.01
Comorbidity	Heart failure	0.53	0.44, 0.63	<0.01
	Diabetes	0.82	0.69, 0.98	0.03
	Dementia	1.51	1.11, 2.06	0.01
Smoking	Non	1.00		
	Ex	1.08	0.91, 1.29	0.36
	Current	1.41	1.08, 1.84	0.01
	Missing	1.67	1.07, 2.62	0.03
BMI	Healthy (18.5-25.9 kg/m^2)	1.00		
	Underweight (<18.5 kg/m^2)	1.51	1.01, 2.26	0.04
	Overweight (26-30 kg/m^2)	1.24	1.04, 1.48	0.02
	Obese (>30 kg/m^2)	1.23	1.01, 1.51	0.04
	Missing	1.60	1.13, 2.27	0.01
Year of event	2009	1.00		
	2010	0.95	0.73, 1.22	0.67
	2011	0.78	0.61, 0.99	0.04
	2012	0.70	0.55, 0.89	<0.01
	2013	0.59	0.47, 0.75	<0.01

*Each odds ratio is adjusted for the other variables in the table.

BMI: Body Mass Index, CI: Confidence Intervals

Table 4: Adjusted* odds ratios for effects of patient and demographic characteristics on having a missed opportunity for prescription of antihypertensive drugs, in eligible patients, prior to stroke or transient ischaemic attack (TIA).

		Odds Ratio	95% CI	P value
Age (years)	<45	1.64	0.87, 3.10	0.13
	45-49	1.50	0.93, 2.40	0.10
	50-54	1.55	1.07, 2.24	0.02
	55-59	1.54	1.11, 2.12	0.01
	60-64	1.12	0.84, 1.49	0.45
	65-69	1.30	1.00, 1.68	0.05
	70-74	1.16	0.92, 1.46	0.21
	75-79	1.00		
	80-84	0.96	0.76, 1.22	0.74
	85-89	1.26	0.98, 1.62	0.08
	90-94	1.70	1.26, 2.29	<0.01
	≥95	3.61	2.18, 5.99	<0.01
Sex	Male	1.00		
	Female	0.85	0.74, 0.97	0.02
Comorbidity	Hypertension	0.09	0.07, 0.11	<0.01
	CHD	0.26	0.21, 0.33	<0.01
	AF	0.35	0.27, 0.47	<0.01
	Diabetes	0.43	0.35, 0.52	<0.01
	Heart failure	0.49	0.33, 0.73	<0.01
	CKD	0.50	0.41, 0.60	<0.01
	PAD	0.62	0.47, 0.81	<0.01
	Cancer	0.78	0.62, 0.98	0.03
	Hypothyroidism	0.79	0.63, 1.00	0.05
	Asthma	0.79	0.62, 1.00	0.05
	Dementia	1.78	1.26, 2.51	<0.01
Multimorbidity	One unit increase	1.28	1.16, 1.42	<0.01
Lifestyle intervention	Weight	0.63	0.48, 0.83	<0.01

*Each odds ratio is adjusted for the other variables in the table.
AF: Atrial Fibrillation; CHD: Coronary Heart Disease, CI: Confidence Intervals, CKD: Chronic Kidney Disease: PAD: Peripheral Artery Disease

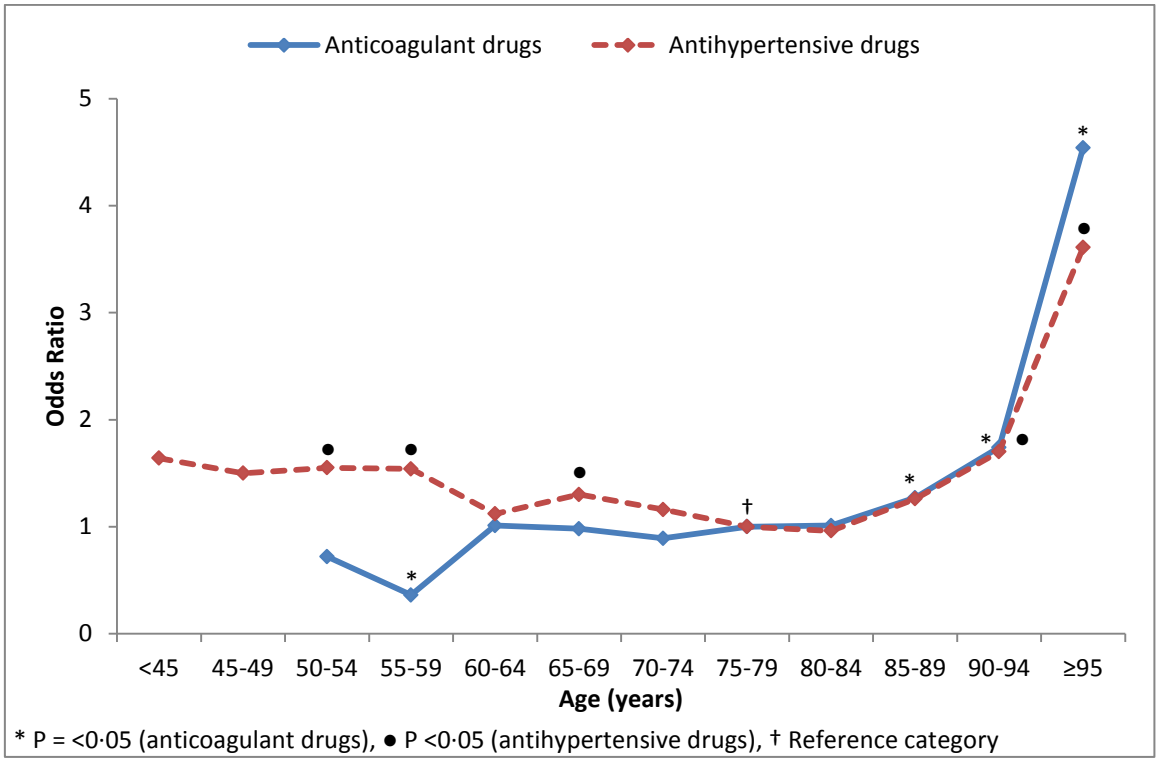

Figure 1: Adjusted odds ratios for effects of age on having a missed opportunity for prescription of anticoagulant and antihypertensive drugs, in eligible patients, prior to stroke or transient ischaemic attack (TIA), with age 75-79 years as the reference category.

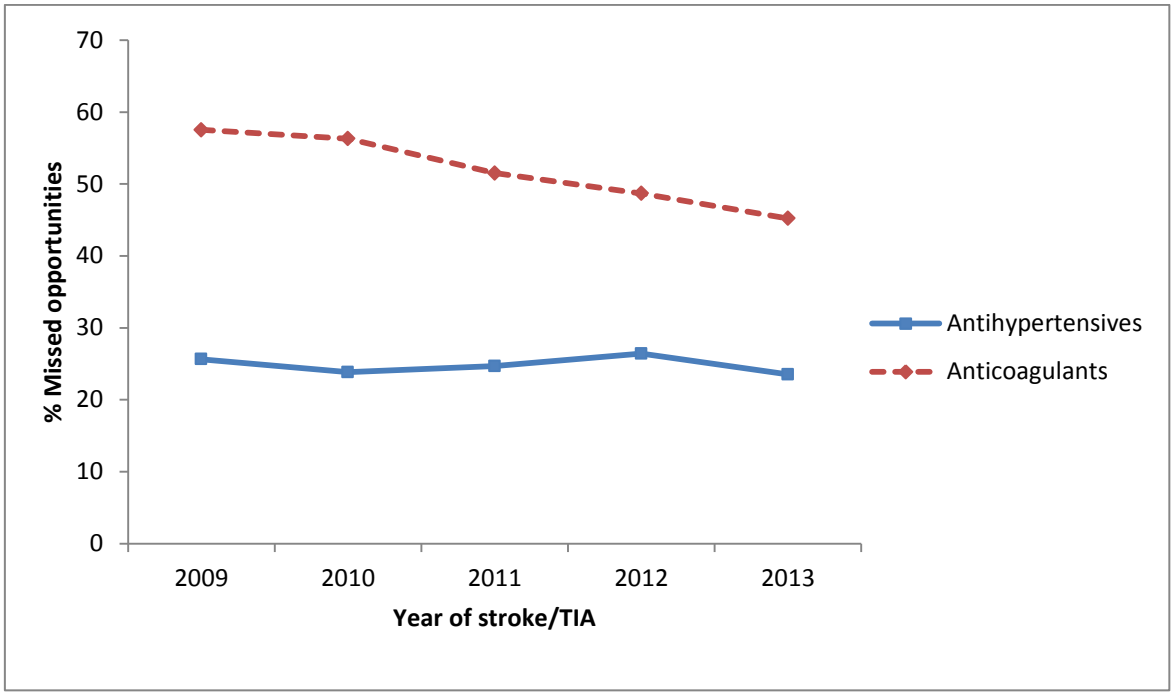

Figure 2: Proportion of missed opportunities for anticoagulant and antihypertensive drug prescribing, in eligible patients, prior to stroke or transient ischaemic attack (TIA) between 2009 and 2013.

Discussion

Half of patients eligible for anticoagulant drugs and a quarter eligible for antihypertensive drugs had a missed opportunity for primary prevention prior to stroke or TIA. Missed opportunities for anticoagulant drug prescribing were more common in females, the very elderly (≥85 years), smokers, patients underweight, overweight or obese or with a diagnosis of dementia; but, declined markedly from 2009 to 2013. In contrast, missed opportunities for antihypertensive drug prescribing did not change between 2009 and 2013 and were more common in patients aged 50-59/65-69 years or over 85 years, males, patients with a diagnosis of dementia or with multimorbidities.

Using estimates of the UK population,[30] stroke incidence[31] and effectiveness of anticoagulant and antihypertensive drugs,[9-11] we determined the potential impact of improving prescribing of anticoagulant and antihypertensive drugs on stroke prevention in the UK. We estimate that, in people aged 35 years and over, 2,900 and 3,100 first strokes could potentially be prevented each year in the UK by prescribing all eligible patients anticoagulant and antihypertensive drugs, respectively (Tables S9 and S10 in the Supplementary Appendix). These estimates demonstrate the potential impact of improving prescription of these drugs for stroke prevention in the UK. Furthermore, stroke is a global issue; the Global Burden of Disease study found stroke was the second leading cause of death and third leading cause of disability-adjusted life-years (DALYs) lost worldwide.[32,33] The absolute numbers of first strokes, stroke-related death and DALYs lost has increased worldwide over the last two decades.[34] UK primary care aims to provide universal access, free at the point of delivery and, in international comparisons, financial barriers to care are very low.[35] Therefore, missed opportunities in the UK are likely to be lower than in countries with restricted access or

barriers to primary health care. Given that the incidence and prevalence of AF has worldwide over the past two decades[4] and hypertension is attributable for over half of strokes globally,[36] improving primary prevention in these patients is key to reduce the global burden of stroke and TIA.

Consistent with the literature we found underuse of anticoagulants for stroke prevention in AF patients.[15,37-42] Our findings support studies which found an association between non-prescribing of anticoagulants and being very elderly (≥85 years),[37,40,43-46] female,[37,47] or having a diagnosis of dementia.[44,48-50] Older age has been reported by clinicians as one of the main reasons for not prescribing anticoagulants.[51] Bleeding risk, falls risk and polypharmacy, particularly in those with a reduced life expectancy are likely to be reasons for reduced prescribing in the elderly.[51] However, under-prescribing in the elderly is particularly relevant because prevalence of AF and stroke risk is increased in the elderly;[52] therefore, given population ageing, underuse of anticoagulants in these high risk patients has important implications for stroke prevention; 39% of patients eligible for anticoagulants in our study were aged 85 years and over. Furthermore, the benefits of anticoagulation in the elderly have been shown to outweigh the risk and the net benefit of anticoagulation is actually greatest in the elderly.[53] Under-prescribing of anticoagulants in females will also contribute to the burden of stroke because female sex is an independent risk factor for stroke in AF patients. Furthermore, strokes in women with AF are associated with increased mortality and disability.[6,7] Therefore, it is counterintuitive and unclear why female AF patients are more likely to have a missed opportunity.

Our study found a relationship between comorbidities and anticoagulant drug prescribing. Having a diagnosis of dementia was associated with increased odds of having a missed opportunity. This finding is supported by other studies[44,48-50] and patients' cognitive ability has been identified as a reason for not prescribing anticoagulant drugs.[51] The relationship between dementia and non-prescribing is important because AF has been identified as a risk factor for dementia[54] and an association between cognitive impairment and poor anticoagulation control observed.[55] On the other hand, we found having a diagnosis of heart failure or diabetes was associated with reduced odds of having a missed opportunity. In addition, stroke patients with a previous TIA had fewer missed opportunities for anticoagulant drug prescribing compared to stroke only or TIA only patients (p=0.02). Heart failure, diabetes, and TIA are independent risk factors for stroke in AFs patients and are included in the CHADS2 stroke risk score. This finding could suggest that GPs consider patients' stroke risk when prescribing anticoagulants. Scowcroft et al (2012) found higher CHADS2 score was associated with increased warfarin prescribing.[56] However, Gallagher et al (2008) found no association between CHADS2 score[44] and warfarin prescribing and Lip et al (2015) reported overuse of anticoagulant drugs in patients at low stroke risk.[57]

To a lesser extent, we found underuse of antihypertensive drugs for primary stroke prevention. The lower proportion of missed opportunities for antihypertensive drugs could be a result of the strong evidence base, safely profile and low cost of these drugs.[14] However, the absolute number of strokes/TIAs with a prior missed opportunity for prevention with antihypertensive drugs was higher than anticoagulant drugs (1,647 vs 1,740 for anticoagulant and antihypertensive drugs, respectively). The management of hypertension has substantially improved over the past two decades[58] and the evidence base

is strong;[14] however, our findings demonstrate that antihypertensive drug prescribing remains suboptimal and is likely to affect a large number of people. This is important because the hypertension is a common comorbidity and is attributable for over half of strokes globally.[36] However, our study focused on uncontrolled hypertension and, therefore, the proportion of missed opportunities does not represent the entire hypertensive population. Similar to anticoagulant drugs, the very elderly (≥90 years) had increased odds of having a missed opportunity for prevention with antihypertensive drugs. However, in contrast to anticoagulants, younger patients (50-59/65-69 years) were also more likely to have a missed opportunity. A UK study which investigated primary CVD prevention also found younger patients were less likely to be prescribed antihypertensive drugs and prescribing increased with age.[59] Contrary to anticoagulant drugs, we found females were less likely to have a missed opportunity for antihypertensive drug prescribing. It is unclear why females are more likely to be prescribed antihypertensive drugs, but this finding is supported by other studies.[45,59-61]

A clear relationship was observed between having a diagnosis of a chronic comorbidity and reduced odds of having a missed opportunity, with the exception of a diagnosis of dementia where the opposite was found. In the UK GPs are incentivised to keep a register and actively review people with chronic diseases;[24] our finding could suggest that hypertension is more often treated in patients on an incentivised register. Other studies have found that hypertension patients with existing CVD are more likely to be prescribed antihypertensive drugs compared to those without CVD.[62,63] The guidelines recommend a lower BP treatment threshold for patients with existing CVD or high CVD risk; however, Falaschetti et al (2014) reported that patients with a 10-year CVD risk ≥20% were less likely to be prescribed

antihypertensive drugs compared to people with existing CVD or diabetes.[58] Similarly, our exploratory analysis found that hypertensive patients with a 10-year CVD risk ≥20% were more likely to have a missed opportunity for antihypertensive prescribing (OR 1.5; Supplementary Appendix). On the other hand, multimorbidity was associated with increased odds of having a missed opportunity which could reflect the influence of polypharmacy or lack of guidelines for antihypertensive prescribing in complex patients. People with a diagnosis of dementia were more likely to have a missed opportunity for antihypertensive drug prescribing. This is an important finding because, similar to AF, hypertension has been associated with increased risk of dementia.[64] Dementia patients are underrepresented in clinical trials and cognitive ability may affect patients' adherence to medication.

The proportion of missed opportunities for anticoagulant drug prescribing significantly reduced during the relatively short time period of our study (58% in 2009 to 45% in 2013). However, the underuse of these drugs remains substantial and there is a need for future research to accelerate the reduction in missed opportunities. Females and the very elderly have increased risk of stroke and are under-prescribed anticoagulants despite these risk factors being incorporated into the CHA_2DS_2-VASc stroke risk score.[13] Future research should particularly aim to improve anticoagulant prescribing in these patient group. However, increased side effects of prevention drugs and lack of evidence for the effectiveness of these drugs in the very elderly should be taken into consideration. Exploratory analysis found the majority of patients with missed opportunities were prescribed aspirin (Supplementary Appendix). However, the most recent guidelines[13] and UK QOF incentives[24] recommend that aspirin is not used for stroke prevention in AF patients. AF patients currently taking aspirin should be identified and subsequently be prescribed anticoagulant drugs. An intervention

comprised of education and behavioural change targeted at both patients and GPs could optimise this process and improve future prescribing practice. Inadequate stroke prevention in AF patients is further complicated by the fact that approximately 474,000 people in the UK are estimated to have undiagnosed AF which exacerbates the scale of missed opportunities.[65] Therefore, improving detection and diagnosis of AF through a systematic approach and appropriate prescribing of anticoagulant drugs could substantially reduce the incidence and burden of stroke and TIA. Although there is a strong evidence base for antihypertensive drugs, future research should aim to improve prescribing of these drugs in people without existing CVD but with high calculated CVD risk. The majority of patients who were eligible for antihypertensive drugs in our sample had a lower BP threshold of 140/90 mmHg which emphasises the importance of consideration of CVD risk when prescribing antihypertensive drugs in primary care, which could be promoted through an intervention. Furthermore, our finding that multimorbidity increased the likelihood of having a missed opportunity for antihypertensive drugs is important because the majority of the patients in our sample had two or more chronic conditions. Patients with multimorbidity are likely to be underrepresented in trials and there is a need for guidelines to more comprehensively address multimorbidity.

The strengths of our study are that the sample size was large, the data are recent, broadly representative of the UK population, and reflects actual primary care practice. In addition, stroke and the main comorbidities are likely to be accurately recorded as they are clinically significant and, in the UK, GPs are incentivised to keep a register of patients with these conditions. However, TIA may be misclassified[66] and, through restricting the definition of comorbidities to QOF clinical codes, comorbidity diagnoses may be missed if they were

recorded using alternative clinical codes. We did not exclude patients with a clinical code indicating anticoagulant or antihypertensive drugs were declined, contraindicated, or there was an adverse reaction because it is unclear if these were historic or current codes; however, this number in our sample was small (7% and 0.7% for anticoagulant and antihypertensive drugs). Furthermore, there may be other legitimate reasons for GPs not prescribing stroke/TIA prevention drugs which are not available in our dataset, such as bleeding risk when prescribing anticoagulant drugs or knowledge of a patient's adherence to medication. We defined a missed opportunity for anticoagulants as no prescription of these drugs to AF patients with a CHADS2 score of ≥1 prior to stroke/TIA. The 2006 AF guidelines allow a prescription of aspirin in patients with a CHADS2 score of 1.[12] However, during the study period, important studies had been published which showed aspirin to be ineffective for stroke prevention[10,53] and this recommendation was superseded in the 2014 guidelines.[13] Therefore, missed opportunities for anticoagulants were based on adherence to best evidence rather than guideline recommendations. Missed opportunities defined by a CHADS2 score ≥2 were explored in a sensitivity analysis (Supplementary Appendices). Exploratory analysis also investigated the impact of updated guidelines regarding use of the CHA_2DS_2-VASc and QRISK2-2014 risk scores (Supplementary Appendices). In addition to non-prescribing, patients' non-adherence to prevention drugs is an important consideration in the context of stroke prevention. A limitation of the dataset is that information on adherence is not available and prescription of anticoagulant or antihypertensive drugs may not reflect patients' medication taking behaviour.

Our study demonstrates the underuse of antihypertensive and anticoagulant drugs for primary stroke/TIA prevention. This is important because strokes in AF patients are

associated with increased disability and mortality compared to strokes in people without AF. Furthermore, hypertension is one of the most prevalent comorbidities worldwide and subsequently missed opportunities for prevention affect a large number of people. Improving prescription of anticoagulant and antihypertensive drugs has the potential to prevent a substantial number of strokes worldwide and reduce the global burden of stroke and TIA.

Authors' contributions

GMT, TM, MC, MGF and RR contributed to the study conception and design. GMT conducted the analysis and GMT, TM, MC, RR, DF and KC were involved in the interpretation of results. GMT drafted the manuscript and TM, MC, MGF, RR, DF and KC provided feedback. All authors read and approved the final manuscript.

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Declaration of interests

Ms. Turner reports grants from the NIHR SPCR, during the conduct of the study. Dr. Calvert reports grants from the European Society Cardiology and personal fees from Astellas, outside the submitted work. Dr. Cheng reports grants from the Peking University Health Science Centre, outside the submitted work. Dr. Feltham, Dr. Ryan, Dr. Fitzmaurice and Dr. Marshall have nothing to disclose.

References

1. Lopez AD, Mathers CD. Measuring the global burden of disease and epidemiological transitions: 2002-2030. Annals of tropical medicine and parasitology 2006;100:481-99.
2. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. The Lancet Global Health 2013;1:e259-e81.
3. Sacco RL. Risk factors for TIA and TIA as a risk factor for stroke. Neurology 2004;62:S7-11.
4. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. Circulation 2013;129:837-47.
5. Danaei G, Finucane MM, Lin JK, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. The Lancet 2011;377:568-77.
6. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27:1760-4.
7. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.
8. Vokó Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JCM, Breteler MMB. J-Shaped Relation Between Blood Pressure and Stroke in Treated Hypertensives. Hypertension 1999;34:1181-5.
9. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. The Cochrane Database Systematic Reviews 2005:Cd001927.
10. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. The Cochrane Database Systematic Reviews 2007:Cd006186.
11. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289:2534-44.
12. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: national clinical guideline for management in primary and secondary care. London: Royal College of Physicians; 2006.
13. National Institute for Health and Clinical Excellence (NICE). Atrial fibrillation: the management of atrial fibrillation. NICE Clinical Guideline 180. 2014.
14. National Institute for Health and Clinical Excellence (NICE). Hypertension: the clinical management of primary hypertension in adults. Clinical Guideline 127. National Clinical Guideline Centre; 2011.
15. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. The American Journal of Medicine 2010;123:638-45.e4.
16. Joffres M, Gillespie C, Robitaille C, Loustalot F, Poulter N, McAlister FA, Johansen H, Baclic O, Campbell N. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. BMJ Open 2013;3:e003423.
17. Khatib R, Schwalm J-D, Yusuf S, et al. Patient and healthcare provider barriers to hypertension awareness, treatment and follow up: A systematic review and meta-analysis of qualitative and quantitative studies. PLoS ONE 2014;9:e84238.
18. Moran GM, Calvert M, Feltham MG, Marshall T. Retrospective case review of missed opportunities for primary prevention of stroke and TIA in primary care: protocol paper. BMJ Open 2014;4:e006622.

19. The Health Improvement Network (THIN). (Accessed October, 2015, at http://www.thin-uk.com/.)
20. THIN data statistics. (Accessed October, 2015, at http://csdmruk.cegedim.com/index.html.)
21. The Health Improvement Network Ethics. (Accessed October, 2015, at http://www.thin-uk.com/mrec.htm.)
22. Maguire A, Blak B, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiology and Drug Safety 2009;18:76-83.
23. Read codes. (Accessed October, 2015, at http://systems.hscic.gov.uk/data/uktc/readcodes/index_html.)
24. Quality and outcomes framework. (Accessed October, 2015, at http://www.hscic.gov.uk/qof.)
25. British National Formulary (BNF). (Accessed October, 2015, at http://www.bnf.org/bnf/index.htm.)
26. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. Pharmacoepidemiology and Drug Safety 2010;19:618-26.
27. McKinlay JB, Link CL, Freund KM, Marceau LD, O'Donnell AB, Lutfey KL. Sources of variation in physician adherence with clinical guidelines: results from a factorial experiment. Journal of General Internal Medicine 2007;22:289-96.
28. Midlov P, Ekesbo R, Johansson L, et al. Barriers to adherence to hypertension guidelines among GPs in southern Sweden: a survey. Scandinavian Journal of Primary Health Care 2008;26:154-9.
29. Ramsay SE, Whincup PH, Wannamethee SG, et al. Missed opportunities for secondary prevention of cerebrovascular disease in elderly British men from 1999 to 2005: a population-based study. Journal of Public Health 2007;29:251-7.
30. Office for National Statistics (ONS) Population Estimates. (Accessed October, 2015, at http://data.london.gov.uk/dataset/office-national-statistics-ons-population-estimates-borough.)
31. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). The Lancet 2005;366:1773-83.
32. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2095-128.
33. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2197-223.
34. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study. The Lancet 2010;383:245-55.
35. Davis K, Ballreich J. Equitable access to care-how the United States ranks internationally. The New England Journal of Medicine 2014;371:1567-70.
36. Lawes CMM, Hoorn SV, Rodgers A. Global burden of blood-pressure-related disease, 2001. The Lancet 2008;371:1513-8.
37. Akao M, Chun YH, Esato M, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. Circulation Journal 2014;78:2166-72.
38. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS ONE 2013;8:e63479.

39. Khan MA, Raja S, Ibrahim MS, Hammersely C. Prevalence and management of atrial fibrillation in primary care: a case study. Primary Health Care Research and Development 2014;15:355-61.
40. Maes F, Dalleur O, Henrard S, et al. Risk scores and geriatric profile: can they really help us in anticoagulation decision making among older patients suffering from atrial fibrillation? Clinical Interventions in Aging 2014;9:1091-9.
41. Ogilvie IM, Welner SA, Cowell W, Lip GY. Characterization of the proportion of untreated and antiplatelet therapy treated patients with atrial fibrillation. The American Journal of Cardiology 2011;108:151-61.
42. Shantsila E, Wolff A, Lip GY, Lane DA. Optimising stroke prevention in patients with atrial fibrillation: application of the GRASP-AF audit tool in a UK general practice cohort. The British Journal of General Practice 2015;65:e16-23.
43. Cowan C, Healicon R, Robson I, et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. Heart 2013;99:1166-72.
44. Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? Journal of Thrombosis and Haemostasis 2008;6:1500-6.
45. Marshall IJ, Wang Y, McKevitt C, Rudd AG, Wolfe CD. Trends in risk factor prevalence and management before first stroke: data from the South London Stroke Register 1995-2011. Stroke 2013;44:1809-16.
46. Partington SL, Abid S, Teo K, Oczkowski W, O'Donnell MJ. Pre-admission warfarin use in patients with acute ischemic stroke and atrial fibrillation: The appropriate use and barriers to oral anticoagulant therapy. Thrombosis Research 2007;120:663-9.
47. Sabouret P, Depret-Bixio L, Cotte FE, Marie P, Bedira N, Blin P. Sex differences in stroke prevention in atrial fibrillation in French primary care. Results of the AFIGP (Atrial Fibrillation In General Practice) database. Clinical Research in Cardiology 2014;103:887-93.
48. Dreischulte T, Barnett K, Madhok V, Guthrie B. Use of oral anticoagulants in atrial fibrillation is highly variable and only weakly associated with estimated stroke risk: cross-sectional population database study. The European Journal of General Practice 2014;20:181-9.
49. Holt TA, Hunter TD, Gunnarsson C, Khan N, Cload P, Lip GY. Risk of stroke and oral anticoagulant use in atrial fibrillation: a cross-sectional survey. The British Journal of General Practice 2012;62:e710-7.
50. Tanislav C, Milde S, Schwartzkopff S, et al. Secondary stroke prevention in atrial fibrillation: a challenge in the clinical practice. BMC Neurology 2014;14:195.
51. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age and Ageing 2011;40:675-83.
52. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: The framingham heart study. JAMA 1994;271:840-4.
53. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. The Lancet 2007;370:493-503.
54. Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. Canadian Medical Association Journal 2012;184:E329-36.
55. Flaker GC, Pogue J, Yusuf S, et al. Cognitive function and anticoagulation control in patients with atrial fibrillation. Circulation Cardiovascular quality and outcomes 2010;3:277-83.
56. Scowcroft AC, Lee S, Mant J. Thromboprophylaxis of elderly patients with AF in the UK: an analysis using the General Practice Research Database (GPRD) 2000-2009. Heart 2013;99:127-32.

57. Lip GY, Rushton-Smith SK, Goldhaber SZ, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. Circulation Cardiovascular Quality and Outcomes 2015;8:S12-20.
58. Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in England: a serial cross-sectional study from 1994 to 2011. The Lancet 2014;383:1912-9.
59. Sheppard JP, Singh S, Fletcher K, McManus RJ, Mant J. Impact of age and sex on primary preventive treatment for cardiovascular disease in the West Midlands, UK: cross sectional study. BMJ 2012;345:e4535.
60. Filippi A, Casula M, Tragni E, et al. Blood pressure and antihypertensive therapy according to the global cardiovascular risk level in Italy: the CHECK Study. European Journal of Cardiovascular Prevention and Rehabilitation 2010;17:562-8.
61. Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension 2004;43:10-7.
62. Roccatagliata D, Avanzini F, Monesi L, et al. Is global cardiovascular risk considered in current practice? Treatment and control of hypertension, hyperlipidemia, and diabetes according to patients' risk level. Vascular Health and Risk Management 2006;2:507-14.
63. Sharma AM, Wittchen HU, Kirch W, et al. High prevalence and poor control of hypertension in primary care: cross-sectional study. Journal of Hypertension 2004;22:479-86.
64. Sharp SI, Aarsland D, Day S, Sonnesyn H, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. International Journal of Geriatric Psychiatry 2011;26:661-9.
65. Atrial fibrillation prevalence estimates in England: application of recent population estimates of AF in Sweden. 2015. (Accessed October, 2015, at file:///C:/Users/gxt513/Downloads/AtrialfibrillationprevalenceestimatesinEngland.pdf.)
66. Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. Stroke 2010;41:1367-70.

Multiple missed opportunities for prevention of stroke and TIA with lipid lowering, anticoagulant and antihypertensive drugs

Methods

The proportion of strokes and TIAs with clinical indications and missed opportunities for more than one stroke and TIA prevention drugs were calculated. In addition, for people eligible for multiple drugs and with missed opportunities for multiple drugs, the combinations of different prevention drugs were explored.

Results

At the time of their stroke or TIA 17,680 (61%) people were eligible for one or more stroke prevention drug: 9,953 (56%) were eligible for one prevention drug, 6,904 (39%) for two and 823 for three (5%). Fifty four percent (9,579/17,680) of people eligible for one or more prevention drug prior to stoke or TIA had a missed opportunity for primary prevention; the majority of these had one missed opportunity (83%: 7,969/9,579), 16% (1,576/9,579) had two missed opportunities and 0.4% (34/9,579) had three. Combinations of different missed opportunities are presented in Appendix 3.

Using estimates of the UK population,[1] stroke incidence[2] and effectiveness of statins, anticoagulant and antihypertensive drugs,[3-7] the number of strokes that could potentially be prevented through prescribing prevention drugs to all people eligible for these drugs was determined (Tables 5 and 6). In people aged 35 years and over, 41,400 first stroke patients would be estimated to have had one or more missed opportunity for prescription of lipid

lowering, anticoagulant or antihypertensive drugs. Based on the relative risk reduction of these drugs, 12,000 strokes could potentially be prevented each year in the UK by optimal prescribing of stroke prevention drugs. Restricting the age range to between 35 and 84 years, 29,000 strokes would have had a prior missed opportunity and 8,000 strokes could have been prevented.

Table 5: Combinations of missed opportunities for prevention of stroke and TIA.

Age band	Number of strokes in the THIN sample		Number of missed opportunities for one or more prevention drug in the THIN sample		Proportion of missed opportunities in THIN (%)		Number of strokes per year in UK		Estimated number of missed opportunities in UK	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
<35	115	124	7	7	6%	6%	0	0	0	0
35-44	301	258	35	33	12%	13%	1,469	896	171	115
45-54	841	652	234	102	28%	16%	2,453	1,097	683	172
55-64	1,669	1,034	736	222	44%	21%	6,712	4,413	2,960	947
65-74	2,462	1,903	1,191	567	48%	30%	18,817	12,744	9,103	3,797
75-84	2,613	2,925	805	955	31%	33%	14,656	20,001	4,515	6,530
≥85	1,232	2,468	509	1,241	41%	50%	9,747	16,677	4,027	8,386
All ages	18,597		6,644		35.7%		109,682		41,405	
<85	14,658		4,880		33.3%		83,258		28,992	

Table 6: Estimated number of strokes prevented in the UK with statin, anticoagulant and antihypertensive drugs.

Age band	Number of strokes in the THIN sample		Estimated number of strokes that could be prevented in the THIN sample		Proportion of strokes that could be prevented in the THIN sample (%)		Number of strokes per year in UK		Estimated number of strokes that could be prevented in UK	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<35	115	124	2	2	1%	1%	0	0	0	0
35-44	301	258	10	9	3%	3%	1,469	896	50	30
45-54	841	652	63	27	7%	4%	2,453	1,097	184	46
55-64	1,669	1,034	195	60	12%	6%	6,712	4,413	784	256
65-74	2,462	1,903	317	159	13%	8%	18,817	12,744	2,426	1,063
75-84	2,613	2,925	230	282	9%	10%	14,656	20,001	1,288	1,931
≥85	1,232	2,468	156	374	13%	15%	9,747	16,677	1,237	2,529
All ages	18,597		1,886		10.1%		109,682		11,823	
<85	14,658		1,352		9.2%		83,258		8,057	

Discussion

Six out of ten patients who had a first stroke or TIA were previously eligible for at least one prevention drug and over half of these had at least one missed opportunity for prevention. In effect, one third of all strokes or TIAs occur in patients who had missed opportunities for prevention. Our findings indicate underuse of lipid lowering, anticoagulant and antihypertensive drugs in primary care in patients whom these drugs are clinically indicated for prevention of stroke or TIA.

Forty-four percent of people eligible for stroke or TIA prevention drugs had clinical indications for two or three prevention drugs. However, the vast majority (83%) of missed opportunities were for just one prevention drug. Future research should investigate why some prevention drugs but not others are prescribed to patients. Improving prescribing of lipid lowering, anticoagulant and antihypertensive drugs has the potential to reduce a substantial number of strokes annually in the UK.

References

1. Office for National Statistics (ONS) Population Estimates. http://data.london.gov.uk/dataset/office-national-statistics-ons-population-estimates-borough. Accessed October, 2015.
2. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *The Lancet.* 2005;366(9499):1773-1783.
3. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2005(3):Cd001927.
4. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2007(3):Cd006186.
5. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* 2003;289(19):2534-2544.
6. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane Database of Systematic Reviews.* 2013;1:Cd004816.
7. Wang W, Zhang B. Statins for the prevention of stroke: a meta-analysis of randomized controlled trials. *PLoS ONE.* 2014;9(3):e92388.

Appendices for Chapter 5

Chapter 6: Residual impairments after TIA

Systematic review: Protocol

A systematic review investigating fatigue, psychological and cognitive impairment following TIA and minor stroke: protocol paper

Primary prevention of stroke and TIA is important to reduce the incidence and burden of these conditions. However, for people who do experience a stroke or TIA, it is important that stroke or TIA-related impairments are identified and patients receive appropriate health care. Impairments post-stroke are well characterised;[1] however, TIA is not currently acknowledged to cause any ongoing impairments.[2] Follow-up care after TIA is focused on prevention of stoke and further TIA.[2] Guidelines describe the acute and follow-up care pathways for stroke and TIA, but recommendations for the management of minor stroke are not explicit.[3] However, the pathway is determined by whether a patient's symptoms have resolved at the time of assessment; therefore, minor stroke patients may receive similar care to TIA patients.[3] Anecdotal evidence suggests that TIA and minor stroke patients may experience ongoing residual impairments.[4] This chapter presents the protocol for a systematic review which aimed to establish the prevalence of fatigue, psychological and cognitive impairment after TIA and minor stroke.

References

1. National Institute for Health and Care Excellence (NICE). Stroke rehabilitation: long-term rehabilitation after stroke. NICE Clinical Guideline 162. 2013.
2. Tyrrell P, Swain S, Rudd A. Diagnosis and initial management of transient ischaemic attack. Royal College of Physicians; 2010.
3. National Institute for Health and Clinical Excellence (NICE). Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE Clinical Guideline 68. 2008.
4. Residual symptoms after transient ischaemic attack (TIA). http://www.healthtalk.org/peoples-experiences/nerves-brain/tia-and-minor-stroke/residual-symptoms-after-transient-ischaemic-attack-tia. Accessed October, 2015.

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SYSTEMATIC REVIEWS

PROTOCOL Open Access

A systematic review investigating fatigue, psychological and cognitive impairment following TIA and minor stroke: protocol paper

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Abstract

Background: Approximately 20,000 people have a transient ischemic attack (TIA) and 23,375 have a minor stroke in England each year. Fatigue, psychological and cognitive impairments are well documented post-stroke. Evidence suggests that TIA and minor stroke patients also experience these impairments; however, they are not routinely offered relevant treatment. This systematic review aims to: (1) establish the prevalence of fatigue, anxiety, depression, post-traumatic stress disorder (PTSD) and cognitive impairment following TIA and minor stroke and to investigate the temporal course of these impairments; (2) explore impact on quality of life (QoL), change in emotions and return to work; (3) identify where further research is required and to potentially inform an intervention study.

Methods/Design: A systematic review of MEDLINE, EMBASE, PsycINFO, CINAHL, Cochrane libraries and grey literature between January 1993 and April 2013 will be undertaken. Two reviewers will conduct screening search results, study selection, data extraction and quality assessment. Studies of adult TIA and minor stroke participants containing any of the outcomes of interest; fatigue, anxiety, depression, PTSD or cognitive impairment will be included. Studies at any time period after TIA/minor stroke, including those with any length of follow-up, will be included to investigate the temporal course of impairments. QoL, change in emotions and return to work will also be documented. The proportion of TIA or minor stroke participants experiencing each outcome will be reported. If appropriate, a meta-analysis will pool results of individual outcomes. Studies will be grouped and analyzed according to their follow-up timeframe into short-term (< 3 months after TIA/minor stroke), medium-term (3 to 12 months) and long term (> 12 months). Sub-analysis of studies with a suitable control group will be conducted. Exploratory sub-analysis of memory and attention domains of cognitive impairment will be conducted.

Discussion: The current treatment goal for TIA and minor stroke patients is secondary stroke prevention. If these patients do experience fatigue, psychological or cognitive impairments then this treatment alone is unlikely to be sufficient. The results of this comprehensive review will increase understanding of treatment needs for this patient group, identify where further research is required and potentially inform an intervention trial.

Keywords: Transient ischemic attack, Minor stroke, Reversible ischemic neurologic deficit, Fatigue, Anxiety, Depression, Post-traumatic stress disorder, Cognitive impairment, Quality of life

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Background

Stroke is caused by an impaired supply of blood to the brain resulting in loss of brain function, and is one of the major causes of mortality and functional disability in the United Kingdom (UK) [1,2]. The severity of strokes differ between patients and can be classified as major stroke, minor stroke and transient ischemic attack (TIA), also known as mini-stroke. The term major stroke broadly refers to strokes that result in long-term or permanent neurological symptoms and may result in disability. Minor stroke is a term that is widely used in research but has not been formally defined, however, it refers to strokes with symptoms lasting longer than 24 hours but where symptoms are mild and non-disabling [3]. TIA is defined by stroke-like symptoms typically lasting less than one hour and no evidence of acute infarction [4]. TIA and minor stroke also create a substantial burden on society and affect a huge proportion of the population. In England, approximately 20,000 people have a TIA and 23,375 people have a minor stroke every year [5].

Fatigue, cognitive and psychological problems after stroke

In addition to functional disability, sequelae following stroke include fatigue, cognitive impairments and psychological impairments, such as anxiety, depression and post-traumatic stress disorder (PTSD) [6]. These impairments are documented in the literature and have a detrimental impact on people's lives [7-10]. Fatigue is multidimensional and comprises physical, emotional and cognitive elements [11]. Fatigue has been shown to impact on stroke survivors' rehabilitation and quality of life (QoL) [12] and is associated with depression [13], inability to return to work [14] and increased fatality post-stroke [15]. The burden of fatigue should not be underestimated, for instance one study found 40% of stroke patients reported fatigue as their worst symptom [16].

Anxiety is universally the most common mental health disorder and is coupled with physical, behavioral and cognitive symptoms [17]. Anxiety and depression frequently occur simultaneously and, in this circumstance, depression is more severe and patients experience higher levels of functional and cognitive impairment [17]. Both major and minor depression have been documented post-stroke and can occur at any time point from the acute stage up to five years post-stroke with an estimated prevalence of 33% [18]. In addition, Ayerbe *et al.* reported that a high proportion of patients with depression post-stroke at one time point remained depressed [19]. Depression is associated with a poor prognosis, decreased QoL and increased mortality [20].

PTSD can develop after exposure to a life-threatening medical event and has been documented post-stroke [21]. Research has shown that occurrence of post-stroke PTSD is independent of physical disability [8]. PTSD has detrimental implications and patients with PTSD have been shown to have an increased risk for a worse physical and mental health prognosis and have greater suicidal intention [8]. It is speculated that a poor health prognosis related to PTSD is associated with both biological mechanisms, such as high blood pressure, and behavioral factors, such as non-adherence to medication [22]. Resultant non-adherence to medication may impact on stroke and TIA survivors as this is essential for secondary prevention of stroke. PTSD also adversely affects people's QoL and normal functioning [23]. Conversely, life-threatening events can also produce a positive psychological change known as post-traumatic growth. McGrath and Linley [24] reported evidence of sustained positive psychological change after acquired brain injury. However the sample size for this study was small. Furthermore post-traumatic growth following stroke is reported to be inversely correlated with anxiety and depression [25]. This concept is relatively new to stroke research and there is only a small amount of literature available, which to our knowledge has not yet been extended to TIA and minor stroke. Therefore this review will be limited to PTSD.

Cognitive impairment is well documented following stroke and exhibits a wide-range of symptoms including difficulty with memory, reading, writing and number skills, visual impairment and difficulty planning and problem solving. A relationship between cognitive and functional impairment has been reported along with a negative impact on rehabilitative outcomes [26]. Cognitive impairment is associated with depression but the directional relationship is unclear [27]. For the purpose of this review, cognitive impairment will encompass impairments of attention, memory, spatial awareness, perception, apraxia and executive functioning as in accordance with the Royal College of Physicians National Clinical Guidelines for Stroke [28].

Impairment after TIA and minor stroke

Fatigue, psychological and cognitive impairment have been shown to occur post-stroke in the absence of functional impairment and independent of stroke severity [29]. Although TIA and minor stroke are characterized by short-lasting symptoms, evidence suggests that this cohort experience residual problems. Coutts *et al.* [30] found that 15% of a sample of TIA and minor stroke patients were disabled at 90 days as defined by a modified Rankin Scale score ≥ 2. Another study reported TIA patients to have comparable QoL scores to stroke patients in all domains with the exception of social isolation [31]. However, results of this study may be unrepresentative of the true stroke population as stroke patients in rehabilitation hospitals and care homes were excluded. Significant fatigue has been reported in a community population of TIA and minor stroke patients with a prevalence, at six months, of 29% and 56% respectively [32]. Qualitative research of people's experiences following TIA or minor stroke revealed that people reported a

variety of residual symptoms [33]. These included functional impairments, such as limb weakness and numbness; cognitive impairments, such as memory difficulties; slurred speech; emotional issues, such as feeling depressed, confused and more emotional [34].

Current treatment guidelines relevant to TIA and minor stroke focus on secondary prevention of stroke [5]. However, no consideration is given to psychological or cognitive impacts of TIA or minor stroke and patients are not routinely offered additional rehabilitative support. Untreated fatigue, psychological or cognitive impairment will result in a reduced QoL and affect people's ability to return to work and social activities.

Aims

Considering the diversity and complexity of residual impairments anecdotally described by people following TIA and minor stroke, it is important to conduct a comprehensive systematic review of the literature. This is a necessary step to develop future intervention studies that will inform treatment recommendations and guidelines. This systematic review therefore aims to:

- Establish the prevalence of fatigue, anxiety, depression, PTSD and cognitive impairment following a TIA or minor stroke and investigate if this prevalence changes over time.
- Explore the impact of TIA and minor stroke on people's QoL, change in emotions and return to work.
- Identify where there are gaps in the understanding of residual problems after TIA and minor stroke.

Methods

Our search strategy, selection of studies, assessment of risk of bias and reporting of results for the review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [35]. This protocol is not registered with Prospective Registering of Systematic Reviews (PROSPERO) as the scope of the research does not meet their current inclusion criteria.

Eligibility criteria

The inclusion of studies in the systematic review will be determined by participants, comparators, outcomes and study designs used by the study and the report characteristics.

Participants

This review will include TIA and minor stroke participants. Studies will be excluded if they recruited major stroke participants or mixed populations, where it is not possible to extract the data of TIA or minor stroke participants. As stroke is a confounding factor for outcomes of interest, participants must have no previous history of stroke and be stroke free in the follow-up period. Alternatively, the study must have subgroup analysis of stroke free participants. Participants must be adults (over 18 years of age) to exclude childhood stroke. Studies that include participants under 18 years of age will be included if over 90% of the sample are adults.

There is not a standard definition of minor stroke however, as suggested by Fischer *et al*. [3], this patient group should have non-disabling symptoms following stroke but be distinct from TIA patients. TIA patients will be defined by short-lasting stroke symptoms (less than 24 hours) with no evidence of acute infarct. Studies where authors describe their population as TIA, minor stroke, mild stroke, reversible ischemic neurologic deficit or non-disabling stroke will be included.

Comparators

Descriptive study designs will be included in this review and, therefore, studies without a comparison group will be included. However, if present, data will be extracted for control groups where participants have no history of stroke, minor stroke or TIA. Participants' data on outcomes before their TIA or minor stroke will also be used as suitable a comparator.

Outcomes

Stroke causes a broad spectrum of impairments; anecdotal evidence from TIA and minor stroke patients emulates these diverse impairments. Given this, exploratory analysis will be conducted to identify the proportion of TIA and minor stroke participants with the following; fatigue, anxiety, depression, PTSD or cognitive impairment. These principle outcomes will be defined by scores above the predefined cut off limit for validated assessments. Studies must either report the frequencies for outcomes or data whereby frequencies can be calculated. There will be no restrictions on the duration of participant follow-up or time since TIA or minor stroke to develop understanding about the temporal course of the outcomes. Information on QoL, change in emotions and return to work or performance at work will also be documented. Studies will be included that report any of the above outcomes.

Study design

Initial scoping searches ascertained that a limited amount of relevant studies have been conducted that include a comparator group. Therefore, all study designs will be included with the exception of single case studies and reviews. Intervention studies may be included if the non-intervention arm consists of TIA or minor stroke patients receiving usual care. Only data from this control arm will be analyzed as this review is not investigating interventions.

Report characteristics

Only human studies will be included. Full papers, conference abstracts and theses will be included. To avoid language bias, non-English papers will be included. For pragmatic and quality of reporting reasons, the review will limit the search to 20 years (1993 to 2013).

Information sources

Electronic searches of the following databases will be conducted; MEDLINE, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR). Databases will be searched from January 1993 to April 2013.

Ongoing studies will be identified by searching clinicaltrials.gov, Stroke Trials Registry (www.strokecenter.org/trials/) and conference abstracts including the American Heart Association International Stroke conference, European Stroke conference and UK Stroke Forum. Conference Proceedings Citation Index (CPCI) will also be searched for conference abstracts. These sources will be searched from 2010 to 2013 as it will be assumed studies presented before these dates will have been completed and published.

Grey literature will be explored including PubliCAT and ScienceDaily.com. The first four pages of Google Scholar results will be searched; this limit was established from scoping searches. Dissertations and theses will be identified from the databases ProQuest Dissertation Thesis Database and thesis.com. References from included studies will be scanned and tracked through the cited reference search in Science Citation Index (SCI).

Search

A comprehensive search strategy has been developed that focuses on the following elements; TIA, minor stroke, fatigue, anxiety, depression, PTSD and cognitive impairment. Search terms have been established by scoping searches. The MEDLINE search strategy is detailed in Additional file 1. This search will be adapted for the other databases.

Study selection

The titles and abstracts of the search results will be screened and full text will be obtained for relevant studies. Two authors (GT and BF) will complete this process independently and any difference in opinion will be resolved by a third reviewer (TM). Full text articles will be reviewed to determine if studies included through screening meet the inclusion criteria. An inclusion checklist has been developed, based on the eligibility criteria, and piloted (Table 1).

Table 1 The inclusion checklist for screened references

Study design	Cross sectional
	Cohort
	Case control
	Case series
	Other (please specify)
	Study objectives relevant to topic
Report characteristics	Full article
	Conference abstract
	Thesis
	Other (please specify)
	Publication date 1993 to 2003
Participants	TIA
	Minor stroke
	Study sample are adults
	Participants have no previous history of stroke/subgroup analysis of those with no history of stroke
	Participants stoke free during follow-up/ subgroup analysis of those stroke free
Comparator (Do NOT exclude if no comparator)	Comparator group present? (If no, go to outcomes)
	No previous history of stroke, minor stroke or TIA
Outcomes	Measure for anxiety
	Measure for depression
	Measure for fatigue
	Measure for PTSD
	Measure for cognition
	Quality of life reported
	Change in emotions reported
	Return to work reported
	Frequencies reported/can be calculated

Data collection process

Data extraction will be performed in duplicate by two independent reviewers (GT and BF) for all of the eligible papers identified through the screening process. A data extraction form has been developed which focuses on population, comparator, outcomes and study design. This form has been informed by the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement [36]. The data extraction form was piloted independently by two researchers (GT and MF) on known papers. A Microsoft Excel document will be used to manage the data extraction.

Quality assessment

Quality assessment of included studies will be performed by two independent reviewers (GT and BF). A quality

assessment form has been devised which focuses on sampling, measurement of outcomes, attrition and analysis (Table 2). This form has been piloted independently by two researchers on known papers (GT and MF). In accordance with the Cochrane Collaboration recommendations, an overall score will not be generated but a risk of bias judgment of 'yes', 'no' or 'unclear' will be given for individual domains [37]. The studies level of quality will be presented in a table and narrative summary. The impact of the studies quality on results will be evaluated in the discussion. If appropriate, a sensitivity analysis will be conducted excluding poor quality studies.

Synthesis and analysis of results

If the outcomes demonstrate homogeneity, the results for individual outcomes will be pooled quantitatively using meta-analysis. The temporal course of fatigue, psychological and cognitive impairment post-stroke has not been well characterized. However, prevalence of post-stroke depression has been shown to have immediate onset, peak at three to six months but also remain high years after stroke [38]. To explore the time course of these impairments following TIA and minor stroke, studies will be grouped into short-term (less than three months after TIA or minor stroke), medium-term (three to twelve months) and long-term (over twelve months). If appropriate, frequencies for each outcome will be combined to create pooled estimates for short, medium and long term timeframes.

A sub-analysis of studies with a suitable control group will also be conducted to determine whether outcome proportions are higher in TIA and minor stroke patients compared to healthy controls. Cognitive impairment covers a spectrum of different domains. Anecdotal evidence suggests that TIA and minor stroke patients experience residual memory and attention complaints. Therefore, exploratory analysis of specifically memory and attention domains of cognitive impairment will be conducted. To investigate the natural history of fatigue, psychological and cognitive impairment after TIA and minor stroke, exploratory analysis of the outcomes for new cases compared to persistent cases will be conducted for studies with more than one time point.

If studies are methodologically heterogeneous, a narrative synthesis of results will be more appropriate. In accordance with the Center for Reviews and Dissemination (CRD), included studies will be summarized in a table detailing study type, sample size, participant characteristics, outcomes and outcome measures [39]. The Economic and Social Research Council (ESRC) guidance report will be used as a framework for a narrative synthesis [40].

Table 2 The quality assessment criteria for included studies

		Judgment (yes/no/unclear)
		Support for judgment
Sampling	Was the study design appropriate to answer the research question?	
	Was the sampling method appropriate?	
	Did the study report how many people were approached and how many agreed to take part?	
	Do those that participate have similar characteristics to those that refused (for example, age, gender, comorbidities, how they were approached)?	
	Is the sample size adequate?	
	Did the study describe how the sample size was determined?	
	Was a suitable definition of TIA/minor stroke used?	
	If applicable, was the control group comparable to cases (consider suitability, recruitment and baseline characteristics)?	
	Did the study demonstrate if the outcomes were present before the TIA/minor stroke (for example, history of depression)?	
Measurement	Was a suitable measurement for outcome used?	
	Has the outcome measure been validated for the population?	
	Was the outcome measure cut-off score predefined?	
	Was the outcome measure administration suitable (for example, self reported, investigator interview)?	
	Were potential confounding variables measured?	
Attrition	Were numbers of dropouts/withdrawals documented at each time point?	
	Were reasons given for dropouts/withdrawals?	
Analysis	Were all outcomes reported?	
	Were confounding variables adjusted for?	

Discussion

Currently the treatment goal for TIA and minor stroke patients is the prevention of subsequent stroke [5]. These patients are not acknowledged to have residual problems which require management. This systematic review will collate literature to establish whether evidence suggests people experience fatigue, anxiety, depression, PTSD or cognitive problems following a TIA or minor stroke. The temporal nature of the prevalence of these impairments after the event will also be investigated. In addition, impact of TIA and minor stroke on QoL, change in emotions and return to work will be explored. This systematic review will identify if there is a lack of literature for any of the outcomes and review the quality of the available evidence.

Implications of results

If it is found that TIA or minor stroke patients have an increased prevalence of fatigue, psychological or cognitive problems, then the current management, without addressing them, is unlikely to be adequate. Dissemination of results will increase the awareness of the treatment needs of TIA and minor stroke survivors. This information will be particularly valuable in the primary care setting where it is likely that this patient group will present with residual complaints.

The comprehensive and systematic search and review of the literature will identify and inform where further research is required. For instance, if a large number of descriptive studies are available for the review, then the findings will inform a subsequent analytical, hypothesis testing, study. Alternatively, the findings from the review might indicate that exploration research has already been conducted and will therefore inform the design of an acceptability and feasibility study. This subsequent study will investigate the effects of an intervention to manage and treat fatigue, psychological and cognitive problems following TIA and minor stroke.

Additional file

Additional file 1: Search strategy for MEDLINE (via Ovid) January 1993 to April 2013. Full electronic search strategy for MEDLINE.

Abbreviations

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CPCI: Conference Proceedings Citation Index; CRD: Center for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Effects; ESRC: Economic and Social Research Council; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; PROSPERO: Prospective Registering of Systematic Reviews; PTSD: post-traumatic stress disorder; QoL: quality of life; SCI: Science Citation Index; STROBE: STrengthening the Reporting of OBservational studies in epidemiology; TIA: transient ischemic attack; UK: United Kingdom.

Competing interests

The authors declared that they have no competing interests.

Authors' contributions

GT drafted the manuscript. TM, MC, MF and CS provided feedback on the manuscript. GT, TM, MC, MF and CS were involved in the design of the review. GT conducted scoping searches, GT and MF piloted the inclusion/exclusion, quality assessment and data extraction forms. GT will be first reviewer and BF will be the second reviewer for the systematic review. All authors read and approved the final manuscript.

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References

1. Adamson J, Beswick A, Ebrahim S: **Is stroke the most common cause of disability?** *Stroke Disabil J Stroke Cerebrovasc* 2004, **13:**171–177.
2. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M: *Coronary Heart Disease Statistics 2012 Edition*. London: British Heart Foundation; 2012:77.
3. Fischer U, Baumgartner A, Arnold M, Nedeltchev K, Gralla J, De Marchis GM, Kappeler L, Mono ML, Brekenfeld C, Schroth G, Mattle HP: **What is a minor stroke?** *Stroke* 2010, **41:**661–666.
4. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, Sherman DG: **Transient ischemic attack - proposal for a new definition.** *New Engl J Med* 2002, **347:**1713–1716.
5. National Institute for Health and Clinical Excellence: *Stroke: Diagnosis and Initial Management of Acute Stroke and Transient Ischemic Attack (TIA)*, CG068. NICE Clinical Guidelines, Number 68. ; 2008. Available from: http://www.ncbi.nlm.nih.gov/books/NBK53295/.
6. Mukherjee D, Levin R, Heller W: **The cognitive, emotional, and social sequelae of stroke: psychological and ethical concerns in post-stroke adaptation.** *Top Stroke Rehabil* 2006, **13:**26–35.
7. De Wit L, Putman K, Baert I, Lincoln NB, Angst F, Beyens H, Bogaerts K, Brinkmann N, Connell L, Dejaeger E, De Weerdt W, Jenni W, Kaske C, Komarek A, Lesaffre E, Leys M, Louckx F, Schuback B, Schupp W, Smith B, Feys H: **Anxiety and depression in the first six months after stroke. A longitudinal multicenter study.** *Disabil Rehabil* 2008, **30:**1858–1866.
8. Sembi S, Tarrier N, O'Neill P, Burns A, Faragher B: **Does post-traumatic stress disorder occur after stroke: a preliminary study.** *Int J Geriatr Psychiatr* 1998, **13:**315–322.
9. Staub F, Bogousslavsky J: **Fatigue after stroke: a major but neglected issue.** *Cerebrovasc Diseases* 2001, **12:**75–81.
10. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E: **Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities.** *J Neurol Neurosur Ps* 1994, **57:**202–207.
11. Annoni JM, Staub F, Bogousslavsky J, Brioschi A: **Frequency, characterization and therapies of fatigue after stroke.** *Neurol Sci* 2008, **29:**S244–S246.
12. Duncan F, Wu SM, Mead GE: **Frequency and natural history of fatigue after stroke: a systematic review of longitudinal studies.** *J Psychosomat Res* 2012, **73:**18–27.
13. Snaphaan L, van der Werf S, de Leeuw FE: **Time course and risk factors of post-stroke fatigue: a prospective cohort study.** *Eur J Neurol* 2011, **18:**611–617.
14. Andersen G, Christensen D, Kirkevold M, Johnsen SP: **Post-stroke fatigue and return to work: a two-year follow-up.** *Acta Neurol Scand* 2012, **125:**248–253.

15. Naess H, Lunde L, Brogger J, Waje-Andreassen U: **Fatigue among stroke patients on long-term follow-up. The Bergen Stroke Study.** *J Neurol Sci* 2012, **312:**138–141.
16. Ingles JL, Eskes GA, Phillips SJ: **Fatigue after stroke.** *Arch Phys Med Rehabil* 1999, **80:**173–178.
17. Shimoda K, Robinson RG: **Effect of anxiety disorder on impairment and recovery from stroke.** *J Neuropsychiatr Clin Neurosci* 1998, **10:**34–40.
18. Hackett ML, Yapa C, Parag V, Anderson CS: **Frequency of depression after stroke: a systematic review of observational studies.** *Stroke* 2005, **36:**1330–1340.
19. Ayerbe L, Ayis S, Rudd AG, Heuschmann PU, Wolfe CD: **Natural history, predictors, and associations of depression five years after stroke: the South London Stroke Register.** *Stroke* 2011, **42:**1907–1911.
20. Naess H, Lunde L, Brogger J, Waje-Andreassen U: **Depression predicts unfavorable functional outcome and higher mortality in stroke patients: the Bergen Stroke study.** *Acta Neurol Scand* 2010, **122:**34–38.
21. Kronish IM, Edmondson D, Goldfinger JZ, Fei KZ, Horowitz CR: **Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks.** *Stroke* 2012, **43:**2192–2197.
22. Edmondson D, Horowitz CR, Goldfinger JZ, Fei KZ, Kronish IM: **Concerns about medications mediate the association of posttraumatic stress disorder with adherence to medication in stroke survivors.** *Br J Health Psychol* 2013. doi:10.1111/bjhp.12022.
23. Noble AJ, Baisch S, Schenk T, Mendelow DA, Allen L, Kane P: **Posttraumatic stress disorder explains reduced quality of life in subarachnoid hemorrhage patients in both the short and long term.** *Neurosurgery* 2008, **63:**1095–1105.
24. McGrath CJ, Linley PA: **Post-traumatic growth in acquired brain injury: a preliminary small scale study.** *Brain Inj* 2006, **20:**767–773.
25. Zhang Zhenxiang YY, Wei R, Li J, Lin B: **Posttraumatic growth, anxiety, depression of stroke survivors.** *Life Science Journal-Acta Zhengzhou University Overseas Edition* 2012, **9:**2237–2240.
26. Cumming TM, Marshall RS, Lazar RM: **Stroke, cognitive deficits, and rehabilitation: still an incomplete picture.** *Int J Stroke* 2013, **8:**38–45.
27. Saxena SK, Ng TP, Yong D, Fong NP, Koh G: **Subthreshold depression and cognitive impairment but not demented in stroke patients during their rehabilitation.** *Acta Neurol Scand* 2008, **117:**133–140.
28. Party ISW: *National Clinical Guidelines for Stroke.* 4th edition. London: Royal College of Physicians; 2012.
29. Starkstein SE, Cohen BS, Fedoroff P, Parikh RM, Price TR, Robinson RG: **Relationship between anxiety disorders and depressive disorders in patients with cerebrovascular injury.** *Arch Gen Psychiatry* 1990, **47:**246–251.
30. Coutts SB, Modi J, Patel SK, Aram H, Demchuk AM, Goyal M, Hill MD: **What causes disability after transient ischemic attack and minor stroke? Results from the CT and MRI in the triage of TIA and minor cerebrovascular events to identify high risk patients (CATCH) study.** *Stroke* 2012, **43:**3018–3022.
31. Franzen-Dahlin A, Laska AC: **Gender differences in quality of life after stroke and TIA: a cross-sectional survey of out-patients.** *J Clin Nurs* 2012, **21:**2386–2391.
32. Winward C, Sackley C, Metha Z, Rothwell PM: **A population-based study of the prevalence of fatigue after transient ischemic attack and minor stroke.** *Stroke* 2009, **40:**757–761.
33. Spurgeon L, Humphreys G, James G, Sackley C: **A Q-methodology study of patients' subjective experiences of TIA.** *Stroke Research and Treatment* 2012. doi:10.1155/2012/486261. Article ID: 486261.
34. *Residual Symptoms After Transient Ischaemic Attack (TIA).* [http://www.healthtalkonline.org/nerves_and_brain/transient_ischaemic_attack/Topic/4076/]
35. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration.** *BMJ* 2009, **339:**b2535.
36. von Elm E, Altman D, Egger M, Pocock S, Gøtzsche P, Vandenbroucke J, STROBE Initiative: **The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies.** *J Clin Epidemiol* 2008, **61:**344–349.
37. Higgins JPT, Green S (Eds): *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org.
38. Whyte EM, Mulsant BH: **Post stroke depression: epidemiology, pathophysiology, and biological treatment.** *Biol Psychiatry* 2002, **52:**253–264.
39. Tacconelli E: **Systematic reviews: CRD's guidance for undertaking reviews in health care.** *Lancet Infect Dis* 2010, **10:**226.
40. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, Britten N, Roen K, Duffy S: *Guidance on the conduct of narrative synthesis in systematic reviews*, ESRC Methods Programme (Unpublished report, University of Lancaster, UK). ; 2006.

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Appendices for Chapter 6

Chapter 7: Residual impairments after TIA

Systematic review: Results

Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: a systematic review

TIA is characterised by short-lasting symptoms and minor stroke refers to strokes when symptoms last longer than 24 hours but where symptoms are mild and non-disabling. [1] It is assumed that patients do not have any ongoing impairments once symptoms have resolved; however, anecdotally, TIA and minor stroke have reported experiencing residual impairments.[2] This chapter presents the findings of the systematic review described in Chapter 6 which aimed to establish the prevalence of fatigue, psychological and cognitive impairment post-TIA and minor stroke.

References

1. Tyrrell P, Swain S, Rudd A. Diagnosis and initial management of transient ischaemic attack. Royal College of Physicians; 2010.
2. Residual symptoms after transient ischaemic attack (TIA). http://www.healthtalk.org/peoples-experiences/nerves-brain/tia-and-minor-stroke/residual-symptoms-after-transient-ischaemic-attack-tia. Accessed October, 2015.

Dissemination

Year	Conference	Location	Oral/Poster
2014	North American Primary Care Research Group (NAPCRG) Annual Meeting	New York, USA	Oral presentation
	Primary Health Care Research Conference (PHCRC)	Canberra, Australia	Oral presentation ***Awarded first time presenter prize**
	Society of Academic Primary Care (SAPC) Annual Conference	Edinburgh, Scotland	Elevator pitch
	National Institute for Health Research (NIHR) School for Primary Care Research (SPCR) Showcase	Oxford, UK	Poster ***Awarded second prize in the best poster competition**
2013	SAPC Annual Conference	Nottingham, UK	Poster
	NIHR SPCR Annual Trainees Meeting	Oxford, UK	Poster
	Annual NIHR Trainees Meeting	Leeds, UK	Poster

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REVIEW ARTICLE

Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: a systematic review

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Keywords:
anxiety, cognitive impairment, depression, fatigue, minor stroke, post-traumatic stress disorder, quality of life, transient ischaemic attack

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Transient ischaemic attack (TIA) and minor stroke are characterized by short-lasting symptoms; however, anecdotal and empirical evidence suggests that these patients experience ongoing cognitive/psychological impairment for which they are not routinely treated. The aims were (i) to investigate the prevalence and time course of fatigue, anxiety, depression, post-traumatic stress disorder(PTSD) and cognitive impairment following TIA/minor stroke; (ii) to explore the impact on quality of life (QoL), change in emotions and return to work; and (iii) to identify where further research is required and potentially inform an intervention study. A systematic review of MEDLINE, EMBASE, PSYCINFO, CINAHL, the Cochrane libraries and the grey literature between January 1993 and April 2013 was undertaken. Literature was screened and data were extracted by two independent reviewers. Studies were included of adult TIA/minor stroke participants with any of the outcomes of interest: fatigue, anxiety, depression, PTSD, cognitive impairment, QoL, change in emotions and return to work. Random-effects meta-analysis pooled outcomes by measurement tool. Searches identified 5976 records, 289 were assessed for eligibility and 31 studies were included. Results suggest high levels of cognitive impairment and depression post-TIA/minor stroke which decreased over time. However, frequencies varied between studies. Limited information was available on anxiety, PTSD and fatigue. Meta-analysis revealed that the measurement tool administered influenced the prevalence of cognitive impairment: Mini-Mental State Examination 17% [95% confidence interval (CI) 7, 26]; neuropsychological test battery 39% (95% CI 28, 50); Montreal Cognitive Assessment 54% (95% CI 43, 66). There is evidence to suggest that TIA/minor stroke patients may experience residual impairments; however, results should be interpreted with caution because of the few high quality studies. Notwithstanding, it is important to raise awareness of potential subtle but meaningful residual impairments.

Introduction

Transient ischaemic attack (TIA) and minor stroke are characterized by short-lasting symptoms [1,2]. These patients are discharged rapidly from hospital and treatment guidelines focus on secondary prevention of stroke [3]. However, there is evidence to suggest that TIA and minor stroke patients may experience residual impairments for which they are not routinely offered treatment. Coutts *et al.* [4] reported 15% of a sample of TIA and minor stroke participants ($n = 499$) were disabled at 90 days as defined by a modified Rankin Scale score ≥2. In addition, Fens *et al.* [5] found that approximately half of a sample of TIA and minor stroke participants ($n = 55$) self-reported cognitive and communication difficulties, which was significantly higher ($P \leq 0.001$) than angina controls ($n = 72$). Anecdotal evidence from patient interviews revealed that TIA and minor stroke patients experienced a variety of ongoing residual symptoms including memory and speech difficulties; feeling confused and more emotional; mild limb weakness and numbness [6]. Subtle but meaningful impairment post-TIA and minor stroke may go undetected. If untreated, these impairments may result in a reduced quality of life (QoL), affect people's ability to return to work and social activities and

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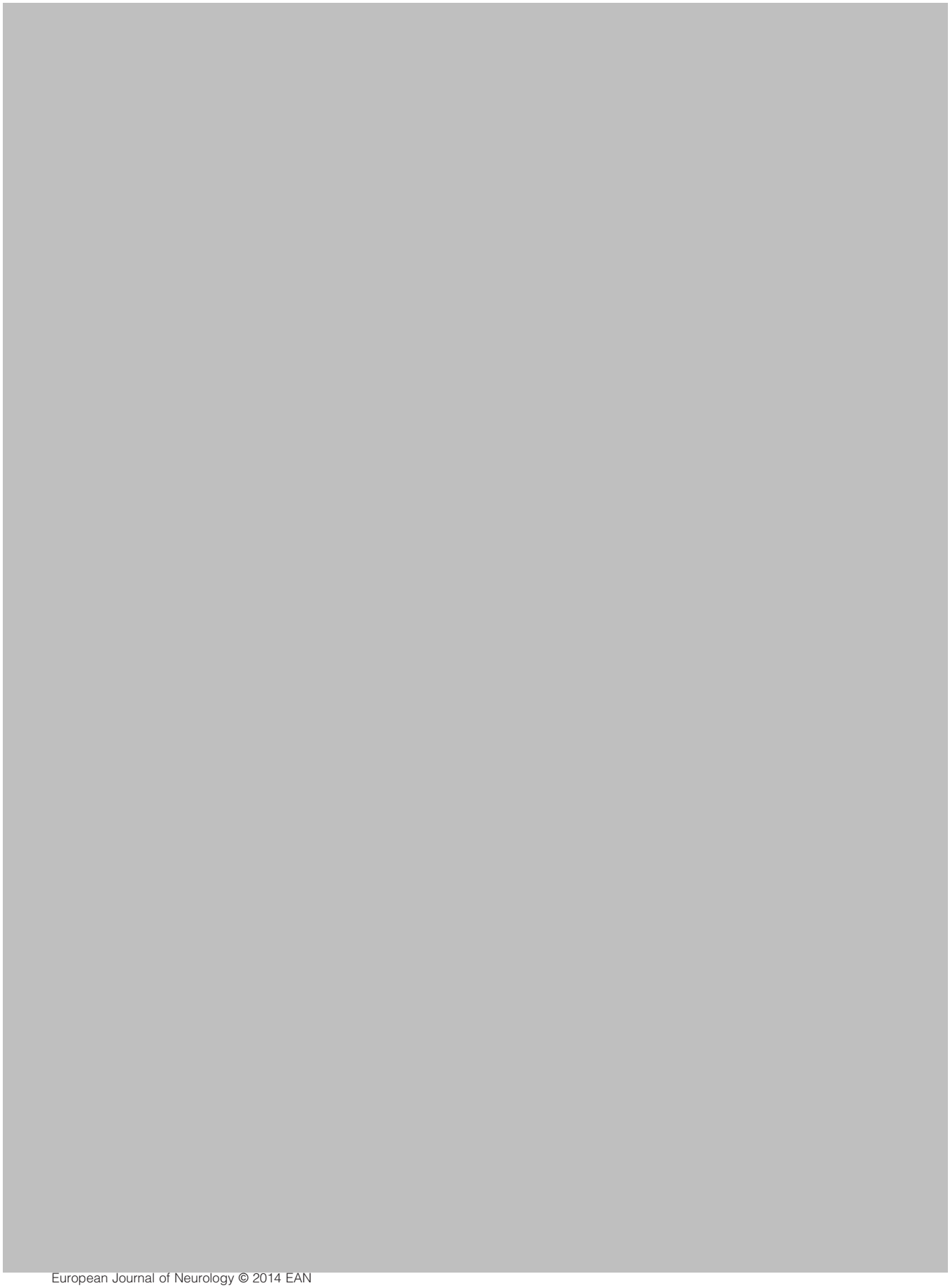

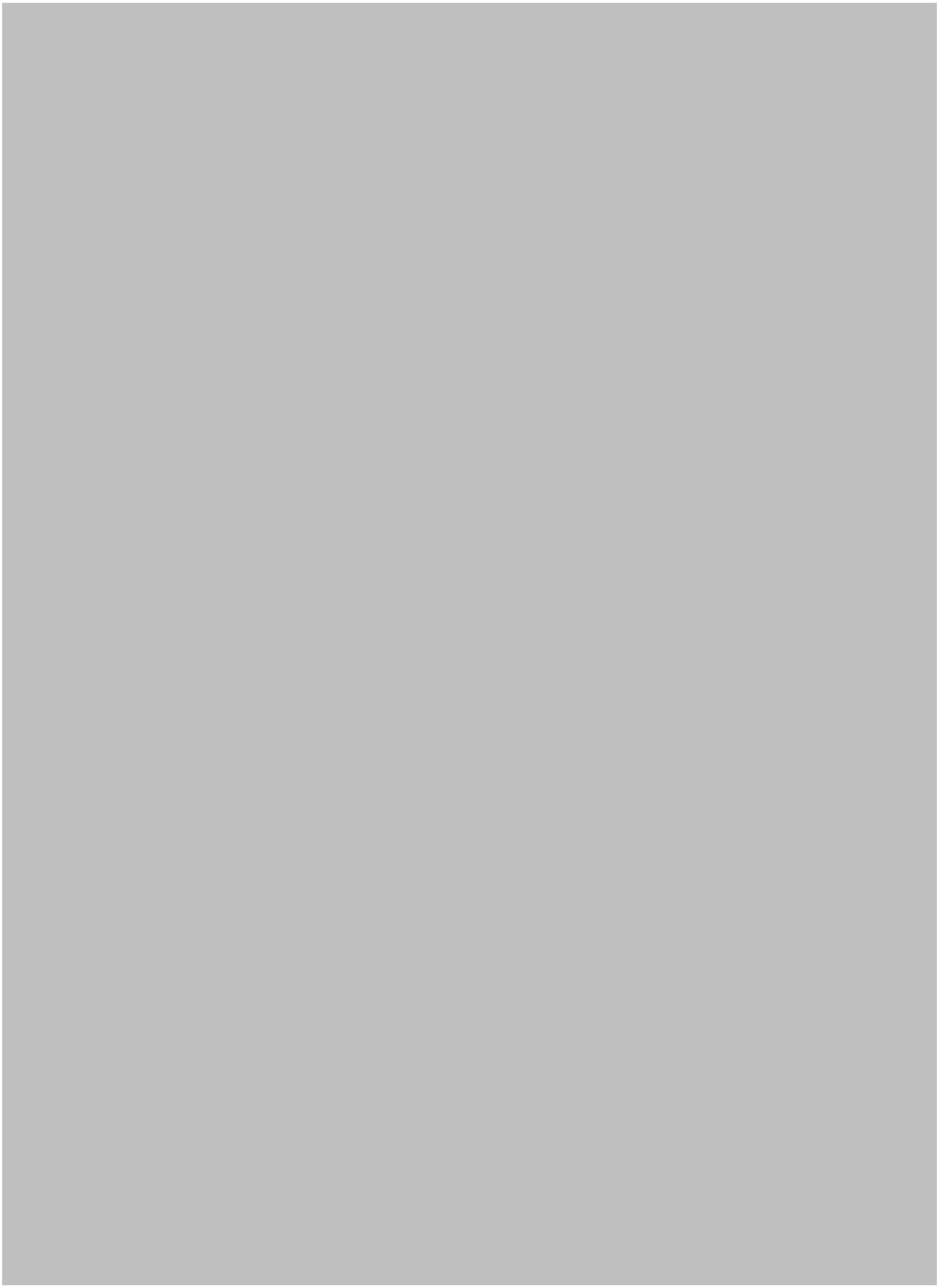

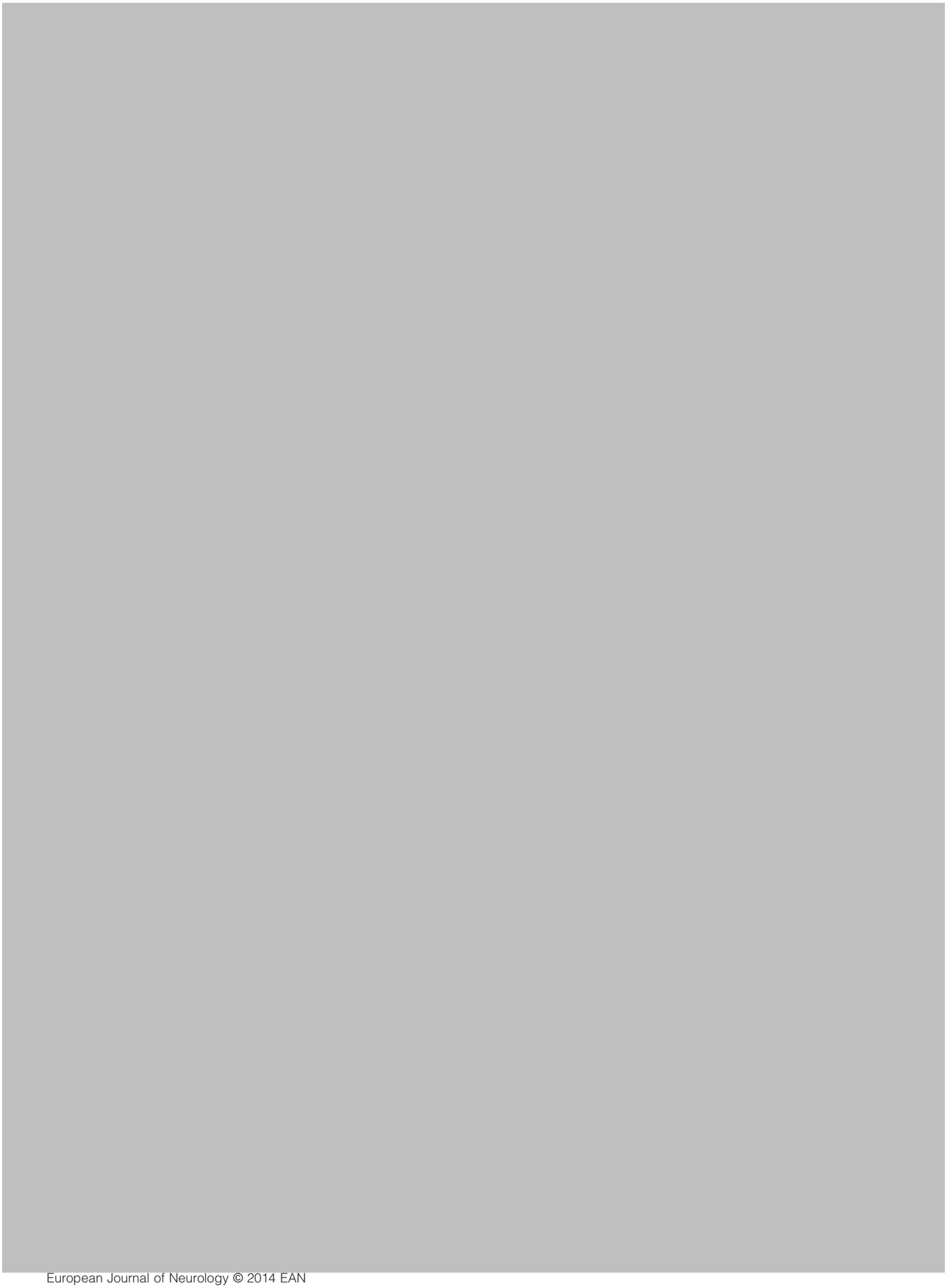

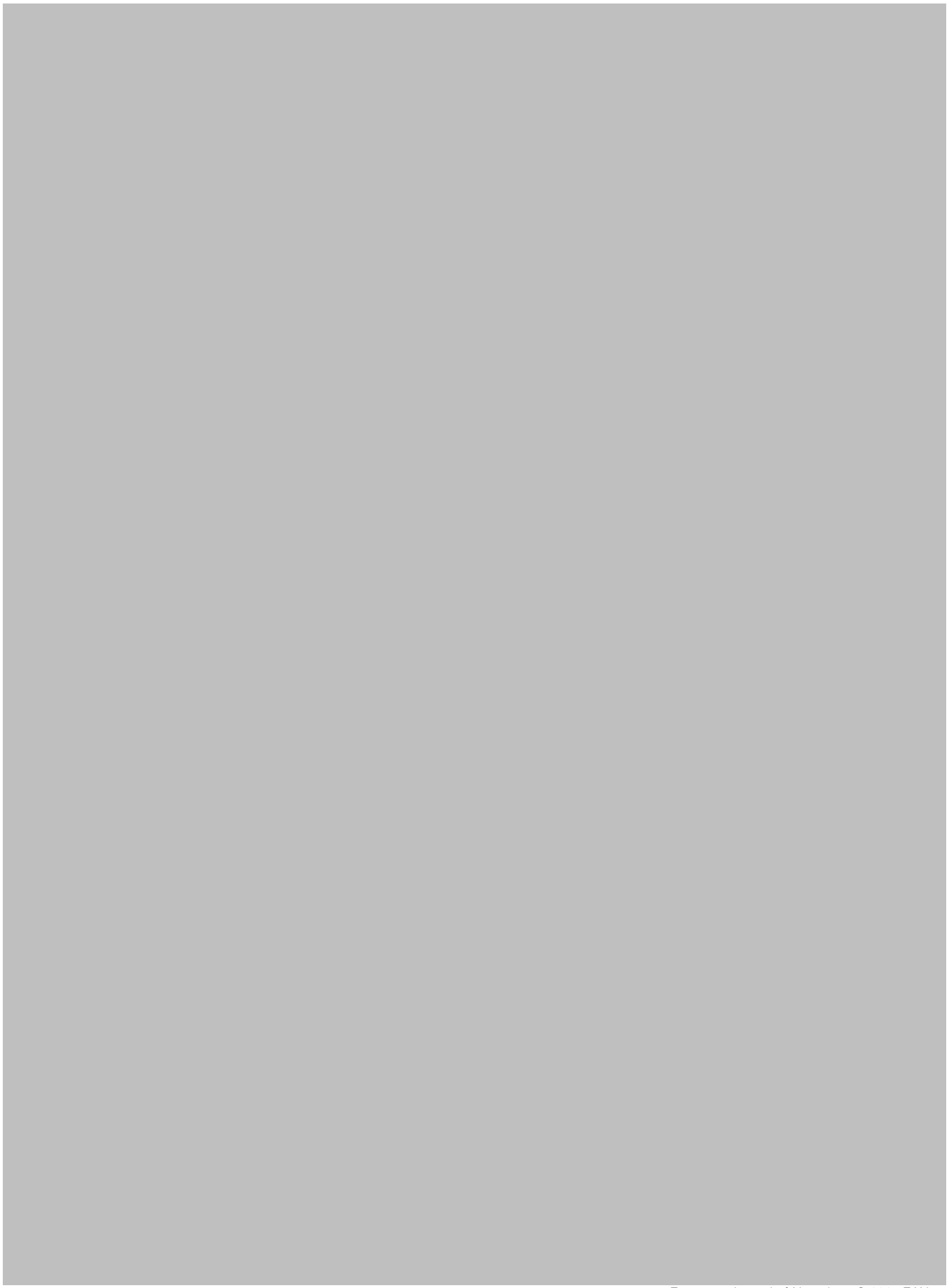

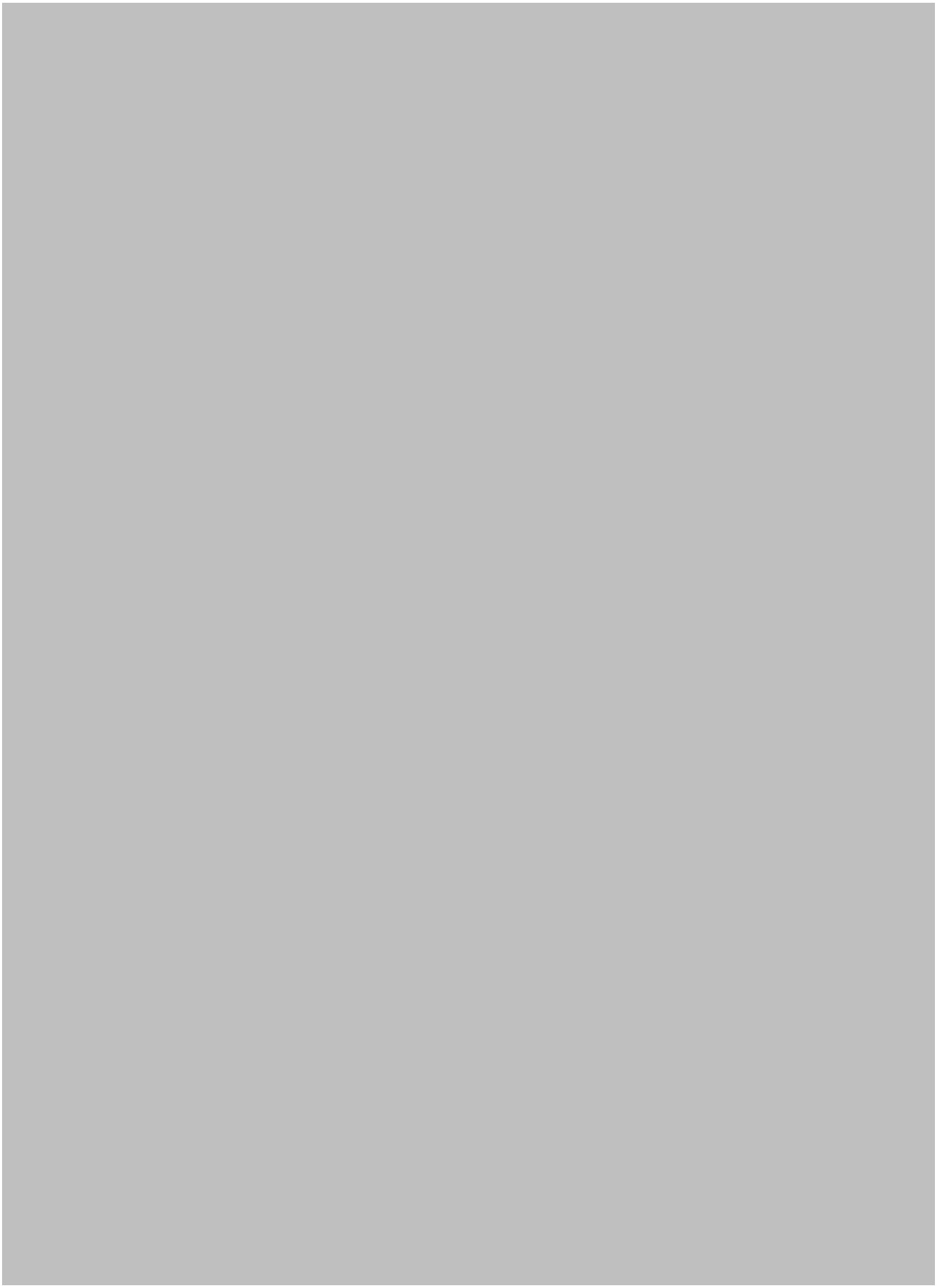

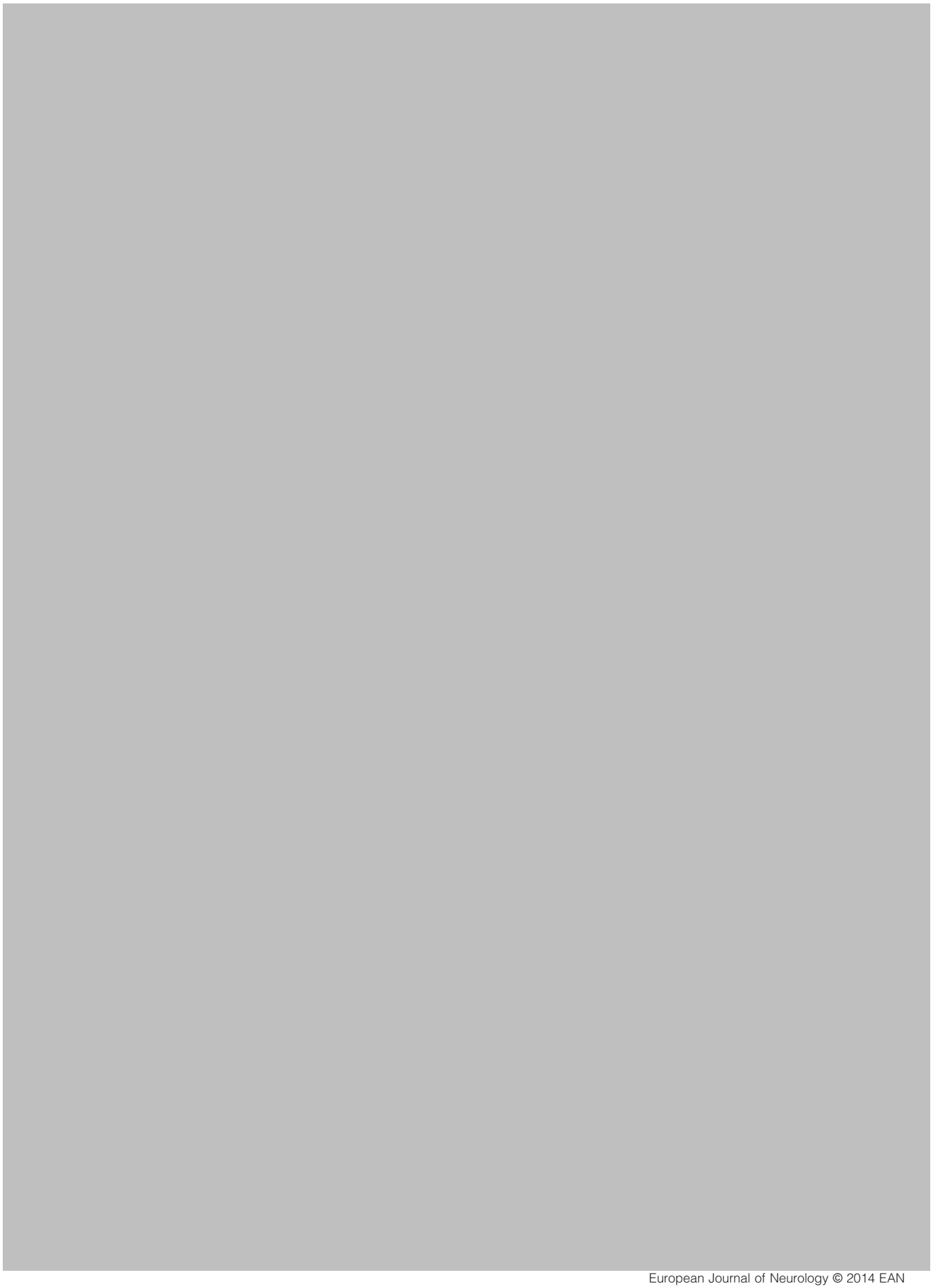

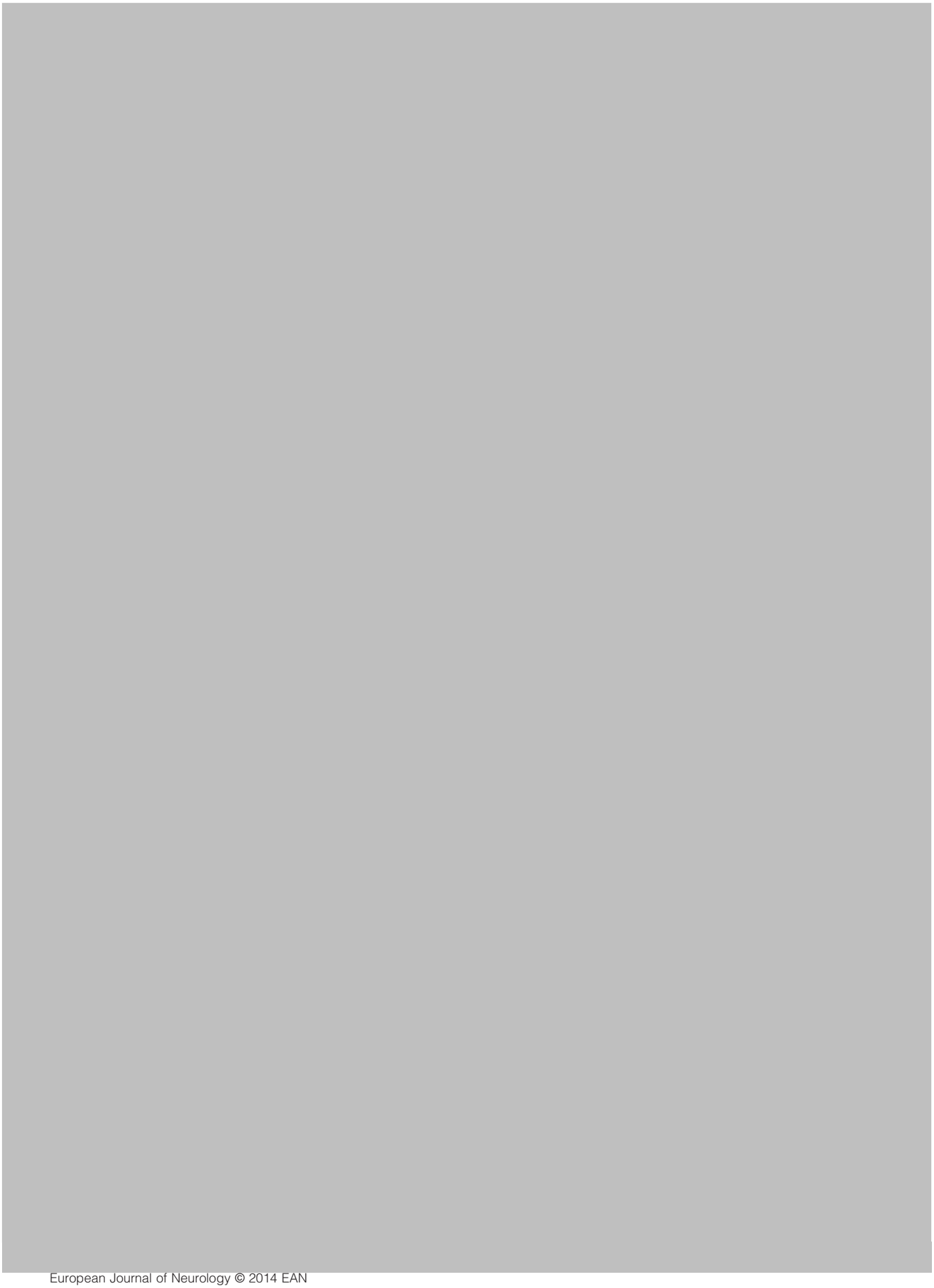

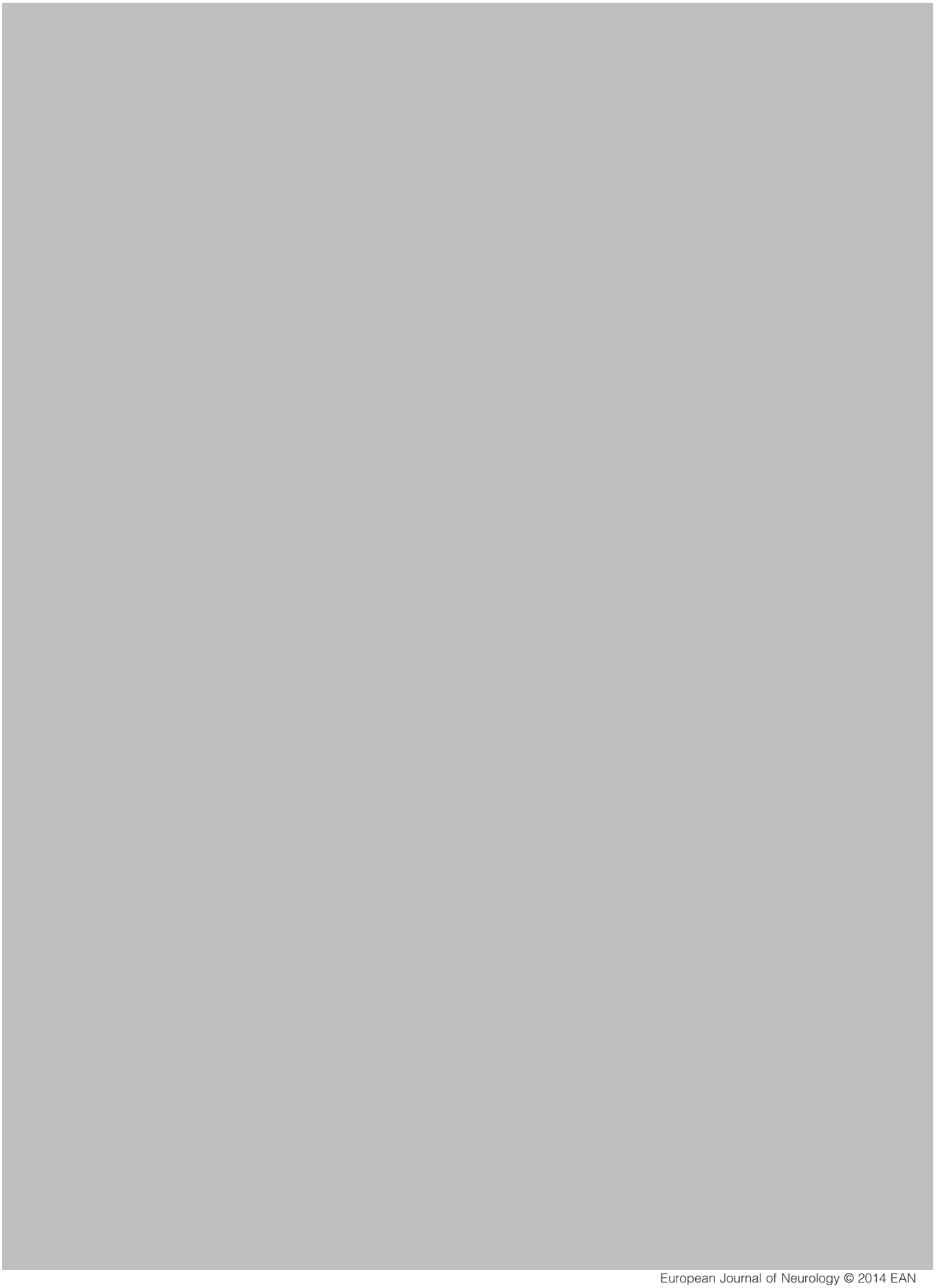

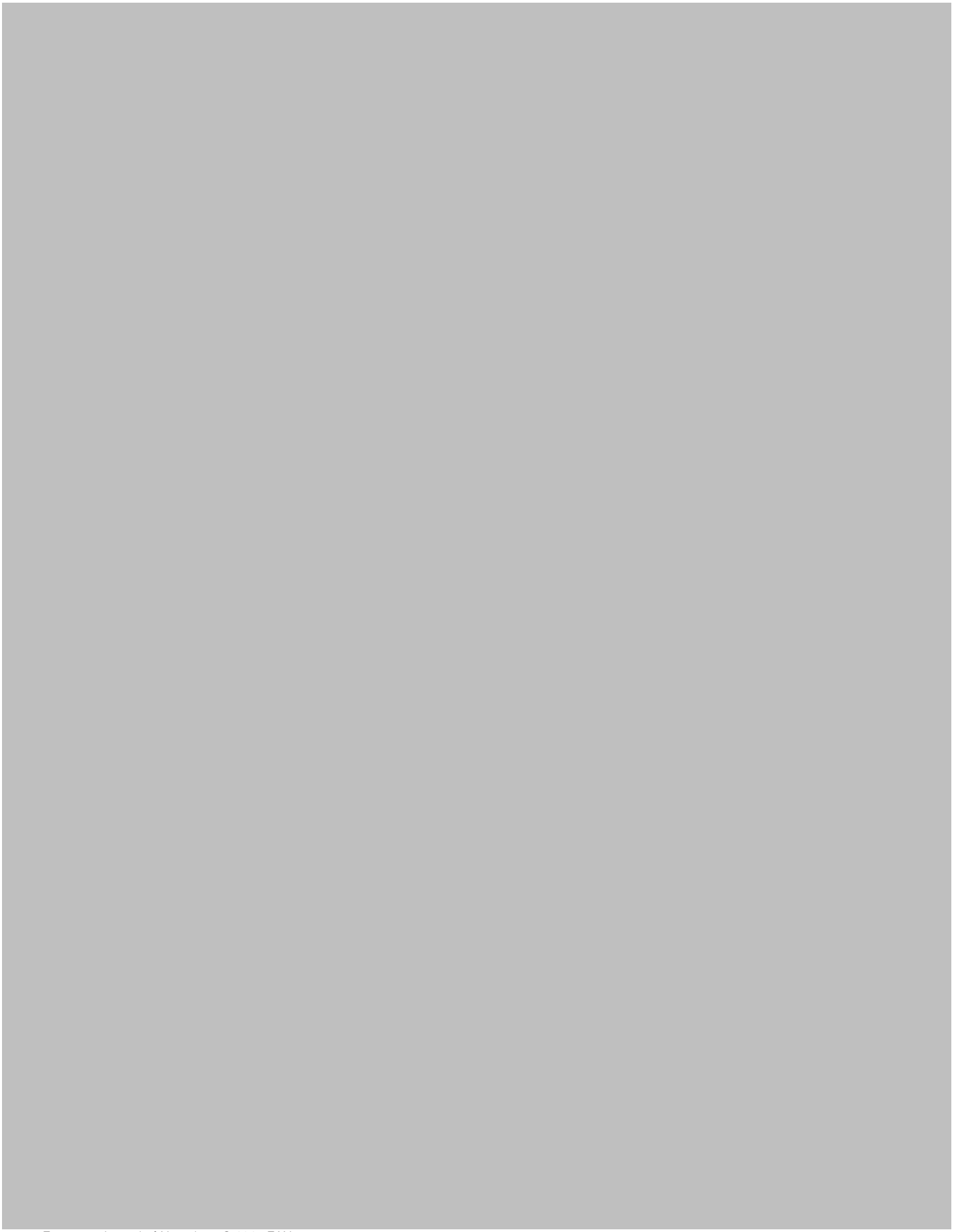

Appendices for Chapter 7

Chapter 8: Residual impairments after TIA

Retrospective cohort study: Protocol

A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper

The systematic review (Chapters 6 and 7) found limited evidence that suggested a relatively high prevalence of cognitive impairment and depression post-TIA and minor stroke. However, there were very few studies that measured fatigue, anxiety and PTSD. Furthermore, there was a lack of high quality studies which had a comparator group or controlled for confounding variables or presence of the impairment prior to TIA or minor stroke. The results were limited in terms of reliability and generalisability and it was unclear whether the prevalence of impairments post-TIA and minor stroke differed to people of a similar age and gender without TIA or minor stroke. Therefore, there was a need for further research to investigate the association between TIA or minor stroke and residual impairments. This chapter describes the protocol for a matched retrospective cohort study which addressed the limitations of existing studies and aimed to investigate the association between TIA and consultation for fatigue, cognitive, or psychological impairment in primary care. The protocol describes the use of electronic primary care medical records extracted from the THIN database to conduct a retrospective age, sex and general practice matched cohort study.

This chapter is presented in the format of the version published in the journal BMJ Open.

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A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper

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ABSTRACT

Introduction: Transient ischaemic attack (TIA) is defined by short-lasting, stroke-like symptoms, and is recognised as a medical emergency. Symptoms are assumed to completely resolve, and treatment is focused on secondary stroke/TIA prevention. However, evidence suggests that patients with TIA may experience ongoing residual impairments, which they do not receive therapy for as standard practice. TIA-induced sequelae could impact on patients' quality of life and ability to return to work or social activities. We aim to investigate whether TIA is associated with subsequent consultation for fatigue, psychological or cognitive impairment in primary care.

Methods and analysis: A retrospective open cohort study of patients with first-ever TIA and matched controls. Relevant data will be extracted from The Health Improvement Network (THIN) database, an anonymised primary care database which includes data for over 12 million patients and covers approximately 6% of the UK population. Outcomes will be the first consultation for fatigue, anxiety, depression, post-traumatic stress disorder or cognitive impairment. Principal analysis will use Kaplan-Meier survivor functions to estimate time to first consultation, with log-rank tests to compare TIA and control patients. Cox proportional hazard models will predict the effect of demographic and patient characteristics on time to first consultation.

Ethics and dissemination: Approval was granted by a THIN Scientific Review Committee (ref: 14-008). The study's findings will be published in a peer-reviewed journal and disseminated at national and international conferences and through social media.

INTRODUCTION

Transient ischaemic attack (TIA) is defined by short-lasting, stroke-like symptoms which usually resolve within 1–2 h without causing cerebral infarction.[1] TIA is associated with an increased risk of subsequent stroke, and treatment is focused on secondary stroke/TIA prevention.[2] It is currently assumed that patients do not experience any TIA-induced sequelae; however, patients have anecdotally reported ongoing residual impairments post-TIA.[3] Fatigue, psychological and cognitive impairments occur post-stroke and could be potential sequelae of TIA. These impairments are associated with reduced quality of life, impaired functioning and increased mortality post-stroke.[4–7] It is important to establish the holistic consequences of TIA; if patients experience ongoing impairments, they could impact on patients' quality of life and ability to return to work or social activities. Therefore, preventative medical management alone, without addressing residual impairments, is unlikely to be adequate. Additionally, these impairments may be subtle and missed by clinicians, but are meaningful for the patient.

We recently conducted a systematic review investigating the prevalence of fatigue, psychological and cognitive impairment following TIA and minor stroke. There was evidence to suggest these patients experience residual impairments; however, existing studies had important limitations.[8] We were unable to determine if the prevalence of impairments post-TIA was greater than that of the general population because few studies included a control group. The association between TIA and subsequent impairments was unclear as most studies did not measure or control for presence of impairments prior to TIA or minor stroke.

This study will address the limitations of existing studies and explore if TIA is associated with subsequent fatigue, psychological or cognitive impairment. If present, there is the potential for TIA-induced impairment to increase stroke risk through biological mechanisms (such as increased blood pressure from anxiety) or behavioural change (such as non-adherence to stroke prevention

medication if these drugs were attributed to post-TIA impairments). This study aims to investigate (1) whether TIA is associated with subsequent consultation for fatigue, psychological or cognitive impairment in primary care and (2) if patients with TIA who consult with these residual impairments are more likely to experience a subsequent stroke.

METHODS AND ANALYSIS

Study design

A retrospective open cohort study of patients with first-ever TIA and controls matched by age (±2 years), sex and general practice.

Data source

Data will comprise of anonymised UK primary care patient records extracted from The Health Improvement Network (THIN). Over 500 general practices contribute to the THIN database which covers approximately 6% of the UK population and has data for over 12 million patients, including 3.6 million current patients.[9] Practices that contribute data to THIN use Vision patient records software which codes clinical data using the Read code clinical classification (V.2)[10] and drug prescriptions which link to the British National Formulary.[11]

Population

Relevant data will be extracted for patients with first-ever TIA aged 18 years and over with no previous history of stroke. For each patient with TIA, we will select five[12] controls free from stroke and TIA and matched on age (±2 years), sex and general practice. The date of TIA will be taken as the index date, and controls will be part of the same general practice as their matched patients with TIA on the index date (figure 1). Controls will be selected from the pool of potential controls without replacement to ensure they only act as a control once. Control patients who experience a TIA in follow-up will become part of the TIA group if they meet the eligibility criteria. For data quality reasons, the index date must occur between 1 January 2000 and the practice's most recent data collection, and have occurred after the practice date of acceptable mortality recording.[13] TIA and control patients must have been registered at their practice for at least 1 year prior to diagnosis to obtain baseline data. Patients will be followed up until they leave the practice, die or suffer a TIA (control patients only) or stroke.

Study variables

Outcome variables

The principal outcomes will be the first consultation for fatigue, anxiety, depression, post-traumatic stress disorder (PTSD) or cognitive impairment. The outcomes will be defined by relevant clinical codes (Read codes) for symptoms and diagnoses, or drug codes (see online supplementary appendix 1). Cognitive impairment will include memory, attention and executive functioning impairments but not dementia. The outcomes will be grouped into three categories: (1) fatigue, (2) cognitive impairment and (3) psychological impairment (comprised of anxiety, depression and PTSD). Stroke will be a secondary outcome, and the first occurrence of a stroke is a censoring event for the principal outcomes.

Exposures variables

A comprehensive list of clinical codes for stroke and TIA has been developed which will identify the eligible population (see online supplementary appendix 2). TIA and control patients must have no clinical codes indicating a previous stroke or TIA prior to the index date.

Follow-up

Follow-up of TIA and control patients will continue until the first occurrence of: death, stroke, patient leaves their practice or the last data collection from the general practice. Diagnosis of another TIA during the follow-up period will be permitted for patients with TIA; however, control patients will be censored on the date a TIA is recorded, and subsequently will become part of the TIA group. Three substudies will be formed for each outcome category (fatigue, psychological or cognitive impairment) and patients will be censored at the first consultation for the relevant outcome.

Predictor variables

The most recent baseline demographic and patient characteristics prior to index date will be extracted including age (at index date), sex, body mass index (BMI),

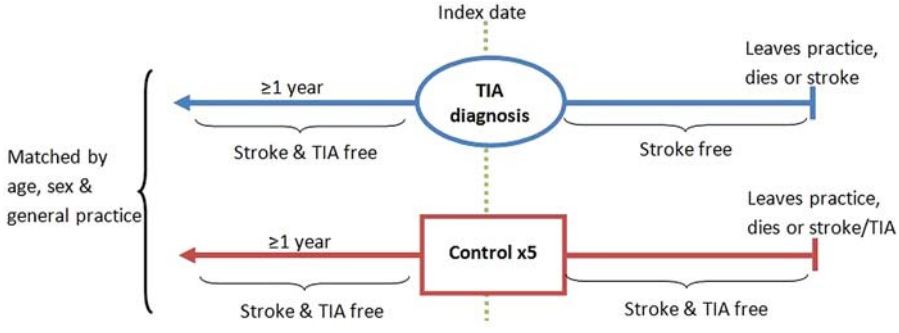

Figure 1 Summary of matching and eligibility criteria for transient ischaemic attack (TIA) and control patients.

Townsend deprivation quintiles,[14] urban/rural residence,[14] smoking status and alcohol consumption. Existing comorbidities may be associated with fatigue, psychological or cognitive impairment; therefore, comorbidities will be measured and comprise of the long-term conditions included in the Quality and Outcomes Framework (QOF), identified by their corresponding Read codes (QOF business rules V.27; see online supplementary appendix 3).[15] Although other conditions may be potential confounders, the QOF incentives scheme means that these conditions are likely to be well recorded, and they include the majority of important conditions. Number of consultations will be reported because patients who consult more would have increased opportunity to report residual impairments. Furthermore, consultations for fatigue, psychological or cognitive impairment prior to the index date will be extracted to control for presence of the outcomes prior to the index date.

Quality checks, missing data and extreme values

Data are unlikely to be missing at random;[16] therefore, no attempt will be made to impute numeric missing data, and continuous variables will be categorised with an additional 'missing' category included. Absence of clinical codes for diagnoses will be taken to indicate the diagnosis is not present. Clinically implausible values for height, weight and BMI will be excluded with Health Survey for England statistics used as a guide.[17]

Analysis

Data management and analysis will be performed using STATA V.12 (StataCorp, College Station, Texas, USA). The principal analysis will use Kaplan-Meier (K-M) survivor functions to estimate time to each outcome for TIA and control patients (ie, first consultation where there is a clinical code indicating fatigue, anxiety, depression, PTSD or cognitive impairment). Log-rank tests will compare TIA and control patients' K-M survivor functions. Cox proportional hazard models will be used to predict the effect of demographic and patient characteristics on time to each outcome. Backwards elimination, with a p-to-eliminate value of >0.05, will select covariates included in the models. General practice will be included as a random effect, and age and sex will be forced into the model to adjust for residual confounding. Fatigue and cognitive impairment will be analysed individually. Anxiety, depression and PTSD will be combined as psychological impairments, but analysed individually in an exploratory analysis. Sensitivity analysis will restrict the analysis to patients with no record of fatigue, psychological or cognitive impairment prior to the index date. To investigate if patients with TIA who consult for residual impairments are more likely to have a stroke, secondary analysis will use K-M survivor functions to estimate time to first stroke for patients with TIA with and without residual impairments. An exploratory analysis will investigate the incidence of stroke in the first year post-TIA. Similar to the principal analysis, demographic and patient characteristics will be adjusted for using Cox proportional hazard models. Exploratory analysis will also investigate the effect of excluding patients with no consultations in follow-up, or those who consult for outcomes within the first month of follow-up.

DISCUSSION

Follow-up for patients with TIA is conducted in primary care; therefore, it is important for primary care clinicians to understand if patients experience TIA-related impairments which require additional treatment to secondary stroke prevention. A systematic review of the literature found evidence to suggest fatigue, psychological and cognitive impairment following TIA. However, the evidence was limited and the review highlighted the need for further research comprised of a large, matched cohort study.[8] Our study will provide a valuable contribution to the literature, increase the understanding of the needs of this patient group, and potentially inform an intervention study.

This study is likely to have a large sample size, and data will be representative of 'real-life' primary care practice as data are collected in routine clinical care. Contrary to most existing studies in this field, we will include a matched control group and will control for the presence of fatigue, psychological and cognitive impairment prior to TIA. Limitations of the study include the accuracy of diagnosis and recording of TIA and our outcomes (fatigue, cognitive and psychological impairment) in primary care. General practitioners are incentivised to keep a register of patients with TIA;[15] however, it has been recognised that TIA can be misdiagnosed.[18] Although TIA may be underdiagnosed, our data will be representative of the current state of TIA diagnoses in primary care. Ideally, we would have included patients with minor stroke in our sample; however, severity of stroke is not coded in the Read clinical coding.

Our outcomes are likely to be under-reported because, although residual impairments could impact on patients' quality of life, they may be subtle and, consequently, patients may not consult in primary care for them. Furthermore, impairments may not be recognised by primary care clinicians, for example, evidence suggests poor recognition and recording of mild cognitive impairment in primary care.[19] However, we have developed an extensive list of clinical codes which encompass symptoms as well as diagnoses and, where possible, included related medication to define outcomes. Diagnosis of depression is incentivised by QOF and is, therefore, likely to be well recorded. General practices are expected to differ in their recording of our outcomes, and to control for this, we will match TIA and control patients on this variable. It is important to note that the THIN database comprises of primary care data; therefore, this study will include primary care consultations for fatigue, psychological and cognitive impairments rather than the incidence of these impairments in the community.

A limitation of using electronic medical records is that duration of our outcomes cannot be determined as we are unable to identify if or when symptoms resolve. Patients may experience fatigue, psychological or cognitive impairment before their index date, and have a clinical code to indicate this. However, if the impairment is still present after the index date, the presence of the impairment may not be recorded again and we will not be able to include the continued presence of this impairment in our analysis. Furthermore, patients with TIA may potentially consult more in primary care because of TIA-related follow-up appointments. This could introduce an ascertainment bias as patients with TIA would have more opportunity to report fatigue, psychological or cognitive impairments compared with those who consult less frequently. We will descriptively report the average number of consultations for TIA and control patients, and discuss the potential impact on our results.

Dissemination

The findings of the study will be published in a peer-reviewed journal, and disseminated at national and international conferences and through social media.

Twitter Follow Grace Moran at @gracemturner

Contributors GMM led the design of the study as doctoral research supervised by TM, MC and MGF. RR was involved in the design of the study and extracted the data from THIN. GMM drafted the manuscript. TM, MC, MGF and RR provided feedback on the manuscript, and all authors approved the final version.

Funding This work is supported by the National Institute for Health Research School for Primary Care Research. This paper presents independent research funded by the National Institute for Health Research.

Ethics approval The NHS South East Multi-centre Research Ethics Committee approved data collection for the THIN database in 2003.[20] Individual studies using anonymised THIN data do not require separate ethical review but must be approved by the independent THIN Scientific Review Committee (SRC). This study was approved by the SRC in February 2014 (reference number: 14-008).

Competing interests None declared.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

REFERENCES

1. Albers GW, Caplan LR, Easton JD, *et al*. Transient ischemic attack—proposal for a new definition. *N Engl J Med* 2002;347:1713–16.
2. National Institute for Health and Clinical Excellence. *Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)*. London: NICE, 2008.
3. Residual symptoms after transient ischaemic attack (TIA). http://www.healthtalk.org/peoples-experiences/nerves-brain/ia-and-minor-stroke/residual-symptoms-after-transient-ischaemic-attack-tia
4. Cumming TB, Brodtmann A, Darby D, *et al*. The importance of cognition to quality of life after stroke. *J Psychosom Res* 2014;77:374–9.
5. Donnellan C, Hickey A, Hevey D, *et al*. Effect of mood symptoms on recovery one year after stroke. *Int J Geriatr Psychiatry* 2010;25:1288–95.
6. Naess H, Lunde L, Brogger J, *et al*. Depression predicts unfavourable functional outcome and higher mortality in stroke patients: the Bergen Stroke Study. *Acta Neurol Scand Suppl* 2010;122(Suppl s190):34–8.
7. Naess H, Lunde L, Brogger J, *et al*. Fatigue among stroke patients on long-term follow-up. The Bergen Stroke Study. *J Neurol Sci* 2012;312:138–41.
8. Moran GM, Fletcher B, Feltham MG, *et al*. Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: a systematic review. *Eur J Neurol* 2014;21:1258–67.
9. CSD Health Research. The Health Improvement Network (THIN). http://www.thin-uk.com/
10. Health and Social Care Information Centre. Read Codes 2014. http://systems.hscic.gov.uk/data/uktc/readcodes
11. British National Formulary (BNF). British National Formulary (BNF) 67 2014. http://www.bnf.org/bnf/index.htm
12. Hennekens CH, Buring JE. *Epidemiology in medicine*. Boston: Little Brown, 1987.
13. Maguire A, Blak B, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf* 2009;18:76–83.
14. CSD Medical Research UK. THIN Data guide for researchers. 2014:1–114.
15. Health and Social Care Information Centre. Quality and Outcomes Framework (QOF). 2014. http://www.hscic.gov.uk/qof
16. Marston L, Carpenter JR, Walters KR, *et al*. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiol Drug Saf* 2010;19:618–26.
17. Health Survey for England. Health Survey for England (HSE)—2012 adult trend tables 2012. http://www.hscic.gov.uk/pubs/hse10trends
18. Castle J, Mlynash M, Lee K, *et al*. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. *Stroke* 2010;41:1367–70.
19. Mitchell AJ, Meader N, Pentzek M. Clinical recognition of dementia and cognitive impairment in primary care: a meta-analysis of physician accuracy. *Acta Psychiatr Scand* 2011;124:165–83.
20. CDS Health Research. The Health Improvement Network Ethics. http://www.thin-uk.com/mrec.htm

Appendices for Chapter 8

Chapter 9: Residual impairments after TIA

Retrospective cohort study: Results

Fatigue, psychological and cognitive impairment following transient ischaemic attack (TIA): a retrospective cohort study in primary care

The systematic review (Chapters 6 and 7) identified the need for a robust study which had a matched control group and adjusts for confounding variables and presence of the impairments prior to TIA. In response, a retrospective cohort study was designed (Chapter 8) which aimed to investigate the association between TIA and consultation for fatigue, psychological or cognitive impairment in an age and gender matched population from the THIN primary care database. This chapter presents the findings of the retrospective cohort study.

Dissemination

Year	Conference	Location	Oral/Poster
2015	North American Primary Care Research Group (NAPCRG) Annual Meeting	Cancun, Mexico	Oral presentation
	International Society for Quality of Life Research (ISOQOL) Annual Conference	Vancouver, Canada	Oral presentation
	University of Birmingham's Research Poster Conference	Birmingham, UK	Poster

This chapter is has been formatted in the style of an original article for The Lancet. The paper is currently under review in a peer-reviewed journal.

Fatigue, psychological and cognitive impairment following transient ischaemic attack (TIA): a retrospective cohort study in primary care

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Abstract

Background

Transient ischaemic attack (TIA) is defined as a brief episode of neurological dysfunction following cerebral ischaemia. Clinical management after TIA is focused on stroke prevention. A number of small studies suggest patients may experience ongoing fatigue, psychological and cognitive impairment.

Methods

A retrospective matched-cohort study using anonymised electronic primary care records extracted from The Health Improvement Network (THIN) database, which covers approximately 6% of the United Kingdom population. First-ever TIA patients with a diagnosis between 2009 and 2013 were matched 1:5 to controls by age, sex, and general practice. In three sub-studies, separate Kaplan-Meier (K-M) survivor functions estimated time to first consultation or drug prescription for fatigue, for psychological impairment and for cognitive impairment. Log rank tests compared TIA patients to controls and Cox regression models adjusted for potential confounders including patient and demographic characteristics.

Findings

The total sample included 55,930 individuals: 9,419 TIA patients and 46,511 controls. The median age was 74 years (IQR 63,82) and 48% were males. The K-M curves showed that TIA patients were more likely than controls to consult for fatigue, psychological impairment and cognitive impairment (P<0.0001). Adjusted hazards ratios were: fatigue 1·43 (95% CI 1·33,1·54), psychological impairment 1·26 (95% CI 1·20,1·31); cognitive impairment 1·45 (95% CI 1·28,1·65).

Interpretation

TIA is associated with significantly increased subsequent consultation for fatigue, psychological impairment and cognitive impairment. These findings challenge the 'transient' characterisation of TIA. Sequelae of TIA may not be limited to increased stroke risk and patients may have ongoing health problems.

Funding

National Institute for Health Research (NIHR) School for Primary Care Research (SPCR).

Research in context

Evidence before this study

We conducted a systematic review investigating prevalence of fatigue, psychological, and cognitive impairment after transient ischaemic attack (TIA) and minor stroke. MEDLINE, EMBASE, PSYCINFO, CINAHL, the Cochrane libraries, and grey literature were searched between January 1993 and April 2013. The comprehensive search strategy included variants of the terms: “TIA”, “minor stroke”, “fatigue”, “anxiety”, “depression”, “PTSD”, and “cognitive impairment”. Studies that reported prevalence of fatigue, psychological, or cognitive impairment post-TIA/minor stroke were included. Studies where participants had a history of stroke or experienced stroke in follow-up were excluded unless subgroup analysis excluding stroke was reported. There was evidence to suggest patients experience cognitive impairment and depression post-TIA/minor stroke, but few studies measured fatigue, anxiety, or PTSD. Only a small number of studies included a comparison group or reported presence of the outcomes prior to TIA or minor stroke. Subsequent to the systematic review, a Dutch study observed higher levels of cognitive impairments following TIA compared to controls. Additionally, a Scottish study found similar frequencies of anxiety/depression in stroke and TIA patients and a German study found nearly a third of TIA patients had PTSD; however, neither study had a control group.

Added value of this study

We found TIA patients had increased risk of consulting for fatigue, psychological, and cognitive impairments in primary care compared to matched controls. This relationship

remained when adjusted for the potential confounding variables and the presence of the impairment prior to TIA.

Implications of all the available evidence

Our findings suggest that impairments exist after initial symptoms of TIA have resolved and challenge the 'transient' characterisation of TIA. We propose that sequelae of TIA are not limited to increased stroke risk; therefore, residual impairments should be an important consideration for primary care clinicians when treating patients following TIA. Future research should develop intervention(s) to improve detection and treatment of fatigue, psychological, or cognitive impairments post-TIA.

Introduction

Transient ischaemic attack (TIA) occurs when a temporary blockage restricts blood flow to the brain producing a range of transient symptoms, including impaired: coordination, spatial awareness, vision, speech, articulation, and limb functioning.[1] Classically, TIA was defined as symptoms lasting for less than 24 hours; however, more recently this time-based classification has been replaced by a tissue-based definition which describes TIA as: 'a brief episode of neurologic dysfunction without evidence of acute infarction'.[2] TIA is considered a medical emergency because patients are at increased risk of stroke.[3]

Guidelines from the United Kingdom (UK) promote rapid evaluation of people with suspected TIA and focus on diagnosing TIA (ruling out an alternative diagnosis, such as migraine), determining the affected vascular territory, and assessing stroke risk.[4,5] Follow-up is focused on management of stroke risk factors through medical, surgical, and lifestyle interventions.[5] While it is recognised that stroke patients may experience ongoing impairments which require rehabilitation, these guidelines do not extend to TIA.[5,6]

We conducted a systematic review investigating the prevalence of fatigue, psychological, and cognitive impairment after TIA and minor stroke.[7] There was evidence to suggest a relatively high prevalence of cognitive impairment and depression post-TIA/minor stroke; however, few studies measured anxiety, post-traumatic stress disorder (PTSD), or fatigue. Furthermore, very few studies had a control group and we were unable to determine if prevalence of these impairments was higher than people at a similar age without TIA/minor stroke. Subsequent to the systematic review, a Dutch study observed evidence that TIA patients had higher levels of cognitive impairment compared to controls.[8] Additionally,

Broomfield et al (2014) found similar rates of depression and anxiety post-TIA compared to post-stroke[9] and Kiphuth et al (2014) reported PTSD in 30% of a sample of TIA patients;[10] however, neither study had a control group. Our study aimed to investigate the association between TIA and consultation for fatigue, cognitive, or psychological impairment in an age and gender matched population from an electronic primary care database. To our knowledge there are no studies that have investigated residual impairments after TIA using routinely collected electronic primary care medical records.

Methods

The full protocol for this study has been published elsewhere,[11] methods are summarised in brief below.

Study design and data source

This is a retrospective matched cohort study of first-ever TIA patients using anonymised, routinely collected, primary care data from The Health Improvement Network (THIN) database.[12] This database covers approximately 6% of the UK population and data are extracted from contributing general practices using Vision patient records software.[12] Analysis of THIN data is ethically approved by the National Health Service (NHS) South-East Multi-centre Research Ethics Committee subject to independent scientific review.[13] This study received approval by a Scientific Review Committee in February 2014 (reference: 14-008).

Population

Patients aged 18 years and over with a first-ever diagnosis of TIA between January 2009 and December 2013 were matched with up to five[14] TIA-free controls. TIA patients were matched to controls on: year of birth (+/- 2 years), sex, general practice, and date of TIA (index date). TIA patients and controls were free from stroke at baseline. The index date must have occurred at least one year after the general practice began using Vision patient records software and after the date of acceptable mortality recording (markers of data quality).[15] TIA patients and matched controls had be registered at their general practice for at least one year prior to the index date to allow baseline data to be recorded by their practice and had to have remained alive and registered for at least one month after the index date to allow time for the outcomes of interest to be recorded.

Variables

There were three separate sub-studies for each of the following outcomes: first consultation post-index date for (i) fatigue, (ii) psychological impairment (comprised of anxiety, depression, and PTSD), and (iii) cognitive impairment. These outcomes were defined by appropriate clinical codes for diagnoses and symptoms. In addition, drug codes for anti-depressant and anti-anxiety drugs were used to define psychological impairment. Cognitive impairment included memory, attention, and executive functioning impairments but not a diagnosis of dementia. For each sub-study, follow-up continued until the first consultation for the relevant outcome (for example consultation for fatigue in the fatigue sub-study) with censoring at the first occurrence of: death, stroke, the patient leaving the practice, or the last data collection from the general practice. Diagnosis of TIA in follow-up was permitted for

TIA patients but controls were censored at the date a TIA diagnosis was recorded and subsequently became eligible for inclusion in the TIA group.

Potential confounding variables were identified using the most recent baseline demographic and clinical characteristics prior to the index date. These included age, sex, body mass index (BMI), Townsend deprivation,[16] urban/rural residence,[16] smoking status, alcohol consumption, and comorbidities. Comorbidities comprised of the chronic conditions included in the UK chronic disease monitoring programme, Quality and Outcomes Framework (QOF; business rules version 27; Table 1).[17] Numbers of consultations in follow-up were recorded because patients who consult more have more opportunities to report residual impairments. To control for presence of the outcomes at baseline (prior to the index date), the most recent consultations prior to the index date for fatigue, psychological, or cognitive impairment were extracted.

Quality checks, missing data, and extreme values

Absence of a clinical code or relevant drug code for an individual diagnosis prior to the index date was taken to indicate the diagnosis was not present. For clinical measurements (height, weight, BMI, blood pressure, and cholesterol), implausible values were excluded based on pre-defined cut-off scores (supplementary table S1). As data are unlikely to be missing at random,[18] no attempt was made to impute numeric missing data. Instead, variables were categorised and a separate 'missing' category was created. Data were initially extracted between 2000 and 2013; however, there was evidence of underreporting of TIA before 2008, with the number of incident TIA events before 2008 less than 15% of recorded TIA

after 2009 (supplementary figure S1). After 2009, this was more stable; therefore, only patients with a TIA recorded from the 1st January 2009 were included.

Analysis

All analysis was conducted using STATA version 12 (StataCorp, College Station, Texas). Kaplan-Meier (K-M) survivor functions were used to estimate time to consultation for each outcome for TIA patients and controls. Log rank tests compared survivor functions of TIA patients and controls. Cox proportional hazard models adjusted for potential confounding of demographic and clinical characteristics. Inclusion of covariates in the model was selected using backwards elimination with a p-to-eliminate value of >0·05. Age and sex were forced into the model, because these were identified as important confounding variables, and general practice was included as a random effect.[19-21] Fatigue, psychological, and cognitive impairments were analysed separately in three sub-studies. Exploratory analysis investigated the impact of excluding patients with presence of the outcome prior to the index date for each sub-study. Further exploratory analyses are presented in the supplementary material.

Role of the funding source

This study is funded by the National Institute for Health Research (NIHR) School for Primary Care Research (SPCR). The funder had no role in study design, data analysis, data interpretation, or writing of the manuscript. GMT had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The total cohort comprised of 55,930 individuals: 9,419 TIA patients and 46,511 controls. The median age was 74 years (IQR 63, 82) and 48% were males. Demographic and clinical characteristics for the fatigue, psychological, and cognitive impairment sub-studies are presented in Table 1.

Fatigue

A total of 55,754 individuals were included in the survival analysis for the fatigue sub-study: 9,250 TIA patients matched to 46,504 controls (176 TIA patients/controls were excluded because fatigue was recorded on the index date). The median follow-up was 17·2 months (range 0 to 60·5 months) for TIA patients and 19·1 months (range 0 to 60·5 months) for controls. Fatigue was recorded in 3,632 individuals; the K-M curves show that TIA patients were more likely to consult for fatigue compared to controls (P<0·0001; Figure 1a). The 10th percentile for time to fatigue was 20·7 months (95% CI 18·6, 23·5) for TIA patients and 42·4 months (95% CI 40·6, 44·8) for controls (Figure 1a). TIA patients had a 43% increased risk of consulting for fatigue compared to controls following adjustment for demographic and clinical characteristics (Hazard Ratio (HR) 1·43: 95% CI 1·33, 1·54; P<0·0001, Table 2).

Table 1: Demographic and clinical characteristics of TIA patients and controls included in the fatigue, psychological, and cognitive impairment sub-studies.

		Control		TIA	
		Frequency	%	Frequency	%
Total		46,511	100	9,419	100
Age	<45	1,416	3·0	279	3·0
	45-49	1,576	3·4	293	3·1
	50-54	2,378	5·1	495	5·3
	55-59	3,092	6·6	600	6·4
	60-64	4,338	9·3	879	9·3
	65-69	5,559	12·0	1,120	11·9
	70-74	6,303	13·6	1,247	13·2
	75-79	7,223	15·5	1,502	15·9
	80-84	6,886	14·8	1,378	14·6
	85-89	5,013	10·8	1,009	10·7
	≥90	2,727	5·9	617	6·6
Sex	Male	22,245	47·8	4,504	47·8
Smoking status	Non	23,435	50·4	4,505	47·8
	Ex	13,970	30·0	2,964	31·5
	Current	5,748	12·4	1,555	16·5
	Missing	3,358	7·2	395	4·2
Alcohol intake	Never	5,954	12·8	1,212	12·9
	Light	7,930	17·0	1,671	17·7
	Moderate	5,617	12·1	1,165	12·4
	High	12,624	27·1	2,630	27·9
	Missing	14,386	30·9	2,741	29·1
BMI	Healthy	14,872	32·0	2,971	31·5
	Underweight	944	2·0	199	2·1
	Overweight	16,552	35·6	3,469	36·8
	Obese	10,220	22·0	2,179	23·1
	Missing	3,923	8·4	601	6·4
Deprivation	1 (least deprived)	12,353	26·6	2,383	25·3
	2	11,171	24·0	2,241	23·8
	3	9,399	20·2	1,908	20·3
	4	7,635	16·4	1,623	17·2
	5 (most deprived)	4,771	10·3	1,073	11·4
	Missing	1,182	2·5	191	2·0
Rurality	Urban	17,642	37·9	3,522	37·4
	Rural	28,867	62·1	5,893	62·6
	Missing	2	0·0	4	0·0

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		Control		TIA	
		Frequency	**%**	**Frequency**	**%**
Comorbidities	Atrial fibrillation	3,273	7·0	1,055	11·2
	Asthma	4,909	10·6	1,176	12·5
	Cancer	4,387	9·4	1,074	11·4
	CHD	6,631	14·3	1,680	17·8
	CKD	7,553	16·2	1,779	18·9
	COPD	2,700	5·8	689	7·3
	Dementia	1,579	3·4	375	4·0
	Depression	8,109	17·4	2,103	22·3
	Diabetes	5,734	12·3	1,376	14·6
	Epilepsy	618	1·3	199	2·1
	Heart failure	1,695	3·6	421	4·5
	Hypertension	20,112	43·2	4,617	49·0
	Hypothyroidism	4,098	8·8	982	10·4
	Learning disability	107	0·2	44	0·5
	Osteoporosis	3,128	6·7	770	8·2
	PAD	1,376	3·0	414	4·4
	Palliative care	319	0·7	89	0·9
	Psychosis	499	1·1	112	1·2
	Rheumatoid arthritis	794	1·7	206	2·2
Impairment prior to index date	Fatigue	10,074	21·7	2,910	30·9
	Psychological impairment	22,127	47·6	5,396	57·3
	Cognitive impairment	1,983	4·3	664	7·0

BMI: Body Mass Index, CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, PAD: Peripheral Artery Disease, TIA: Transient Ischaemic Attack

*BMI: Healthy (18·5-25·9 kg/m^2); Underweight (<18·5 kg/m^2); Overweight (26-30 kg/m^2); Obese (>30 kg/m^2)

Table 2: Adjusted* hazard ratios for the effects of demographic and clinical characteristics on consultations for fatigue in TIA patients and controls.

		Hazard Ratio	P value	95% CI	
TIA/ control	TIA	1·43	<0·001	1·33	1·54
Age	<45	1·05	0·67	0·85	1·29
	45-49	0·81	0·07	0·64	1·02
	50-54	0·84	0·05	0·70	1·00
	55-59	0·90	0·22	0·76	1·06
	60-64	0·84	0·03	0·72	0·98
	65-69	0·82	0·01	0·71	0·95
	70-74	1·00			
	75-79	1·05	0·49	0·92	1·19
	80-84	1·14	0·04	1·01	1·29
	85-89	1·08	0·27	0·94	1·24
	≥90	0·93	0·47	0·77	1·13
Sex	Female	1·11	0·01	1·03	1·20
Impairment prior to index date	Fatigue	2·77	<0·001	2·57	2·99
	Psychological impairment	1·18	<0·001	1·08	1·29
Impairment post index date	Psychological impairment	1·57	<0·001	1·46	1·70
	Cognitive impairment	1·18	0·03	1·01	1·37
BMI	Healthy	1·00			
	Underweight	1·11	0·37	0·88	1·41
	Overweight	1·04	0·39	0·96	1·12
	Obese	0·99	0·78	0·90	1·08
	Missing	0·77	0·01	0·64	0·92
Alcohol intake	Never	1·00			
	Light	1·24	<0·001	1·09	1·41
	Moderate	1·17	0·04	1·01	1·36
	Heavy	1·17	0·02	1·03	1·33
	Missing	1·18	0·01	1·04	1·34
Comorbidities	Dementia	0·65	<0·001	0·51	0·82
	Heart failure	1·17	0·04	1·01	1·35
	Palliative care	1·57	0·01	1·14	2·18
	Multimorbidity	1·09	<0·001	1·07	1·12
Health authority	West Midlands	1·00			
	Yorkshire & Humber	0·81	0·17	0·60	1·09
	North West	1·08	0·44	0·89	1·30
	East Midlands	1·04	0·77	0·79	1·37
	North East	1·09	0·55	0·82	1·44
	East of England	1·05	0·63	0·86	1·29
	London	0·93	0·49	0·76	1·14

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		Hazard Ratio	P value	95% CI	
Health authority	South East Coast	0·83	0·08	0·68	1·02
	South Central	1·05	0·65	0·84	1·32
	South West	1·02	0·82	0·83	1·26
	Northern Ireland	1·25	0·06	0·99	1·57
	Scotland	1·21	0·06	0·99	1·48
	Wales	1·02	0·86	0·84	1·23

BMI: Body Mass Index, CI: Confidence Interval, TIA: Transient Ischaemic Attack

* Each hazard ratio is adjusted for the other variables in the table

†BMI: Healthy (18·5-25·9 kg/m^2); Underweight (<18·5 kg/m^2); Overweight (26-30 kg/m^2); Obese (>30 kg/m^2)

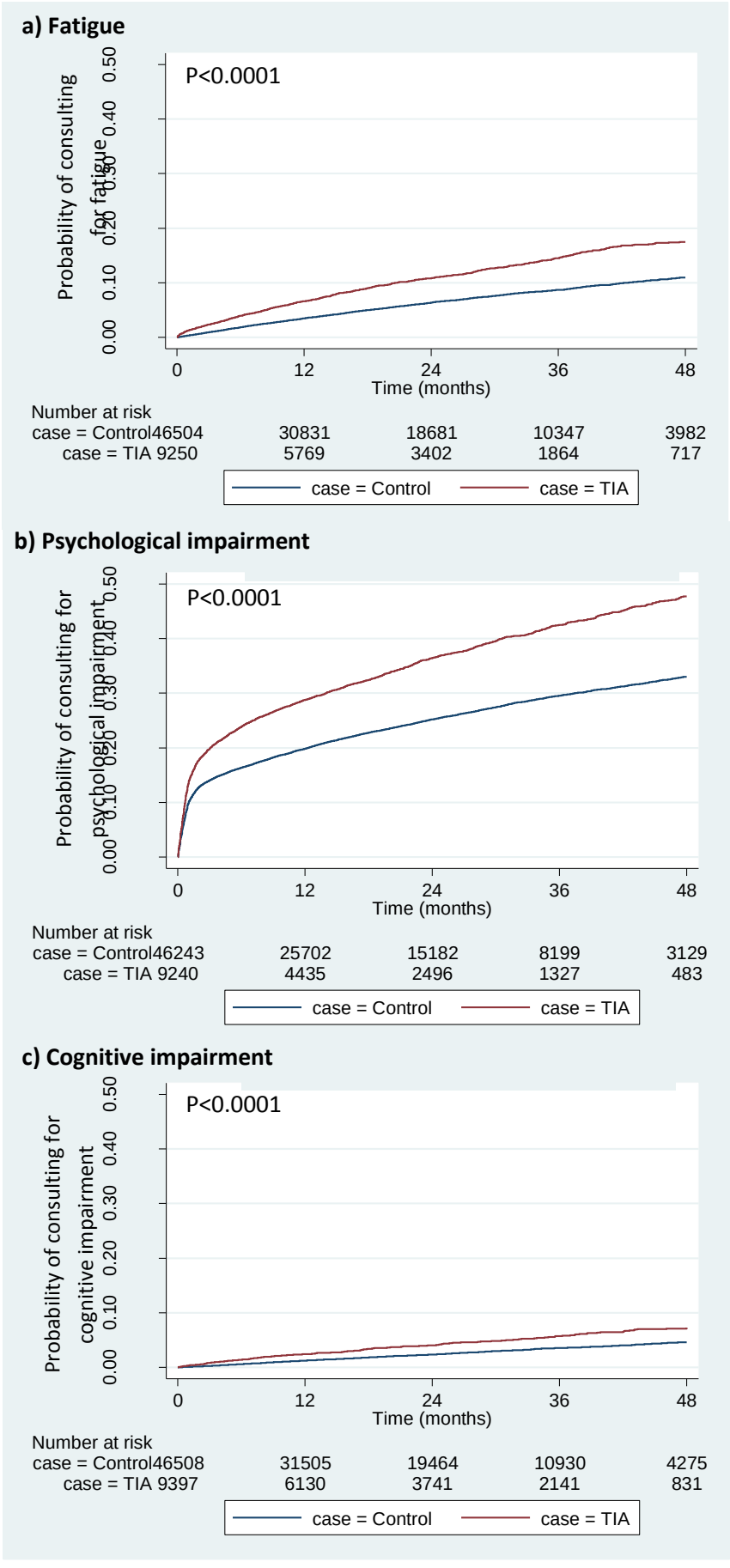

Figure 1: Kaplan-Meier (K-M) failure estimates for TIA patients and controls consulting for:

(a) fatigue

(b) psychological impairment

(c) cognitive impairment

The maximum follow-up time was 60·5 months for each sub-study; however, the K-M graphs are cut-off at 48 months when approximately <10% of the sample remains.

Psychological impairment

A total of 55,483 individuals were included in the survival analysis for the psychological impairment sub-study: 9,240 TIA patients matched to 46,243 controls (447 TIA patients/controls were excluded because psychological impairment was recorded on the index date). The median follow-up was 11·2 months (range 0 to 60·5 months) for TIA patients and 14·4 months (range 0 to 60·5 months) for controls. Psychological impairment was recorded in 14,285 individuals; of these, 11,040 consulted for depression, 2,691 anxiety, 546 anxiety and depression, and 8 PTSD. The K-M curves show that TIA patients were more likely to consult for/ be prescribed drugs for psychological impairment compare to controls (P<0·0001; Figure 1b). The 25th percentile for time to psychological impairment was 7·1 months (95% CI 6·2, 8·2) for TIA patients and 23·5 months (95% CI 22·5, 24·6) for controls (Figure 1b). Following adjustment for demographic and clinical characteristics, TIA patients had a 26% increased risk of consulting for psychological impairment compared to controls (HR 1·26: 95% CI 1·20, 1·31; P<0·0001, Table 3).

Table 3: Adjusted* hazard ratios for the effects of demographic and clinical characteristics on consultations for psychological impairment in TIA patients and controls.

		Hazard Ratio	P value	95% CI	
TIA/ control	TIA	1·26	<0·001	1·20	1·31
Age	<45	1·20	<0·001	1·08	1·33
	45-49	1·15	0·01	1·04	1·27
	50-54	1·13	0·01	1·04	1·24
	55-59	1·15	<0·001	1·05	1·25
	60-64	1·01	0·74	0·94	1·09
	65-69	1·01	0·86	0·93	1·09
	70-74	1·00			
	75-79	1·10	0·01	1·02	1·17
	80-84	1·10	0·01	1·03	1·18
	85-89	1·18	<0·001	1·09	1·28
	≥90	1·24	<0·001	1·13	1·36
Sex	Female	1·28	<0·001	1·23	1·33
Impairment prior to index date	Psychological impairment	4·46	<0·001	4·25	4·68
	Cognitive impairment	1·21	<0·001	1·12	1·30
	Fatigue	1·16	<0·001	1·12	1·21
Impairment post index date	Cognitive impairment	1·40	<0·001	1·29	1·53
	Fatigue	1·30	<0·001	1·23	1·37
Smoking status	Non	1·00			
	Ex	1·15	<0·001	1·11	1·20
	Current	1·24	<0·001	1·17	1·31
	Missing	0·88	0·01	0·80	0·96
Alcohol intake	Never				
	Light	0·89	<0·001	0·83	0·95
	Moderate	0·92	0·02	0·86	0·99
	Heavy	0·89	<0·001	0·84	0·95
	Missing	0·95	0·11	0·89	1·01
BMI	Healthy	1·00			
	Underweight	1·06	0·36	0·93	1·21
	Overweight	1·00	0·99	0·96	1·05
	Obese	1·09	<0·001	1·04	1·15
	Missing	1·03	0·48	0·95	1·12
Deprivation	1 (least deprived)	1·00			
	2	0·98	0·54	0·94	1·04
	3	1·01	0·62	0·96	1·07
	4	1·08	0·01	1·02	1·15
	5 (most deprived)	1·17	<0·001	1·09	1·25
	Missing	1·11	0·08	0·99	1·25

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		Hazard Ratio	P value	95% CI	
Comorbidities	Atrial fibrillation	0·53	<0·001	0·49	0·57
	Asthma	0·56	<0·001	0·53	0·60
	Cancer	0·56	<0·001	0·52	0·60
	CHD	0·58	<0·001	0·55	0·62
	CKD	0·56	<0·001	0·53	0·59
	COPD	0·63	<0·001	0·58	0·68
	Diabetes	0·66	<0·001	0·62	0·71
	Epilepsy	0·55	<0·001	0·47	0·63
	Heart Failure	0·57	<0·001	0·52	0·63
	Hypertension	0·57	<0·001	0·54	0·60
	Hypothyroidism	0·61	<0·001	0·57	0·65
	Osteoporosis	0·60	<0·001	0·56	0·64
	PAD	0·57	<0·001	0·52	0·63
	Rheumatoid arthritis	0·59	<0·001	0·53	0·67
	Multimorbidity	1·86	<0·001	1·80	1·92
Health authority	West Midlands	1·00			
	Yorkshire & Humber	1·37	<0·001	1·21	1·54
	North West	1·09	0·06	1·00	1·20
	East Midlands	1·12	0·04	1·01	1·25
	North East	1·16	0·05	1·00	1·35
	East of England	1·23	<0·001	1·11	1·36
	London	1·00	0·96	0·88	1·13
	South East Coast	1·17	<0·001	1·07	1·28
	South Central	1·24	<0·001	1·15	1·35
	South West	1·19	<0·001	1·08	1·31
	Northern Ireland	1·43	<0·001	1·29	1·58
	Scotland	1·16	<0·001	1·07	1·27
	Wales	1·29	<0·001	1·17	1·43

BMI: Body Mass Index, CHD: Coronary Heart Disease, CI: Confidence Interval, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, PAD: Peripheral Artery Disease, TIA: Transient Ischaemic Attack

* Each hazard ratio is adjusted for the other variables in the table

†BMI: Healthy (18·5-25·9 kg/m^2); Underweight (<18·5 kg/m^2); Overweight (26-30 kg/m^2); Obese (>30 kg/m^2)

Cognitive impairment

A total of 55,905 individuals were included in the survival analysis for the cognitive impairment sub-study: 9,397 TIA patient matched to 46,508 controls (25 TIA patients/controls were excluded because cognitive impairment was recorded on the index date). The median follow-up time was 18·8 months (range 0 to 60·5 months) for TIA patients and 20·0 months (range 0 to 60·5 months) for controls. Cognitive impairment was recorded in 1,425 individuals; the K-M curves show that TIA patients were more likely to consult for cognitive impairment compared to controls (P<0·0001; Figure 1c). The 5th percentile for time to cognitive impairment was 31·1 months (95% CI 25·9, 35·6) for TIA patients and 52·7 months (95% CI 48·6, 56·4) for controls (Figure 1c). Following adjustment for demographic and clinical characteristics, TIA patients had a 45% increased risk of consulting for cognitive impairment compared to controls (HR 1·45: 95% CI 1·28, 1·65; P<0·0001, Table 4).

Table 4: Adjusted* hazard ratios for the effects of demographic and clinical characteristics on consultations for cognitive impairment in TIA patients and controls.

		Hazard Ratio	P value	95% CI	
TIA/ control	TIA	1·45	<0·001	1·28	1·65
Age	<50	0·14	<0·001	0·07	0·26
	50-54	0·36	<0·001	0·23	0·54
	55-59	0·44	<0·001	0·31	0·61
	60-64	0·39	<0·001	0·29	0·53
	65-69	0·67	<0·001	0·52	0·86
	70-74	1·00			
	75-79	1·61	<0·001	1·33	1·94
	80-84	2·01	<0·001	1·66	2·44
	85-89	2·09	<0·001	1·72	2·54
	≥90	1·67	<0·001	1·28	2·19
Sex	Female	0·96	0·50	0·87	1·07
Impairment prior to index date	Cognitive impairment	5·55	<0·001	4·78	6·45
	Fatigue	1·47	<0·001	1·30	1·65
Impairment post index date	Psychological impairment	1·74	<0·001	1·55	1·96
BMI	Healthy	1·00			
	Underweight	1·13	0·47	0·81	1·59
	Overweight	0·90	0·10	0·80	1·02
	Obese	0·82	0·01	0·71	0·95
	Missing	0·66	<0·001	0·53	0·83
Rurality	Urban	1·24	0·01	1·06	1·46
Comorbidities	Dementia	0·35	<0·001	0·25	0·47
Health authority	West Midlands	1·00			
	Yorkshire & Humber	0·63	0·08	0·37	1·06
	North West	1·14	0·31	0·88	1·48
	East Midlands	0·96	0·90	0·54	1·72
	North East	0·98	0·90	0·72	1·33
	East of England	1·12	0·43	0·84	1·51
	London	0·98	0·87	0·77	1·25
	South East Coast	0·94	0·65	0·71	1·24
	South Central	0·87	0·25	0·68	1·11
	South West	1·04	0·79	0·79	1·37
	Northern Ireland	1·38	0·07	0·98	1·95
	Scotland	1·49	<0·001	1·13	1·95
	Wales	0·97	0·86	0·67	1·39

BMI: Body Mass Index, CI: Confidence Interval, TIA: Transient Ischaemic Attack

* Each hazard ratio is adjusted for the other variables in the table

†BMI: Healthy (18·5-25·9 kg/m^2); Underweight (<18·5 kg/m^2); Overweight (26-30 kg/m^2); Obese (>30 kg/m^2)

Exploratory analysis

The effect of excluding individuals with a record of the outcome prior to the index date was explored. In this exploratory analysis, 42,836 individuals were included in the survival analysis for the fatigue sub-study (6,400 TIA patients and 36,436 controls); 28,390 in the psychological impairment sub-study (4,013 TIA patients and 24,377 controls); and 53,265 in the cognitive impairment sub-study (8,739 TIA patients and 44,526 controls). Results showed that a significant difference between TIA patients and controls remained for all three impairments (P<0·0001; Figure 2). The 5th percentile for time to consultation for fatigue was 15·9 months for TIA patients and 41·6 months for controls; the 10th percentile for time to consultation/ drug prescription for psychological impairment was 12·6 months for TIA patients and 24·2 months for controls; and the 5th percentile for time to consultation for cognitive impairment was 24·9 months for TIA patients and 48·2 months for controls. Adjusted hazards ratios increased to 1·75 (95% CI 1·57, 1·94) for fatigue, 1·66 (95% CI 1·50, 1·84) for psychological impairment, and 1·54 (95% CI 1·35, 1·77) for cognitive impairment. Further exploratory analyses are presented in the supplementary material.

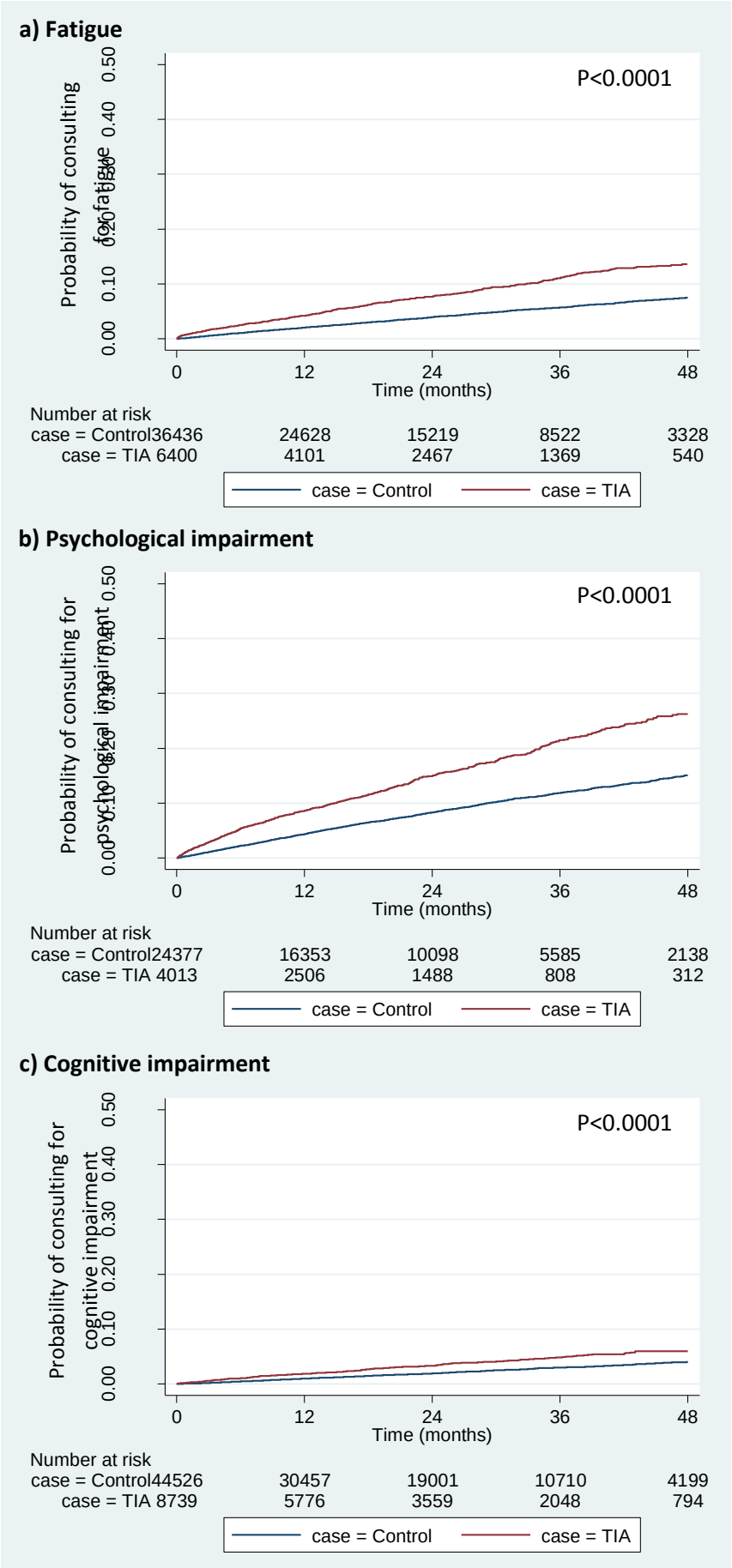

Figure 2: Kaplan-Meier (K-M) failure estimates for TIA patients and controls with no record of the impairment prior to the index date and consulting for:

(a) fatigue

(b) psychological impairment

(c) cognitive impairment

The maximum follow-up time was 60·5 months for each sub-study; however, the K-M graphs are cut-off at 48 months when approximately <10% of the sample remains.

Discussion

We found TIA patients in a large UK general practice population had increased risk of consulting for fatigue, psychological, and cognitive impairment compared to matched controls. TIA patients had an increased risk of 43% for consulting for fatigue, 26% for psychological impairment, and 45% for cognitive impairment compared to controls. TIA patients remained more likely to consult for these impairments compared to controls following adjustment for potential confounding variables and when patients with these outcomes prior to the index TIA were excluded. Our findings suggest that for many patients TIA is not a transient event and patients experience impairments after initial symptoms have resolved.

The systematic review conducted prior to our study found a limited number of studies that measured residual impairment after TIA and included a control group.[7] None of the included studies that measured fatigue or PTSD had a control group. Only one study that measured anxiety included a control group and found a statistically significant difference in frequency of anxiety between TIA and control patients;[22] however, two depression studies which included controls reported no difference.[22,23] Three studies which measured cognitive impairment and included a comparison group were included in the systematic review.[24-26] Two of these studies found a statistically significant difference in frequency of cognitive impairment between TIA patients and controls. However, most of the studies included in the systematic review which had a control group did not adjust for confounding variables and the sample sizes were relatively small (<350 participants). Subsequent to the systematic review, a Dutch study found a reduction in cognitive functioning in TIA patients compared to controls in all cognitive domains except episodic memory; however, the sample size was

relatively small (n=189) and the TIA patients and controls were not matched.[8] Other studies conducted after our systematic review which investigated psychological impairment post-TIA did not include a control group.[9,10] Our study addressed limitations of existing studies and found increased risk of consulting for fatigue, psychological, and cognitive impairment in TIA patients compared to controls.

TIA is characterised by transient stroke-like symptoms and, by definition, does not cause permanent cerebral infarction.[2] In the absence of visible cerebral infarction, there are a number of potential explanations for our findings. Firstly, neurobiological consequences of TIA: contrary to the tissue-based definition, TIA may cause microinfarcts that are not detected by neuroimaging with computed tomographic (CT) or magnetic resonance imaging (MRI). Microinfarcts have been detected by histological examination and pooled analysis of autopsy studies from community prospective cohorts found an association between microinfarcts and dementia.[27] Studies have found evidence of abnormal neural activity in TIA patients with no lesions on conventional MRI compared to controls.[28,29] Furthermore, these studies reported an association between abnormal neural activity and cognitive impairment. Secondly, residual impairments post-TIA could be a result of the psychological impact of the event. Psychological impact of TIA and minor stroke has been described in qualitative research.[30] A psychological mechanism has been proposed for post-stroke depression[31] and depression after minor stroke has been found to be independent of cerebral lesions.[32] Furthermore, an association between depression and cognitive impairment has been reported post-stroke.[33] Thirdly, diagnosis of TIA in clinical practice may not adhere to the tissue-based definition. Therefore, patients may have presence of cerebral infarction which could be responsible for the residual impairments and, by definition, should have a diagnosis

of stroke. Although the tissue based-definition was proposed in 2003, it has not been universally adopted. The time-based definition (symptoms lasting <24 hours) is still used by the World Health Organisation (WHO)[34] and the National Institute for Health and Care Excellence (NICE) guidelines.[5] Within the UK, brain imaging is not routinely used to diagnose TIA; therefore, diagnoses of TIA within our study would have been based on clinical diagnosis rather than the tissue based diagnosis.[5] A systematic review found evidence of ischaemic lesion in a third of TIA patients diagnosed according to the time-based definition.[35]

Our findings challenge the 'transient' characterisation of TIA, a misconception which may result in patients receiving inadequate health care post-TIA. Primary care is where TIA patients present with residual impairments. Although symptoms may be subtle and detection may present a challenge, primary care clinicians should consider the holistic consequences of TIA and recognise that these patients may require therapy additional to stroke prevention. Furthermore, policy makers should tailor recommendations and guidelines to facilitate optimal care for TIA patients in light of our findings. Regardless of the mechanism for impairments post-TIA, our findings represent 'real-life' TIA diagnoses in primary care and GPs need to understand their patients' therapeutic needs in this context.

Future research should establish the severity, onset, duration, and natural history of residual impairments post-TIA. Additional research should develop intervention(s) to identify TIA patients with fatigue, psychological, or cognitive impairments and improve the healthcare and rehabilitation of these patients in a cost-effective way. An intervention may be as simple as extending existing stroke services to TIA patients or more specialised intervention(s) may be necessary. It is important for future research to determine the mechanism underlying the

association between TIA and residual impairments. Understanding this association will facilitate the development of a rehabilitation intervention and could challenge the current definition of TIA.

The main strengths of our study are the very large sample; data was available from different regions across the UK; and data are representative of real-life primary care practice. The study design addressed limitations of existing studies in this field by including a control group and controlling for confounding variables particularly presence of fatigue, psychological, or cognitive impairment prior to the index date. Recording of these impairments is likely to vary between general practices; therefore, we matched TIA patients and controls on this variable and included it as a random effect in the regression models.

A limitation of the study concerns the recording of TIA in primary care; although GPs are incentivised to keep a register of TIA patients in the UK, TIA may be misdiagnosed[36,37] or underreported.[38] Misdiagnosis of a TIA 'mimic' (e.g. migraine with TIA-like symptoms) as TIA may dilute the association between TIA and residual impairments; alternatively, diagnosing minor stroke as TIA may overestimate the association. However, diagnosis of TIA within the THIN database has been validated.[39] In addition, Read codes do not contain information on whether a tissue- or time-base definition was used to diagnose TIA. Furthermore, there are limitations regarding the recording of our outcomes; the use of primary care patient records relies on patients consulting with fatigue, psychological, or cognitive impairment and clinicians recording these in patients' electronic medical records. Clinical codes for signs and symptoms were used in addition to clinical codes for diagnoses to define our outcomes. Therefore, our findings may not be equivalent to clinical diagnoses of fatigue, psychological,

or cognitive impairment; for example, there was no distinction between clinical diagnosis of anxiety and feeling anxious in our analysis. Our definition of depression and anxiety included prescriptions for drugs to treat these conditions; however, these could be repeat prescriptions which did not require a face-to-face consultation. Exploratory analysis revealed that the sharp increase in consultations for psychological impairment post-index date (Figure 1b) was explained by prescriptions for anti-depressant drugs. Although presence of the impairment prior to the index date was adjusted for in the regression model, the primary analysis does not distinguish between prevalent and incident consultations; however, this was explored in supplementary analysis. Another limitation with the recording of our outcomes is that a patient could consult for an impairment prior to the index date but this may not be recorded again after the index date when the impairment persists. Therefore, the continued presence of this impairment would not be included in our analysis. Stroke prevention medication was not included as a confounder in the analysis. There is some evidence that beta-blockers may cause fatigue;[40] however, as they are not recommended as a first line treatment for hypertension in this age group[41] it is unlikely that many patients were prescribed them. Although TIA patients and controls were matched on age, sex, and general practice, a limitation is that they were not matched on vascular risk factors which are potential confounders. Bias may be introduced in our study because: (i) TIA patients consulted more in follow-up and, therefore, would have more opportunity to report impairment(s) and (ii) patients may be more conscious of their health following a TIA compared to controls resulting in increased reporting of impairments. It is important to emphasise that not all patients who experienced impairments post-TIA would have consulted their GP for them in primary care; therefore, our findings do not represent

incidence of fatigue, psychological, or cognitive impairment post-TIA in the community. Finally, time to consultation may not reflect the onset of the impairments as patients may have waited before consulting their GP.

Conclusion

TIA patients are more likely to consult for fatigue, psychological, and cognitive impairment in primary care compared to controls. These findings challenge the 'transient' characterisation of TIA and suggest that these patients may require therapy beyond stroke prevention. Dissemination of our finding to primary care clinicians and policy makers is important to increase detection and treatment of residual impairments after TIA.

Authors' contributions

GMT, TM, MC, MGF, and RR contributed to the study conception and design. GMT conducted the analysis and GMT, TM, MC, MGF, and RR were involved in the interpretation of results. GMT drafted the manuscript and TM, MC, MGF, and RR provided feedback. All authors read and approved the final manuscript.

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Declaration of interests

Ms. Turner reports grants from NIHR SPCR, during the conduct of the study. Dr. Calvert reports grants from the European Society Cardiology and personal fees from Astellas, outside the submitted work. Dr. Feltham, Dr. Ryan, and Dr. Marshall have nothing to disclose.

References

1. Kirkpatrick S, Locock L, Giles MF, Lasserson DS. Non-focal neurological symptoms associated with classical presentations of transient ischaemic attack: qualitative analysis of interviews with patients. *PLoS ONE* 2013; **8**(6): e66351.
2. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack-proposal for a new definition. *The New England Journal of Medicine* 2002; **347**(21): 1713-6.
3. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology* 2004; **62**(11): 2015-20.
4. Intercollegiate Stroke Working Party. National clinical guideline for stroke. Fourth ed: London: Royal College of Physicians; 2012.
5. National Institute for Health and Care Excellence (NICE). Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE Clinical Guideline 68; 2008.
6. National Institute for Health and Care Excellence (NICE). Follow up after a transient ischaemic attack (TIA). http://cks.nice.org.uk/stroke-and-tia#!scenario:3 (accessed October 2015).
7. Moran GM, Fletcher B, Feltham MG, Calvert M, Sackley C, Marshall T. Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: a systematic review. *European Journal of Neurology* 2014; **21**(10): 1258-67.
8. Van Rooij FG, Schaapsmeerders P, Maaijwee NA, et al. Persistent cognitive impairment after transient ischemic attack. *Stroke* 2014; **45**(8): 2270-4.
9. Broomfield N, Quinn T, Abdul-Rahim A, Walters M, Evans J. Depression and anxiety symptoms post-stroke/TIA: prevalence and associations in cross-sectional data from a regional stroke registry. *BMC Neurology* 2014; **14**(1): 198.
10. Kiphuth IC, Utz KS, Noble AJ, Köhrmann M, Schenk T. Increased prevalence of posttraumatic stress disorder in patients after transient ischemic attack. *Stroke* 2014.
11. Moran GM, Calvert M, Feltham MG, Ryan R, Marshall T. A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper. *BMJ Open* 2015; **5**(4): e008149.
12. CSD Health Research. The Health Improvement Network (THIN). http://www.thin-uk.com/ (accessed October 2015).
13. CDS Health Research. The Health Improvement Network Ethics. http://www.thin-uk.com/mrec.htm (accessed October 2015).
14. Hennekens CH, Buring JE. Epidemiology in medicine. Boston: Little, Brown 1987.
15. Maguire A, Blak B, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiology and Drug Safety* 2009; **18**(1): 76-83.
16. CSD Medical Research UK. THIN Data guide for researchers, 2014.
17. Health and Social Care Information Centre. Quality and Outcomes Framework (QOF). 2014. http://www.hscic.gov.uk/qof (accessed October 2015).
18. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiology and Drug Safety* 2010; **19**(6): 618-26.
19. Dong Y, Venketasubramanian N, Chan BP-L, et al. Brief screening tests during acute admission in patients with mild stroke are predictive of vascular cognitive impairment 3–6 months after stroke. *Journal of Neurology, Neurosurgery and Psychiatry* 2012; **83**(6): 580-5.
20. El Husseini N, Goldstein LB, Peterson ED, et al. Depression and antidepressant use after stroke and transient ischemic attack. *Stroke* 2012; **43**(6): 1609-16.

21. Radman N, Staub F, Aboulafia-Brakha T, Berney A, Bogousslavsky J, Annoni JM. Poststroke fatigue following minor infarcts: a prospective study. *Neurology* 2012; **79**(14): 1422-7.
22. Brittle NG. Functional, cognitive and emotional outcomes after transient Ischaemic attack: a systematic review and controlled cohort study: University of Birmingham [M.Phil]; 2012.
23. Bakker FC, Klijn CJ, van der Grond J, Kappelle LJ, Jennekens-Schinkel A. Cognition and quality of life in patients with carotid artery occlusion: a follow-up study. *Neurology* 2004; **62**(12): 2230-5.
24. Guyomard V, Metcalf AK, Naguib MF, Fulcher RA, Potter JF, Myint PK. Transient ischaemic attack, vascular risk factors and cognitive impairment: a case-controlled study. *Age and Ageing* 2011; **40**(5): 641-4.
25. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. *Stroke* 2012; **43**(2): 464-9.
26. Wilson DM, Madden M, Power M, Fullerton K, Wiggam MI, Passmore AP. Cognitive impairment after first ever TIA. *International Journal of Stroke* 2010; **5**(s3): 49-.
27. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *The Lancet Neurology* 2012; **11**(3): 272-82.
28. Guo J, Chen N, Li R, et al. Regional homogeneity abnormalities in patients with transient ischaemic attack: a resting-state fMRI study. *Clinical Neurophysiology* 2014; **125**(3): 520-5.
29. Guo J, Wang S, Li R, et al. Cognitive impairment and whole brain diffusion in patients with carotid artery disease and ipsilateral transient ischemic attack. *Neurological Research* 2014; **36**(1): 41-6.
30. Hillsdon KM, Kersten P, Kirk HJS. A qualitative study exploring patients' experiences of standard care or cardiac rehabilitation post minor stroke and transient ischaemic attack. *Clinical Rehabilitation* 2013; **27**(9): 845-53.
31. Fang J, Cheng Q. Etiological mechanisms of post-stroke depression: a review. *Neurological Research* 2009; **31**(9): 904-9.
32. Altieri M, Maestrini I, Mercurio A, et al. Depression after minor stroke: prevalence and predictors. *European Journal of Neurology* 2012; **19**(3): 517-21.
33. Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in postacute older adult stroke patients. *Archives of Physical Medicine and Rehabilitation* 2013; **94**(9): 1747-52.
34. WHO MONICA Project Principal Investigators. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *Journal of Clinical Epidemiology* 1988; **41**(2): 105-14.
35. Brazzelli M, Chappell FM, Miranda H, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Annals of Neurology* 2014; **75**(1): 67-76.
36. Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. *Stroke* 2010; **41**(7): 1367-70.
37. Schrock JW, Glasenapp M, Victor A, Losey T, Cydulka RK. Variables associated with discordance between emergency physician and neurologist diagnoses of transient ischemic attacks in the emergency department. *Annals of Emergency Medicine* 2012; **59**(1): 19-26.
38. Johnston SC, Fayad PB, Gorelick PB, et al. Prevalence and knowledge of transient ischemic attack among US adults. *Neurology* 2003; **60**(9): 1429-34.
39. Ruigómez A, Martín-Merino E, Rodríguez LA. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). *Pharmacoepidemiology and Drug Safety* 2010; **19**(6):579-85.

40. Koella WP. CNS-related (side-)effects of beta-blockers with special reference to mechanisms of action. *European Journal of Clinical Pharmacology* 1985; **28 Suppl**: 55-63.
41. National Institute for Health and Clinical Excellence (NICE). Hypertension: the clinical management of primary hypertension in adults. Clinical Guideline 127. National Clinical Guideline Centre; 2011.

Appendices for Chapter 9

Chapter 10: Discussion

Discussion

This final chapter will discuss the key findings; strengths and limitations; interpretation and implications of findings; and areas for future research. The research within this thesis aimed to determine: (i) the extent to which people that had a stroke or TIA had prior missed opportunities for prevention with pharmacotherapy and (ii) if TIA patients experience ongoing residual impairments after initial symptoms have resolved.

Summary of findings

The first research theme investigated primary prevention of stroke and TIA. Primary prevention with pharmacotherapy was found to be inadequate in primary care; over half of people with stroke or TIA had not been prescribed appropriate drug therapy when one or more prevention drug had been clinically indicated (Chapters 3- 5). There were missed opportunities for prevention in 49% of stroke or TIA patients who had been eligible for lipid lowering drugs, 52% for anticoagulant drugs and 25% for antihypertensive drugs. There was a significant decrease in the proportion of missed opportunities for anticoagulant drug prescribing between 2009 and 2013, but no change for lipid lowering and antihypertensive drugs. Different clinical and demographic characteristics were associated with missed opportunities for each prevention drug (Chapters 3-5).

The second research theme explored fatigue, psychological and cognitive impairments after TIA. A systematic review of the literature revealed there was limited evidence, but suggested a relatively high prevalence of cognitive impairment and depression post-TIA and minor stroke. However, there was a lack of high quality studies that included a control group and

adjusted for confounding variables or presence of the impairment pre-TIA or minor stroke (Chapters 6 and 7). The retrospective cohort study addressed the limitations of existing studies and found TIA patients had increased risk of consulting for fatigue, psychological, and cognitive impairment in primary care compared to matched controls (Chapters 8 and 9). This relationship remained when potential confounding variables and the presence of the impairment prior to TIA were adjusted for.

Strengths and limitations

The research contributes novel findings to the field of stroke and TIA research. Each study followed pre-specified, peer-reviewed protocols which were published in Open Access scientific journals (Chapters 3, 6 and 8).[1-3] In addition, the findings were reported in accordance with PRISMA guidelines,[4] for the systematic review, and STROBE guidelines, [5] for the case series analysis and retrospective cohort study. Findings have been disseminated through four publications and 16 presentations at national and international conferences: seven oral presentations, one elevator pitch presentation and eight poster presentations. Furthermore, the research has been recognised through a number of regional and international awards, including:

Missed opportunities for prevention of stroke and TIA

- Distinguished paper presentation at the North American Primary Care Research Group (NAPCRG) Annual Meeting. Cancun, Mexico, October 2015.
- 'Best abstract from Health and Population Sciences' at the College of Medical and Dental Sciences Festival of Graduate Research. Birmingham, UK, March 2015

Residual impairments after TIA: systematic review

- 'Australian Association for Academic Primary Care (AAAPC) first time presenter award' at the Primary Health Care Research Conference (PHCRC). Canberra, Australia, July 2014.
- Second prize 'Best poster competition' at the National Institute for Health Research (NIHR) School for Primary Care Research (SPCR) Showcase. Oxford, UK, September 2014.

Missed opportunities for prevention of stroke and TIA

The strengths and limitations of using routine electronic primary care medical records are discussed in Chapter 2. To summarise, the strengths include the large sample size (THIN includes data on >12 million patients); geographical spread of data across the UK and data are representative of the UK population;[6] collection of data in a non-interventional manner which reflects real-life primary care practice; availability of clinical and prescribing data; and accessibility of the data which reduces time and resources required. The main limitations are that the data is reliant on GPs recording patients' information and data are primarily collected for clinical management rather than research; therefore, there may be missing or incomplete data. Stroke and TIA were found to be underreported before 2009 (Appendix A2.1 and A3.1) and recording of TIA may be less reliable compared to stroke because of patients not seeking medical care and misdiagnosis. Furthermore, accuracy of clinical data is influenced by QOF incentives which may result in better recording of chronic conditions included in QOF. Conversely, non-QOF conditions may be underreported and changes to QOF may cause fluctuations in recording of related clinical data.[7] In addition, data within

THIN are coded and some information, such as stroke severity or subtypes, is not included in the Read code system.[8]

For the case series analysis, the identification of patients eligible for prevention drugs is likely to be reliable because recording of the comorbidities which define eligibility are incentivised by QOF. However, some of the clinical data used for the CVD risk equations, such as cholesterol, may be missing. Furthermore, BP is subject to fluctuations and there may be measurement error which has implications for identifying people eligible for antihypertensive drugs; however, the average of three BP measurements was used. The prescribing data, which was used to identify missed opportunities, is likely to be accurate because prescriptions are automatically retained in the patient's electronic record through Vision software, which is used to print prescriptions.[9] Use of data from routine primary care medical records are likely to be an accurate reflection of the information the GP had available to make prescribing decisions.[10]

The generalisability of the results may be limited to the UK because UK national guidelines were used to define missed opportunities. In addition, the NHS provides universal, free access to health care; therefore, missed opportunities may be greater in countries with restricted access to primary health care. The guidelines are continually updated and the impacts of revised recommendations were investigated in exploratory analyses. However, the evidence which informs guideline recommendations is often known by GPs prior to the official updates. Therefore, generalisability of missed opportunities is dependent on whether knowledge of adherence to best evidence or adherence to the guidelines is required. Although outside the scope of this study, the methodology used does not provide insight

into why prevention drugs were not prescribed to eligible patients prior to stroke and if drugs were previously prescribed and subsequently stopped or never prescribed.

Residual impairments after TIA: systematic review

Systematic reviews are considered the gold standard to synthesise existing evidence.[11] The advantages include the rigorous identification and synthesis of existing literature, assessment of the quality of the evidence and transparency in reporting. However, systematic reviews are a time-consuming approach that relies on accurate identification of all relevant literature. Although systematic and rigorous methods were employed to search literature, identification of all relevant studies cannot be guaranteed. The systematic review was conducted in accordance with Cochrane[12] and CRD[13] guidelines. At a review level, the strengths were that a comprehensive search strategy was employed which extended to grey literature; non-English language papers were included; and two reviewers independently completed the searches, screened titles and abstracts, identified eligible studies, extracted data and assessed quality of the included studies. However, the main limitations were that authors were not contacted to obtain missing data and the inclusion of abstracts limited the amount of data available to extract and the ability to assess quality. Furthermore, stroke in follow-up was an exclusion criterion; therefore, bias may have been introduced because the participants within the systematic review may be lower risk compared to TIA patients in the general population.

The quality of the primary data included in the review was a significant limitation since evidence synthesised through relatively low quality studies limits the quality of the review's findings and affects the reliability and generalisability of results. The majority of studies had

small sample sizes and were likely to be underpowered because the outcomes of interest for my systematic review were predominantly secondary outcomes in the individual studies. Furthermore, the individual studies may have included stroke patients in their sample, but only data on TIA and minor stroke patients were extracted for the review. A limited number of studies were available for fatigue, anxiety, PTSD and the secondary outcomes QoL, return to work and emotionalism. Most studies (22 out of 31) were conducted in secondary care; therefore, generalisability of results to the general TIA population may be reduced. For instance, TIA patients managed in a secondary care setting may have experienced stressors associated with the hospital environment which could have led to increased anxiety.

The measurement tools used to measure impairments varied between studies which may impact on findings; this was particularly evident for cognitive impairment where MoCA and MMSE tests were found to give different frequencies of cognitive impairment when used in the same study at the same time point.[14,15] The generalisability of results was affected by the variations in the definition of minor stroke (see Appendix 5.2), recruitment being limited to a single site in two-thirds of the studies and heterogeneity in the study populations and methodologies used. Most studies included did not have a comparator group so it was unclear if the frequency of outcomes post-TIA or minor stroke was different to that of the general population. The meta-analysis pooled prevalence of cognitive impairment by measurement tool (MoCA, MMSE and neuropsychological test battery). However, the pooled point estimates should be interpreted with caution because there was considerable heterogeneity and studies varied in terms of case mix, study design and time point of assessment. It could be argued that it was not appropriate to do a meta-analysis given this heterogeneity; however, the pooled estimates were used to demonstrate how the

prevalence of cognitive impairment post-TIA and minor stroke varies depending on measurement tool used rather than to quantify prevalence.

Residual impairments after TIA: retrospective cohort study

The strength and limitations of using routine electronic primary care medical records discussed previously apply to the retrospective cohort study. Use of these electronic medical records is novel to the field which researches residual impairments after TIA and the study addressed limitations of previous studies. The main strengths of the retrospective cohort study were the very large sample size (>55,000 people) and that matched controls, which were from the same source population as TIA patients, were included. Furthermore, potential confounding variables and presence of the impairment pre-TIA were adjusted for. As opposed to other studies in this field, the study explored multiple different impairments post-TIA (fatigue, psychological and cognitive impairment). The use of electronic medical records, which were collected in a non-interventional way, prevented bias that traditional prospective cohort studies are susceptible to, including volunteer and observer bias.[16]

There were limitations related to the identification of the exposure (TIA) and outcomes (fatigue, psychological or cognitive problems). TIA diagnoses were identified using clinical codes (Read codes) and were not verified. TIA is difficult to diagnose[17] and the association between TIA and residual impairments could be diluted if non-TIA patients were included in the TIA group. On the other hand, TIA is often underreported and it is likely that some of the control patients would have, unbeknown to them or the GP, had a TIA. The new proposed definition of TIA is tissue-based (no evidence of permanent brain infarction) rather than the old time-based definition (symptoms less than 24 hours).[18] However, the clinical codes used

to identify TIA diagnoses do not contain information on how TIA is defined. Use of brain imaging to diagnose TIA is not routine in the UK;[19] therefore, it is likely that some of the TIA group would have brain infarction and should technically be defined as minor stroke rather than TIA. However, the study is representative of current primary care practice and clinical diagnoses from medical records are more reliable than other methods such as self-report.[20] In terms of identification of outcomes, bias may be introduced because TIA patients consulted more in follow-up compared to controls and, therefore, had greater opportunity to report impairments to their GP. In addition, people may be more aware of their health following a TIA and, consequently, may be more likely to report impairments to their GP compared to controls.[16] Furthermore, use of routine primary care data limits the information available on the outcomes such as onset, duration, severity and impact on people's lives.

The study used a primary care population; therefore, results may not be generalisable to the general UK population. There could be TIA patients with residual impairments who did not consult their GP which may result in underestimation impairments post-TIA. Alternatively, TIA patients consulting in primary care could represent the most impaired TIA patients overestimating the association between TIA and residual impairments. Due to time constraints, the retrospective cohort study did not include patient public involvement (PPI). Therefore, outcomes that are important to patients may have been missed. However, TIA patients were informally involved in the selection outcomes through anecdotal evidence and my personal experience working with TIA patients on a previous study.

Interpretation and implications of findings

Missed opportunities for primary prevention of stroke and TIA

Sixty percent of people who experienced a stroke or TIA had been eligible for one or more prevention drug and, therefore, had an opportunity for primary prevention with pharmacotherapy prior to their stroke or TIA. However, over half of people with one or more prevention drug clinically indicated were not prescribed these drugs at the time of their stroke or TIA, which amounts to a third of all first strokes and TIAs. The majority of these (83%: 7,969/9,579) had a missed opportunity for just one prevention drug. A large number of strokes and TIAs could potentially be prevented through improving prescribing of lipid lowering, anticoagulant and antihypertensive drugs in people in whom these drugs are clinically indicated. Despite evidence based guidelines, prescribing of stroke and TIA prevention drugs in primary care remains suboptimal.

Lipid lowering drugs

Out of the three prevention drugs, lipid lowering drugs were the most common clinically indicated; 55% (16,028/29,043) of the study population were eligible for these drugs at the time of their stroke or TIA. The largest absolute number of missed opportunities occurred for lipid lowering drugs: 7,836 compared to 1,647 for anticoagulant drugs and 1,740 for antihypertensive drugs. Furthermore, compared to anticoagulant and antihypertensive drugs, lipid lowering drugs had the potential to prevent the greatest number of strokes when findings were extrapolated to UK population and stroke incidence estimates (Chapters 3 and 4). These findings suggest that, out of the three prevention drugs, improving prescribing of lipid lowering drugs would have the greatest impact on stroke prevention.

The potential impact on stroke and TIA prevention through improving prescribing of lipid lowering drugs is an important finding because these drugs are usually considered in the context of CHD prevention and there is controversy surrounding their prescription for prevention of stroke and CVD.[21] The debate was further fuelled by the updated lipid lowering guidelines which lowered the recommended prescribing threshold from a 10-year CVD risk of 20% to 10%, thereby, increasing the number of people eligible for these drugs.[22] This promoted concerns about medicalisation of otherwise healthy patients and creates further challenges for clinicians to communicate stroke risk to an otherwise healthy patient.[23] The majority of lipid lowering drugs prescribed are statins[24] which have a bad reputation in the media,[25,26] particularly in regard to statin-induced side effects.[27] Furthermore, the relative risk reduction of stroke for statins is low (22%; 95% CI 11% to 32%); therefore, a large number of people need to be treated to prevent one stroke.[28] Inertia of previous practice, lack of agreement with the guidelines, lack of outcome expectancy and patients' preferences are some of the barriers identified by Cabana et al (1999) for clinicians adhering to guidelines and these are likely to be relevant to statin prescribing.[29] However, it is important to overcome these barriers because statins have the potential to be the most effective drug to prevent strokes and TIAs and subsequently reduce the burden of these conditions.

Other studies have investigated the proportion of all eligible patients offered preventative treatment rather than looking at the extent to which opportunities were missed in stroke and TIA patients. Very high rates of compliance with lipid lowering guidelines have been reported in UK primary care for primary prevention (80%) and secondary prevention (74%).[30] However, younger patients were more likely to be on treatment and their study's population

mean age was 20 years younger than our analysis. This is broadly consistent with our findings that many older patients who went on to have a stroke/TIA were not treated. A more comparable study analysed data from the THIN database between 2008 and 2010. Similarly to us, they found 56% of patients eligible for primary CVD prevention lipid lowering drugs were not on treatment.[31] Other studies have found between 21% and 50% of patients with hypercholesterolemia were not on lipid lowering drugs.[32-34]

Anticoagulant drugs

Strokes in people with AF cause more death and disability compared to strokes in people without AF.[35] Therefore, primary prevention of stroke and TIA is particularly important in these patients to reduce the burden of stroke. Anticoagulant drugs should be prescribed to AF patients at high stroke risk[36] and in practice this is the majority of people; 90% of people in our sample with a diagnosis of AF were eligible for anticoagulant drugs at the time of their stroke or TIA. Although nearly all patients with AF should be prescribed anticoagulant drugs, this class of prevention therapy had the highest proportion of missed opportunities: 52% compared to 49% for lipid lowering drugs and 25% for antihypertensive drugs. Anticoagulant drugs have the greatest relative risk reduction of stroke out of the three prevention drugs;[28,37-39] therefore, it is counterintuitive that these drugs are least likely to be prescribed.

Risk of bleeding is one of the main reasons for GPs not prescribing anticoagulant drugs[40] and, in preventative health care, clinicians need to balance the risk of inflicting harm to the patient verses reducing a patient's risk of stroke. Shared decision making is important for patient-centred care and patients should be actively engaged in this decision.[41] Older age had also been reported as a reason for not prescribing anticoagulant drugs.[40] It could be

argued that non-prescribing in the elderly is reasonable, particularly given increased bleeding risk[42] and polypharmacy.[43] Furthermore, there may be organisational restraints related to warfarin prescribing such as access to a warfarin clinic and international normalisation ratio (INR) monitoring .[44,45] Updated AF guidelines recommend aspirin is not prescribed for stroke prevention;[36] however, in previous guidelines aspirin was considered acceptable for people with moderate stroke risk.[46] Reluctance of clinicians to change practice and patients to change medication may also be barriers of anticoagulant prescribing.[29]

Despite the barriers to anticoagulant drug prescribing, the benefits of anticoagulation have been shown to outweigh this risk.[47] Furthermore, the net benefit of anticoagulation is greatest in the elderly,[47] new novel oral anticoagulants have been approved which reduce the need for INR monitoring[48] and there is strong evidence base to support the recommendation that aspirin should not be prescribed for stroke prevention.[36] Therefore, under prescribing of anticoagulants may not be justifiable. There have been a number of improvements in management of AF, including better understanding of stroke risk in these patients and development of CHA_2DS_2-VASc;[49] introduction of novel oral anticoagulants;[48] updated guideline recommendations[36] and QOF incentives;[50] and development of audit tools like GRASP-AF (identifies AF patients eligible for anticoagulation).[51] The significant reduction in missed opportunities for anticoagulant drugs between 2009 and 2013 may reflect these changes.

Prescription of antihypertensive drugs for stroke prevention in AF has been explored by other studies and, concurrent with my finding, most reported underuse of these drugs.[52] Similar to my study, Holt et al (2012) reported missed opportunities for stroke prevention with anticoagulants in 48% of eligible AF patients using the QResearch database.[53] However, their study used a score of CHADS2 ≥2 to define eligibility and did not report the number of people who had suffered a stroke; therefore, it was unclear what proportions of anticoagulants were being prescribed for primary or secondary stroke prevention. Other UK primary care studies found 45% of AF patients with a CHADS2 score ≥2[54] and 40% with a CHA_2DS_2-VASc ≥1[55] were not prescribed anticoagulant drugs, but again the proportion of people in their samples with stroke were not reported. International studies have reported similar levels of under prescribing of anticoagulant drugs in eligible AF patients which ranged from 38% to 46%.[56-59]

Antihypertensive drugs

The smallest proportion of missed opportunities for prevention of stroke and TIA was found in people eligible for antihypertensive drugs. However, because a larger number of people were eligible for these drugs compared to anticoagulant drugs, the absolute numbers of missed opportunities for antihypertensive prescribing was second highest out of the three prevention drugs. Hypertension is highly prevalent[60] and was the most common comorbidity in our sample (as defined by QOF Read codes). However, the missed opportunities analysis focused on uncontrolled hypertension. People with a Read code indicating hypertension but their average recorded BP was <140/90 mmHg were excluded from the analysis, which comprised of 64% (9,405/14,646) of people with a clinical code for hypertension. This suggests that the most primary care patients with a record of hypertension have controlled

BP and the majority with uncontrolled BP are prescribed antihypertensive drugs. The well-established evidence base and safety profile are potential reasons why antihypertensive drugs were better prescribed compared to lipid lowering and antihypertensive drugs.[61] In addition, patients' awareness of BP and that lowering BP will improve health may facilitate prescribing of antihypertensive drugs.[62] Lessons learnt from antihypertensive drug prescribing could potentially be applied to improve prescription of lipid lowering and anticoagulant drugs. On the other hand, although prescription of antihypertensive drugs may be high, the proportion of people with controlled BP remains low.[30,63]

Other studies which have investigated the use of antihypertensive drugs in the context of CVD prevention vary in the proportions they report of treated hypertensive patients.[30,34,64-66] England has been found to have worse treatment rates compared to the United States and Canada.[64,66] A UK study comparable to the study within this thesis used primary care data from 19 general practices in the West Midlands and found high levels of antihypertensive drug prescribing in 86% of eligible people without CVD and 91% of people with CVD.[30] This was concurrent with my finding that people with CVD were more likely to be treated compared to those without. However, the median age of their sample was lower than my study (54 years vs 74 years, respectively) which might explain the higher prescribing rates. A German study also found a higher proportion of hypertensive patients with CVD were treated compared to those without CVD, but a bigger difference in prescribing was observed: 85% of people with CVD compared to 55% without CVD.[63] However, this study did not differentiate between pharmacotherapy and non-pharmacotherapy interventions. Improving prescribing of antihypertensive drugs to eligible people without existing CVD (primary prevention) should be a target for future research. Other international studies have

reported higher proportions of antihypertensive drugs prescribed to hypertensive patients, compared to my study, ranging from 87% to 97%.[32,34,65]

Behavioural change to improve prescribing of prevention drugs

Lipid lowering, anticoagulant and antihypertensive drugs for primary prevention of stroke and TIA are currently under prescribed in primary care (Chapters 3-5). Improving prescribing of these drugs has the potential to reduce the incidence and subsequent burden of stroke and TIA; however, interventions are required to change behaviour and should target clinicians, patients and policy makers. The behaviour change wheel framework is a comprehensive and systematic approach to intervention development to change behaviour which could be used in the context of improving prescribing of stroke and TIA prevention drugs (Figure 1).[67] The basis of the framework is the understanding of behaviour to identify targets for interventions and selection of appropriate intervention functions and policy categories to change behaviour.[67] The centre of the behaviour change wheel is the 'behaviour system', a model to understand behaviour known as COM-B: Capability (physical and psychological), Opportunity (social and physical) and Motivation (automatic and reflective), which have a bidirectional relationship with Behaviour.[67] When developing an intervention, the COM-B model can be used to understand behaviour and which component(s) need to be targeted to achieve behaviour change. The middle circle of the behaviour change wheel comprises of nine intervention functions: education, persuasion, incentivisation, coercion, training, enablement, modelling, environmental restructuring and restrictions (Figure 1).[67] The outer circle contains seven policy categories: environmental/ social planning, communication/ marketing, legislation, service provision, regulation, fiscal measures and guidelines.[67] Different approaches are likely to be required for each

prevention drug because different behaviours are associated with non-prescribing of lipid lowering, anticoagulant and antihypertensive drugs.[32,33,52,68,69] However, some intervention functions will be relevant for all three drugs and are discussed below and summarised in Figure 1.

There are potential medicolegal implications of missed opportunities for prevention of stroke and TIA. For a person in whom prevention drugs were indicated but not prescribed prior to stroke or TIA, an argument of medical negligence could be made on the grounds of failure to follow national, evidence-based guidelines without adequate justification. Identifying missed opportunities for prevention of stroke and TIA would be facilitated by accessibility and ease of searching electronic medical records. It has been suggested that medical negligence lawyers could take advantage of this by fishing for missed opportunity cases by searching electronic medical records of anyone who has suffered a stroke or TIA.[70] Dissemination of medicolegal accountability could be an effective form of coercion to improving prescription of primary prevention drugs. However, an important consideration is that guidelines are recommendations and not the law. Medicolegal fear may also have negative repercussions for shared decision making and clinicians' professional judgment during prescribing decisions.

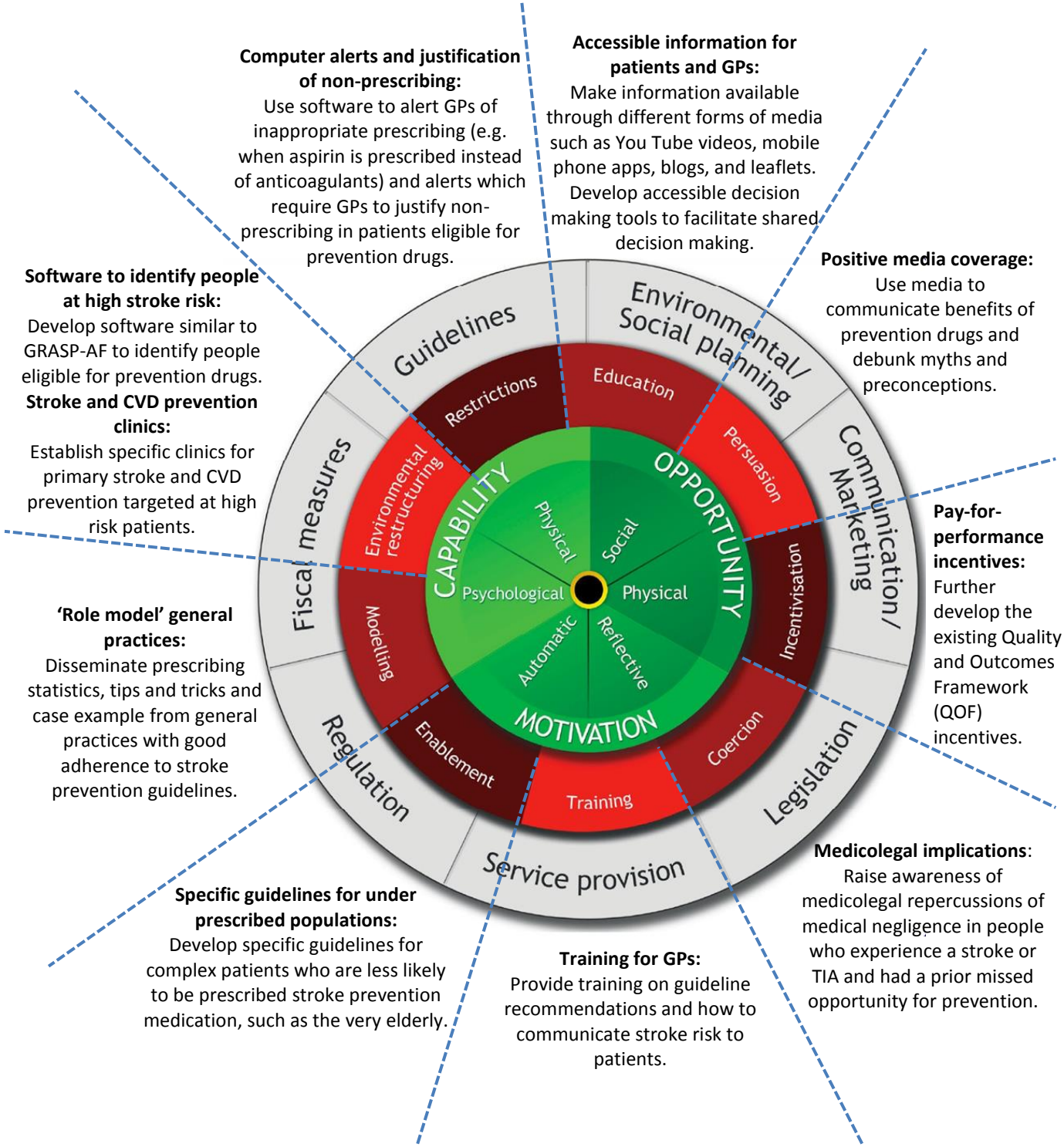

Figure 1: The behaviour change wheel with examples of potential intervention functions targets to improve prescribing of stroke and TIA prevention drugs. Adapted from Michie (2012).[67]

In contrast to coercion, incentivisation through pay-for-performance could improve prescribing of prevention drugs. The latest QOF guidance (2015/2016) for AF is now in line with the 2014 AF NICE guideline recommendations[36] and incentivises prescription of anticoagulants to AF patients with a recorded CHA_2DS_2-VASc score ≥2.[50] The impact of this on prescribing behaviour should be evaluated. QOF also incentivises prescription of statins to people who have a new diagnosis of hypertension, are aged between 30 and 75 years and have a 10-year CVD risk of ≥20%.[50] Extension of this QOF indicator to include all people with 10-year CVD risk of ≥10% or 20% and people with existing CVD has the potential to improve statin prescribing. Antihypertensive prescribing for primary stroke prevention could also be further incentivised by QOF. However, there may be substantial cost implications of this approach.

Strokes and TIAs predominantly occur in the elderly, the median age of the sample for the missed opportunities study was 74 years (IQR 64 to 82). The study's findings were extrapolated to the UK population and stroke incidence to estimate numbers of strokes that potentially could be prevented by prescribing all eligible patients prevention drugs (Chapters 4 and 5). These estimates suggested that the greatest reduction in strokes can be obtained through prescribing in the very elderly. This has important implications because the population is ageing and age is one of the most important risk factors for stroke and TIA. However, very elderly age was associated with non-prescribing of all three prevention drugs. Therefore, interventions to improve prescribing in the very elderly may be the most efficient way to reduce incidence of stroke and TIA. Development of guidelines specifically tailored to prescribing prevention drugs in the elderly, particularly the very elderly, which address issues concerning side effects and polypharmacy may facilitate prescribing of stroke

prevention drugs to these high risk patients. However, there is a lack of evidence for this population and further research is required.

Organisational barriers, including time constraints in consultations and ability to identify patients at high stroke risk,[29] are likely to hinder primary prevention of stroke and TIA. Specialised stroke and TIA prevention clinics could be established for people at high stroke risk. This could be done in primary care or the community and would allow protected time to address stroke and TIA prevention with patients; however, organisational, time and financial barriers may hinder this approach. The GRASP-AF audit tool has been developed for use in primary care to identify AF patients at high stroke risk.[51] Similar software could be developed to identify patients eligible for lipid lowering and antihypertensive drugs to facilitate the prescribing of these drugs. Alternatively software could be developed to discourage inappropriate prescribing or non-prescribing, such as alerts if aspirin is prescribed instead of anticoagulant drugs to AF patients or compulsory recording of reasons for not prescribing stroke prevention drugs to patients who are eligible. Patients' adherence to medication has been cited as a barrier to not prescribing stroke prevention drugs.[71-73] Patients' adherence could potentially be improved by training and education interventions[67] which provide accessible information on stroke risk and prevention drugs, potentially through different forms of media such as information sheets, You Tube videos, mobile phone applications and blogs. Specific training for GPs on communication of stroke risk and further development of decision making tools could also facilitate shared decision making.[41]

Negative perceptions of stroke prevention drugs, particularly statins, may affect wiliness of clinicians to prescribe drugs and deter patients from taking these drugs.[25-27] Therefore,

persuasion-based interventions through a media campaign to promote a positive image of stroke prevention medication may reduce misconceptions about these drugs and could also be used to educate people about stroke risk. The media campaign to raise awareness of symptoms of stroke (the F.A.S.T campaign) has been shown to be effective.[74] General practice are likely to vary in their prescribing habits and use of 'role model'[67] general practices, who have a good record of prescribing stroke prevention drugs, could be used to act as examples for other practices to aspire to, provide tips and tricks and take part in educational events.[75]

Residual impairments after TIA

Systematic review

The systematic review demonstrated that residual impairments post-TIA are under-researched and existing studies had important methodological limitations. However, the review suggested there may be a relatively high prevalence of depression and cognitive impairment post-TIA and minor stroke. This finding was supportive of the hypothesis that these patients may experience ongoing residual impairments; however, it was unclear if the prevalence of depression and cognitive impairment post-TIA and minor stroke was different to people the same age and sex without TIA or minor stroke. In addition, there were very few studies that measured fatigue, anxiety and PTSD post-TIA and minor stroke. The systematic review also highlighted methodological issues regarding choice of measurement tool to detect residual impairments in TIA and minor stroke patients. Residual impairments in these patients may be subtle and, therefore, measurement tools validated in stroke patients may not be appropriate.[14,15] Furthermore, most studies did not report presence of

the impairment pre-TIA or minor stroke. Therefore, impairments post-TIA and minor stroke could represent prevalent cases rather than TIA/minor stroke-related impairment. Most studies also did not adjust for potential confounding variables; therefore, the true relationship between TIA or minor stroke and residual impairments may be distorted.[76] The association between TIA or minor stroke and fatigue, psychological and cognitive impairments could not be determined from the findings of the systematic review. Therefore, there was a need to conduct a matched cohort study to robustly measure this association.

Retrospective cohort study

To my knowledge, use of electronic primary care medical records to conduct a retrospective cohort study is a novel method for the field of research which investigates residual impairments after TIA. However, due to the use of Read codes to identify diagnoses, minor stroke patients could not be included using this method. The retrospective cohort study found that people presenting with a diagnosis of TIA in primary care had significantly increased risk of consulting for fatigue, psychological and cognitive impairments compared to matched controls. This association remained when presence of the impairment pre-TIA and potential confounding variables were adjusted for. These findings suggest that some patients may experience residual impairments post-TIA and consult for these impairments in primary care.

The association between TIA and consultation for fatigue, psychological and cognitive impairment is complicated by the definition of TIA. TIA was first classified in 1958[77] and the definition has continuously been updated, evolving from a time-based to tissue-based definition which was most recently updated in 2009.[18] However, the tissue-based definition

is not consistently used in clinical practice or research and, in the UK, brain imaging is not routinely employed to diagnose TIA.[19] Consequently, the people with a diagnosis of TIA included in the retrospective cohort study are likely to comprise of people with and without presence of brain infarcts.[78] According to the tissue-based definition, this sample would technically be considered a mix of TIA and minor stroke patients. The mechanism of TIA-related impairments is unknown, but a potential mechanism could be presence of brain infarcts in minor stroke patients which have been diagnosed as TIA. Therefore, to distinguish between TIA and minor stroke, it is important to establish whether the association between TIA and residual impairments remains if the study population is restricted to TIA patients with no evidence of brain infarction.

The importance of distinguishing between TIA and minor stroke is debatable. If TIA patients with no evidence of brain infarction do not experience residual impairments, routine use of brain imaging to differentiate between TIA and minor stroke could be useful for clinicians to understand the prognosis of their patients and provide appropriate care. Furthermore, studies have found that the short-term stroke risk in 'TIA patients with infarction' is significantly higher than 'TIA without infarction'.[79-81] This suggests distinction between TIA and minor stroke would be useful to understand patients' risk of stroke. Routine neuroimaging, within 24 hours, has been recommended by the AHA/ASA.[18] However, the cost-benefit and practical implications of this should be considered.

The time-based definition of TIA is used by the NICE guidelines for diagnosis and initial management of stroke and TIA.[82] Therefore, it may be more informative for clinicians to understand the prognosis of people presenting in primary care with a diagnosis of TIA in the

context of how TIA is routinely diagnosed currently, which is represented by the retrospective cohort study, and the precise definition of TIA or mechanism of impairments is less important. In addition, as opposed to presence of brain infarcts, the mechanism of TIA-related impairments could be a result of presence of microinfarcts which are not detectable by existing imaging technologies[83] or the psychological impact of experiencing a TIA[84,85] as discussed in Chapter 9. The inconsistent use of the definition of TIA is confusing for clinicians and patients and has implications for policy recommendations and research of TIA patients. The definition of TIA should be standardised; however, this has practical implications because it would require the routine use of brain imaging. In the meantime, it is important for guidelines and researchers to be explicit in their definition of TIA.

TIA was originally considered to be a benign condition; however, evidence of the association between TIA and increase risk of stroke changed this view.[86] TIA is now considered a medical emergency and the importance of stroke prevention in these patients is recognised.[87] The findings of the retrospective cohort study challenge the understanding of TIA further because they suggest that TIA may not be a transient condition and the holistic consequences of TIA are not limited to increased stroke risk. These novel findings suggest that further care, beyond stroke prevention, may be required for TIA patients. Although the mechanism of post-TIA impairments is not understood and may be affected by how TIA is defined, appropriate care and treatment of TIA patients is required in the current context of TIA diagnoses and presentation of TIA in primary care. Residual impairments are likely to impact on patients' QoL and ability to return to work or normal activities. The Oxford vascular study found that TIA patients had statistically significant lower QoL compared to matched controls at one month and five years post-TIA.[88] A study of first-ever minor stroke

patients found that patients with depression attributed to minor stroke had a higher proportion of disability and lower QoL scores at one year.[89] Qualitative research which interviewed family members of minor stroke patients reported that patients had difficulty with complex activities and this caused burden to family members.[90] It is important to establish the health and social care needs of these patients and their families to ensure patients receive adequate follow-up care.

TIA patients, their carers and family members, clinicians and policy makers, are the key stakeholders for this research and important targets for knowledge transfer. Although further understanding of residual impairments post-TIA is required, immediate dissemination of findings are important. TIA patients should be informed that they may have ongoing fatigue, cognitive or psychological impairments following resolution of initial symptoms and be encouraged to consult in primary care if they experience these impairments. Furthermore, this information should be disseminated to carers and family members to facilitate recognition of impairments. Awareness of residual impairments post-TIA should be raised amongst stroke doctors and nurses in secondary care so they can equip patients upon discharge. Furthermore, primary care clinicians should be made aware of residual impairments to improve detection and treatment of impairments when TIA patients are followed up in primary care. Screening people with a diagnosis of TIA for residual impairments in primary care could potentially facilitate identification of impairments. Findings should also be disseminated to policy makers and guideline recommendations updated to incorporate potential impairments post-TIA both in the context of detection and rehabilitation.

Future research

Missed opportunities for prevention of stroke and TIA

In accordance with the behavioural change wheel framework, future research to improve prescribing of drugs for stroke and TIA prevention in primary care requires an understanding of prescribing behaviour.[67] The barriers and facilitators for prescribing of prevention drugs need to be identified and intervention(s) developed to target these. A multifaceted intervention including involvement of clinicians, policy makers and patients is likely to be required. Differences in the barriers to prescribing for each prevention drug should also be taken into consideration.[32,33,52,68,69] The proposed future research focuses on stroke and TIA prevention in the context of prescribing prevention drugs; however, other areas of intervention to improve stroke and TIA prevention include public health campaigns to reduce stroke and TIA risk factors and interventions to improve patients' adherence to stroke prevention medication.

Areas for future research have been suggested in Chapters 4 and 5. However, a comprehensive and systematic programme of research has the greatest potential to develop an effective intervention(s) which can be successfully translated into practice.[67,91] This could comprise of a mixed methods approach with three phases: (i) identify barriers and facilitators to prescribing; (ii) develop an intervention(s); and (iii) evaluate the intervention(s) as described in detail below.

Phase one: Identify barriers and facilitators for primary stroke and TIA prevention

A mixed method approach, comprised of a systematic review, qualitative interviews and THIN database analysis, to understand prescribing behaviour and identify barriers and facilitators linked to the COM-B model.[67]

Cabana et al (1999) developed a framework of barriers to physicians' adhering to guidelines.[29] Other studies have identified barriers specifically related to dyslipidaemia, AF and hypertension guidelines.[32,33,52,68,69] The existing literature should be synthesised through a systematic review to identify the barriers and facilitators relevant to prescribing of lipid lowering, anticoagulant and antihypertensive drugs. Qualitative interviews should be conducted to further develop an understanding of barriers and facilitators from the perspective of primary care clinicians and patients. Results should be compared with the findings of the systematic review. In addition, quantitative analysis using the THIN database could be used to determine the proportion of missed opportunities for primary stroke and TIA prevention in all patients, not just prior to stroke or TIA. This analysis could also quantify the proportion of people with missed opportunities who had previously been prescribed stroke and TIA prevention drugs and prescriptions were stopped compared to those never prescribed prevention drugs. This would inform the intervention to determine the extent it would need to be targeted at supporting initiation or continuation of prevention drugs.

Phase two: Develop an intervention(s)

Based on the findings in phase one, relevant intervention functions and policy categories should be identified.[67] Potential interventions are detailed in Figure 1. The intervention may

be complex with multiple components and should be designed in accordance with the Medical Research Council (MRC) guidance for developing a complex intervention.[91] Primary care clinicians, patients and policy makers are key stakeholders and their involvement to co-create the intervention would be essential to ensure the quality, relevance and success of the intervention. Existing interventions and their effectiveness should be considered.

Phase three: Evaluate feasibility and effectiveness of the intervention

The feasibility and effectiveness of intervention(s) developed in phase two should be evaluated. A pilot study may be required to test the feasibility and acceptability followed by a clinical trial to evaluate the effectiveness. Clinical trials are considered the gold standard to evaluate an intervention.[91] A mixed methods approach which collects qualitative and quantitative data should be conducted to obtain a comprehensive assessment of the intervention. A health economics component would also be important to measure the cost-effectiveness. Key stakeholders should be included in the trial design and interpretation and dissemination of findings.

Residual impairments after TIA

Research investigating residual impairments after TIA is in the early stages and further research is required to develop a more comprehensive understanding of these impairments and expand the evidence base. The future research suggested below is described in the context of TIA patients; however, would also relevant to minor stroke patients.

The natural history of fatigue, psychological and cognitive impairment post-TIA should be established to determine the onset and duration of these impairments. The severity of fatigue, psychological and cognitive impairment post-TIA should also be established. Severity

should be considered in terms of clinical relevance and impact on patients' QoL. These outcomes could be achieved through a prospective cohort study which includes measurement of impairments at multiple time points in follow-up using validated tools and patient reported outcomes. Recruitment and follow-up for a prospective cohort study which investigated functional, cognitive and emotional outcomes after TIA (FACE TIA) has been completed, but the results of this study have not yet been published.[57] However, it is likely that further prospective cohort studies will be required to establish a comprehensive understanding of impairments post-TIA. Furthermore, future studies should include PPI (input from patients, carers and family members) as an integral component to develop the research question, co-design the study, interpret findings and develop dissemination plans. Working with TIA patients and their families would be important for the success of the study through ensuring the research is relevant to patients, improve the quality of the study (such as advising on language used in questionnaires), making sure the research is acceptable for participants and targeting key stakeholders for dissemination.[92]

The mechanism of residual impairments post-TIA should be explored. The first step would to be to determine if TIA patients with no evidence of brain infarction experience fatigue, psychological or cognitive impairment. This could potentially be included as an outcome in the prospective cohort study proposed above. The mechanism that proposes TIA-related impairments are induced through psychological impact of a TIA could be investigated by exploring if psychological impairment in the acute stage post-TIA is associated with ongoing residual impairments. The neurobiological mechanism (presence of microinfarcts) was another mechanism proposed in Chapter 9. However, with current imaging technologies it

would be challenging to determine if presence of microinfarcts are associated with impairment post-TIA.[83]

Future research is required to develop interventions focused on improving identification of impairments post-TIA in primary care and providing appropriate therapy or rehabilitation. A greater understanding of impairments post-TIA will optimise development of an intervention; however, in the meantime, it is still important to address patients' needs in the context of current diagnosis of TIA and the findings of the retrospective cohort study. The first step to improve detection of fatigue, psychological or cognitive problems post-TIA in primary care is to educate primary care clinicians to increase awareness of potential impairments post-TIA. Following this, the optimum way to screen for residual impairments in primary care should be identified. Additional investigation is required to determine the impact of residual impairments post-TIA on patients' lives and, in turn, inform what therapy, rehabilitation and support is required by these patients. This should comprise of qualitative interviews with patients, carers and family members and quantitative measures including patient reported outcomes and return to work. It may be possible to extend existing stroke services to TIA patients or an intervention tailored to TIA patients may be required.

Conclusion

The studies presented within this thesis addressed two important topics in the area of stroke and TIA research: (i) primary prevention of stroke and TIA and (ii) residual impairments after TIA. The findings demonstrated inadequate prescribing, in primary care, of lipid lowering, anticoagulant and antihypertensive drugs in people whom these drugs were clinically indicated prior to stroke or TIA. Approximately two thirds of people who experienced stroke or TIA had a primary prevention drug clinically indicated, but over half of these (54%) had one or more missed opportunity for prevention. Different clinical and demographic characteristics were associated with missed opportunities for each prevention drug and a reduction in missed opportunities between 2009 and 2013 was only observed for anticoagulant drugs. Improving prescribing of lipid lowering, anticoagulant and antihypertensive drugs has the potential to reduce the incidence and subsequent burden of stroke and TIA.

Robust estimates of the prevalence of fatigue, psychological, and cognitive impairment in patients with TIA and minor stroke could not be determined from the existing literature, which was limited. However, the retrospective cohort study found TIA patients had increased risk of consulting for fatigue, psychological, and cognitive impairments in primary care compared to matched controls. The findings challenge the transient characterisation of TIA and suggest that existing guideline recommendations for management of TIA, which focus on stroke prevention, may not be adequate. Dissemination of findings to patients, primary care clinicians and policy makers is important to increase detection and treatment of residual impairments after TIA and improve patient care.

References

1. Moran GM, Calvert M, Feltham MG, Marshall T. Retrospective case review of missed opportunities for primary prevention of stroke and TIA in primary care: protocol paper. *BMJ Open.* 2014;4(11):e006622.
2. Moran GM, Calvert M, Feltham MG, Ryan R, Marshall T. A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper. *BMJ Open.* 2015;5(4):e008149.
3. Moran GM, Fletcher B, Calvert M, Feltham MG, Sackley C, Marshall T. A systematic review investigating fatigue, psychological and cognitive impairment following TIA and minor stroke: protocol paper. *Systematic Reviews.* 2013;2:72.
4. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. http://www.prisma-statement.org/. Accessed October, 2015.
5. STROBE Statement: strengthening the reporting of observational studies in epidemiology. http://www.strobe-statement.org/?id=available-checklists. Accessed October, 2015.
6. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in Primary Care.* 2011;19(4):251-255.
7. Welch C. Longitudinal Recording of Health Indicators. 2012; https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/mi/recording_in_thin/long_record. Accessed October, 2015.
8. Health and Social Care Information Centre (HSCIC). Read codes. http://systems.hscic.gov.uk/data/uktc/readcodes. Accessed October, 2015.
9. In Practice Systems (INPS). Vision Software. http://www.inps.co.uk/vision/health-improvement-network-thin. Accessed October, 2015.
10. Shephard E, Stapley S, Hamilton W. The use of electronic databases in primary care research. *Family Practice.* 2011;28(4):352-354.
11. Mulrow CD. Systematic Reviews: Rationale for systematic reviews. *BMJ.* 1994;309(6954):597-599.
12. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. *The Cochrane Collaboration* 2011.
13. Centre for Reviews and Dissemination (CRD). Systematic Reviews. CRDs guidance for undertaking reviews in health care. 2008; https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed October, 2015.
14. Blackburn DJ, Bafadhel L, Randall M, Harkness KA. Cognitive screening in the acute stroke setting. *Age and Ageing.* 2013;42(1):113-116.
15. Pendlebury ST, Markwick A, de Jager CA, Zamboni G, Wilcock GK, Rothwell PM. Differences in cognitive profile between TIA, stroke and elderly memory research subjects: a comparison of the MMSE and MoCA. *Cerebrovascular Diseases.* 2012;34(1):48-54.
16. Delgado-Rodríguez M, Llorca J. Bias. *Journal of Epidemiology and Community Health.* 2004;58(8):635-641.
17. Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. *Stroke.* 2010;41(7):1367-1370.

18. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease: The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke.* 2009;40(6):2276-2293.
19. Tyrrell P, Swain S, Rudd A. Diagnosis and initial management of transient ischaemic attack. Royal College of Physicians; 2010.
20. Bergmann MM, Byers T, Freedman DS, Mokdad A. Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. *American Journal of Epidemiology.* 1998;147(10):969-977.
21. Kmietowicz Z. New analysis fuels debate on merits of prescribing statins to low risk people. *BMJ.* 2014;348:g2370.
22. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline 181. National Clinical Guideline Centre; 2014.
23. Goldacre B, Smeeth L. Mass treatment with statins. *BMJ.* 2014;349:g4745.
24. Health and social care information centre (HSCIC). Prescription cost analysis, England - 2013 http://www.hscic.gov.uk/catalogue/PUB13887. Accessed October, 2015.
25. Hope J. Mail Online: Statins can weaken muscles and joints: Cholesterol drug raises risk of problems by up to 20 per cent. 2013; http://www.dailymail.co.uk/health/article-2335397/Statins-weaken-muscles-joints-Cholesterol-drug-raises-risk-problems-20-cent.html. Accessed October, 2015.
26. Naish J. Mail Online: Why taking statins might be pointless - and even bad for you. 2010; http://www.dailymail.co.uk/health/article-1340299/Why-taking-statins-pointless--bad-you.html. Accessed October, 2015.
27. Hope J. Mail Online: Have benefits of statins been exaggerated? Advocates distorted statistics and downplayed side-effects say experts 2015; http://www.dailymail.co.uk/health/article-2962513/Have-benefits-statins-exaggerated.html. Accessed October, 2015.
28. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews.* 2013;1:CD004816.
29. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA.* 1999;282(15):1458-1465.
30. Sheppard JP, Fletcher K, McManus RJ, Mant J. Missed opportunities in prevention of cardiovascular disease in primary care: a cross-sectional study. *The British Journal of General Practice.* 2014;64(618):e38-46.
31. Wu J, Zhu S, Yao GL, Mohammed MA, Marshall T. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in UK general practice: a national retrospective cohort study. *PLoS ONE.* 2013;8(7):e67611.
32. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2010;17(5):530-540.
33. Missault L, Witters N, Imschoot J. High cardiovascular risk and poor adherence to guidelines in 11 069 patients of middle age and older in primary care centres. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2010;17(5):593-598.

34. Roccatagliata D, Avanzini F, Monesi L, et al. Is global cardiovascular risk considered in current practice? Treatment and control of hypertension, hyperlipidemia, and diabetes according to patients' risk level. *Vascular Health and Risk Management.* 2006;2(4):507-514.
35. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke.* 1996;27(10):1760-1764.
36. National Institute for Health and Clinical Excellence (NICE). Atrial fibrillation: the management of atrial fibrillation. Clinical Guideline 180. National Clinical Guideline Centre; 2014.
37. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2005(3):Cd001927.
38. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *The Cochrane Database of Systematic Reviews.* 2007(3):Cd006186.
39. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* 2003;289(19):2534-2544.
40. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. *Age and Ageing.* 2011;40(6):675-683.
41. Seaburg L, Hess EP, Coylewright M, Ting HH, McLeod CJ, Montori VM. Shared decision making in atrial fibrillation: where we are and where we should be going. *Circulation.* 2014;129(6):704-710.
42. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100.
43. Hughes M, Lip GYH. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM.* 2007;100(10):599-607.
44. Ingelgard A, Hollowell J, Reddy P, Gold K, Tran K, Fitzmaurice D. What are the barriers to warfarin use in atrial fibrillation?: Development of a questionnaire. *Journal of Thrombosis and Thrombolysis.* 2006;21(3):257-265.
45. Nieuwlaat R, Capucci A, Lip GY, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. *European Heart Journal.* 2006;27(24):3018-3026.
46. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: national clinical guideline for management in primary and secondary care. Clinical Guideline 36. National Clinical Guideline Centre; 2006.
47. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *The Lancet.* 2007;370(9586):493-503.
48. Biondi-Zoccai G, Malavasi V, D'Ascenzo F, et al. Comparative effectiveness of novel oral anticoagulants for atrial fibrillation: evidence from pair-wise and warfarin-controlled network meta-analyses. *HSR Proceedings in Intensive Care and Cardiovascular Anesthesia.* 2013;5(1):40-54.
49. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137(2):263-272.
50. Health and social care information centre (HSCIC). 2015/ 2016 General Medical Services (GMS) Contract Quality and Outcomes Framework (QOF). 2014; http://www.hscic.gov.uk/qofbrv32. Accessed October, 2015.

51. GRASP-AF audit tool. http://www.nottingham.ac.uk/primis/tools-audits/list-of-audit-tools/grasp-suite/grasp-af/grasp-af.aspx. Accessed October, 2015.
52. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *The American Journal of Medicine.* 2010;123(7):638-645.e634.
53. Holt TA, Hunter TD, Gunnarsson C, Khan N, Cload P, Lip GY. Risk of stroke and oral anticoagulant use in atrial fibrillation: a cross-sectional survey. *The British Journal of General Practice.* 2012;62(603):e710-717.
54. Cowan C, Healicon R, Robson I, et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. *Heart.* 2013;99(16):1166-1172.
55. Shantsila E, Wolff A, Lip GY, Lane DA. Optimising stroke prevention in patients with atrial fibrillation: application of the GRASP-AF audit tool in a UK general practice cohort. *The British Journal of General Practice.* 2015;65(630):e16-23.
56. Akao M, Chun YH, Esato M, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. *Circulation Journal.* 2014;78(9):2166-2172.
57. Friberg L, Hammar N, Ringh M, Pettersson H, Rosenqvist M. Stroke prophylaxis in atrial fibrillation: who gets it and who does not? Report from the Stockholm Cohort-study on Atrial Fibrillation (SCAF-study). *European Heart Journal.* 2006;27(16):1954-1964.
58. Lip GY, Rushton-Smith SK, Goldhaber SZ, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. *Circulation. Cardiovascular Quality and Outcomes.* 2015;8(2 Suppl 1):S12-20.
59. Sabouret P, Depret-Bixio L, Cotte FE, Marie P, Bedira N, Blin P. Sex differences in stroke prevention in atrial fibrillation in French primary care. Results of the AFIGP (Atrial Fibrillation In General Practice) database. *Clinical Research in Cardiology.* 2014;103(11):887-893.
60. Danaei G, Finucane MM, Lin JK, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *The Lancet.* 2011;377(9765):568-577.
61. National Institute for Health and Clinical Excellence (NICE). Hypertension: the clinical management of primary hypertension in adults. Clinical Guideline 127. National Clinical Guideline Centre; 2011.
62. Oliveria SA, Chen RS, McCarthy BD, Davis CC, Hill MN. Hypertension knowledge, awareness, and attitudes in a hypertensive population. *Journal of General Internal Medicine.* 2005;20(3):219-225.
63. Sharma AM, Wittchen HU, Kirch W, et al. High prevalence and poor control of hypertension in primary care: cross-sectional study. *Journal of hypertension.* 2004;22(3):479-486.
64. Joffres M, Falaschetti E, Gillespie C, et al. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. *BMJ Open.* 2013;3(8):e003423.
65. Liddy C, Singh J, Hogg W, et al. Quality of cardiovascular disease care in Ontario, Canada: missed opportunities for prevention - a cross sectional study. *BMC Cardiovascular Disorders.* 2012;12(1):74.
66. Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension.* 2004;43(1):10-17.
67. Michie S, van Stralen M, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation Science.* 2011;6(1):42.

68. Palm F, Kleemann T, Dos Santos M, et al. Stroke due to atrial fibrillation in a population-based stroke registry (Ludwigshafen Stroke Study) CHADS2, CHA2DS2-VASc score, underuse of oral anticoagulation, and implications for preventive measures. *European Journal of Neurology.* 2013;20(1):117-123.
69. Partington SL, Abid S, Teo K, Oczkowski W, O'Donnell MJ. Pre-admission warfarin use in patients with acute ischemic stroke and atrial fibrillation: The appropriate use and barriers to oral anticoagulant therapy. *Thrombosis Research.* 2007;120(5):663-669.
70. Marshall T. Electronic ambulance chasing: patient records, guidelines, and the law. *British Journal of General Practice.* 2015;65(632):152-153.
71. Kedward J, Dakin L. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *The British Journal of General Practice.* 2003;53(494):684-689.
72. Lin ND, Martins SB, Chan AS, et al. Identifying barriers to hypertension guideline adherence using clinician feedback at the point of care. *Annual Symposium Proceedings / AMIA Symposium.* 2006:494-498.
73. Midlov P, Ekesbo R, Johansson L, et al. Barriers to adherence to hypertension guidelines among GPs in southern Sweden: a survey. *Scandinavian Journal of Primary Health Care.* 2008;26(3):154-159.
74. Flynn D, Ford GA, Rodgers H, Price C, Steen N, Thomson RG. A time series evaluation of the FAST national stroke awareness campaign in England. *PLoS ONE.* 2014;9(8):e104289.
75. AF Association and BMS-Pfizer Alliance. Grasp the initiative: Supporting the use of GRASP-AF in primary care to help reduce the risk of AF-related stroke. 2012:1-28.
76. Skelly AC, Dettori JR, Brodt ED. Assessing bias: the importance of considering confounding. *Evidence-Based Spine-Care Journal.* 2012;3(1):9-12.
77. Fisher CM. Intermittent cerebral ischemia. Cerebral Vascular Diseases; 1958; New York, NY.
78. Brazzelli M, Chappell FM, Miranda H, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Annals of Neurology.* 2014;75(1):67-76.
79. Ay H, Koroshetz WJ, Benner T, et al. Transient ischemic attack with infarction: a unique syndrome? *Annals of Neurology.* 2005;57(5):679-686.
80. Purroy F, Montaner J, Rovira A, Delgado P, Quintana M, Alvarez-Sabin J. Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. *Stroke.* 2004;35(10):2313-2319.
81. Redgrave JN, Coutts SB, Schulz UG, Briley D, Rothwell PM. Systematic review of associations between the presence of acute ischemic lesions on diffusion-weighted imaging and clinical predictors of early stroke risk after transient ischemic attack. *Stroke.* 2007;38(5):1482-1488.
82. National Institute for Health and Clinical Excellence (NICE). Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE guideline 68. 2008.
83. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *The Lancet Neurology.* 2012;11(3):272-282.
84. Altieri M, Maestrini I, Mercurio A, et al. Depression after minor stroke: prevalence and predictors. *European Journal of Neurology.* 2012;19(3):517-521.
85. Fang J, Cheng Q. Etiological mechanisms of post-stroke depression: a review. *Neurological Research.* 2009;31(9):904-909.
86. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *The Lancet Neurology.* 2007;6(12):1063-1072.
87. Intercollegiate Stroke Working Party. National clinical guideline for stroke. Fourth ed. London: Royal College of Physicians; 2012.
88. Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. *Neurology.* 2013;81(18):1588-1595.

89. Shi YZ, Xiang YT, Yang Y, et al. Depression after minor stroke: the association with disability and quality of life - a 1-year follow-up study. *International Journal of Geriatric Psychiatry.* 2015:doi: 10.1002/gps.4353.
90. Tellier M, Rochette A, Lefebvre H. Impact of mild stroke on the quality of life of spouses. *International Journal of Rehabilitation Research.* 2011;34(3):209-214.
91. Medical Research Council (MRC). Developing and evaluating complex interventions: new guidance.
92. INVOLVE. Briefing note three: Why involve members of the public in research? http://www.invo.org.uk/posttyperesource/why-should-members-of-the-public-be-involved-in-research/. Accessed October, 2015.

Appendices

Appendix 1: Missed opportunities for stroke and TIA prevention: protocol

A1.1 Supplementary material

Supplementary material published online for Publication 1 (presented as published):

Moran GM, Calvert M, Feltham MG, Marshall T. Retrospective case review of missed opportunities for primary prevention of stroke and TIA in primary care: protocol paper. *BMJ Open* 2014;4:e006622. doi:10.1136/bmjopen-2014-006622

Appendix 1: Read code lists for stroke and transient ischaemic attack (TIA)

Stroke Read codes

Read code	Description
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrhage from intracranial artery, unspecified
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accident due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
G62z.00	Intracranial haemorrhage NOS
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS

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Read code	Description
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction – cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G671000	Acute cerebrovascular insufficiency NOS
G676000	Cerebral infarct due cerebral venous thrombosis, nonpyogenic
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G6W..00	Cerebral infarction due unspecified occlusion/stenosis precerebral arteries
G6X..00	Cerebral infarction due/ unspecified occlusion or stenosis/cerebral arteries
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries

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Read code	Description
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebral infarction due/unspecified occlusion or stenosis/cerebral arteries
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6E00	[X]Subarachnoid haemorrhage from intracranial artery, unspecified
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cerebral infarct due unspecified occlusion/stenosis precerebral arteries
Fyu5600	[X]Other lacunar syndromes
Fyu5700	[X]Other vascular syndromes/brain in cerebrovascular diseases

TIA Read codes

Read code	Description
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G656.00	Vertebrobasilar insufficiency
G657.00	Carotid territory transient ischaemic attack
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
Fyu5500	[X]Other transient cerebral ischaemic attacks+related syndromes

Appendix 2: Read codes for diagnoses including history of and resolved Read codes.

Diagnosis	Read codes
Atrial fibrillation*	G573.% (excluding G5731, G5736)
Asthma*	H33..%, H3120, 173A.
Cancer*	B0... - B32z., B34.. -B6z0. (excluding B677.), Byu.. - Byu41, Byu5. - ByuE0, K1323, K01w1
CHD*	G3-G309, G30B-G330z (except G310), G33z-G3401, G342-G365X, G38-G3z, Gyu3% (except Gyu31)
CKD*	1Z12. -1Z16, 1Z1B. – 1Z1L., K053. - K055.
COPD*	H3…, H31..% (excluding H3101, H31y0, H3122), H32..%, H36.. - H3z.. (excluding H3y0., H3y1.), H5832
Dementia*	Eu02.%, E00..%, Eu01.%, E02y1, E012.%, Eu00.%, E041., Eu041, F110. – F112., F116.
Depression*	E0013, E0021, E112.%, E113.%, E118., E11y2, E11z2, E130., E135., E2003, E291., E2B.., E2B1., Eu204, Eu251, Eu32.% (excluding Eu32A, Eu32B, Eu329), Eu33.%, Eu341, Eu412
Diabetes mellitus*	C10.., C109J, C109K, C10C., C10D., C10E.%, C10F.% (Excluding C10F8), C10G.%, C10H.%, C10M.%, C10N.%, PKyP.
Epilepsy*	F25..% (excluding F2501, F2504, F2511, F2516, F256.%, F258. – F25A., F25y4, F25G., F25H.), F1321, SC200
Familial hypercholesterolemia	1W2.., C320.11, C3200, C3201, C3204, C3205
Heart Failure*	G58..%, G1yz1, 662f. – 662i., 585f., G5yy9
Hypertension*	G2..., G20..%, G24.. - G2z.. (Excluding G24z1, G2400, G2410, G27..), Gyu2., Gyu20
Hypothyroidism*	C03..%, C04..%
Learning disabilities*	E3…%, Eu7..%, Eu814 – Eu817, Eu81z, 918e
Osteoporosis*	N330.% (Excluding N3308, N3309), N3312, N3313, N3316, N3318 – N331B, N331H – N331M, NyuB0, NyuB1, NyuB8, N3314, N3315, N3746, NyuB2
PAD*	G73.., G73z.% (Excluding G73z1), Gyu74, G734., G73y.
Palliative care*	1Z01., 2JE.., 8B2a., 8BA2., 8Bae., 8BAP., 8BAS., 8BAT., 8BJ1., 8CM1.% (excluding 8CM15), 8CM4., 8CMb., 8CME., 8CMQ., 8CMW3, 8H6A., 8H7g., 8H7L., 8HH7., 8IEE., 9367, 9c0L0, 9c0M., 9c0N., 9c0P., 9EB5., 9G8.., 9K9.., 9Ng7., 9NgD., 9NNd., 9NNf0, ZV57C
Psychosis, schizophrenia, bipolar affective disease*	E10..%, E110.%, E111.%, E1124, E1134, E114. – E117z, E11y.% (excluding E11y2), E11z., E11z0, E11zz, E12..%, E13..% (excluding E135.), E2122, Eu2..%, Eu30.%, Eu31.%, Eu323, Eu328, Eu333, Eu32A, Eu329
Rheumatoid arthritis*	N040.%, N041., N042.% (excluding N0420), N047., N04X., N04y0, N04y2, Nyu11, Nyu12, Nyu1G, Nyu10, G5yA., G5y8.

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Read code	Description
History of Read codes	
Asthma	14B4.00
Atrial fibrillation	14AN.00
CHD	14A3.00-14A5.00, 14AH.00, 14AJ.00, 14AL.00, 14AT.00, 14AW.00, G32..12
COPD	14B3.12
Dementia	1461.00
Diabetes	1434.00
Epilepsy	1473.00
Heart failure	14A6.00, 14AM.00
Hypothyroidism	1432.00
Osteoporosis	14GB.00
Psychosis, schizophrenia	1464.00, 146H.00, ZV11000- ZV11112
Rheumatoid arthritis	14G1.00
Resolved Read codes	
Atrial Fibrillation	212R.00
Asthma	2126200, 212G.00
Depression	212S.00
Diabetes	2126300, 212H.00
Epilepsy	2126000, 212J.00
Heart failure	2126400
Hypertension	2126100, 212K.00
Osteoporosis	2126500
Psychosis, schizophrenia, bipolar affective disease	212T.00-212X.00, E100500, E101500, E102500, E103500, E105500, E107500, E110600, E111600, E114600, E115600, E116600, E117600, Eu22300, Eu26.00, Eu31700, Eu32900, Eu32A00

CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, PAD: Peripheral Arterial Disease
*QOF business rules version 27 (http://www.pcc-cic.org.uk/article/qof-business-rules-v27)

Appendix 3: British National Formulary (BNF) chapters and Read codes indicating on medication

*BNF chapters (version 67)**

	BNF chapter	Description
Anticoagulant drugs	2.8.1	Parenteral anticoagulants
	2.8.2	Oral anticoagulants
Antihypertensive drugs	2.2.1	Thiazides and related diuretics
	2.4	Beta-adrenoceptor blocking drugs (excluding propranolol)
	2.5.1	Vasodilator antihypertensive drugs
	2.5.2	Centrally acting antihypertensive drugs
	2.5.3	Adrenergic neurone blocking drugs
	2.5.5	Drugs affecting the renin-angiotensin system
	2.6.2	Calcium-channel blockers
Lipid regulating drugs	2.12	Lipid-regulating drugs (excluding Omega-3 fatty acid compounds: Omacor®, Prestylon®, Maxepa®)
Indicates smoking lifestyle intervention	4.10.2	Nicotine dependence

* BNF v67 2014. http://www.bnf.org/bnf/index.htm

Read codes indicating prescribed anticoagulant or lipid regulating drugs*

Prevention drug	Read code	Description
Anticoagulant drugs	66Q..00	Warfarin monitoring
	66Q..11	Anticoagulant monitoring
	66Q1.00	Initial warfarin assessment
	66Q2.00	Follow-up warfarin assessment
	66Q4.00	Warfarin dose changed
	66Q6.00	Warfarin therapy started
	66Q9.00	Warfarin dose unchanged
	66QA.00	Warfarin treatment plan
	66QB.00	Annual warfarin assessment
	66QC.00	Anticoagulation monitoring - secondary care
	66QD.00	Anticoagulation monitoring - primary care
	66QF.00	Slow induction of warfarin therapy
	66QG.00	International normalised ratio derived warfarin dose
	66QH.00	Warfarin daily dose
	66QZ.00	Warfarin monitoring NOS
	88A5.00	Anticoagulant therapy
	88A5000	Bridging anticoagulant therapy with low molecular weight heparin
	8B2K.00	Anticoagulant prescribed by third party
	8B3T.00	Aspirin OTC
	8B61.00	Anticoagulant prophylaxis
	8B61000	Warfarin anticoagulation prophylaxis
	8CAu.00	Patient advised of anticoagulant dose
	8CMW900	On anticoagulation care pathway
	8HHW.00	Referral for warfarin monitoring
	9k27.00	Home visit for anticoagulation monitoring
	9NkC.00	Seen in community anticoagulation clinic
	9NkD.00	Seen in hospital anticoagulation clinic
	9NkE.00	Seen in general practitioner anticoagulation clinic
	Z1Q2C00	Giving anticoagulant therapy
	ZV1C200	[V]personal history of long term (current) use of warfarin
Lipid regulating drugs	8B3z.00	Over the counter statin therapy

* There were no Read codes indicating antihypertensive drugs prescribed

Appendix 4: Read codes indicating exceptions and white coat hypertension

	Read codes	Description
Exception Read codes		
Anticoagulant drugs	14LP.00	Warfarin allergy
	8I25.00	Warfarin contraindicated
	8I2o.00	Dabigatrin contraindicated
	8I2R.00	Anticoagulation contraindicated
	8I3d.00	anticoagulation declined
	8I3E.00	Warfarin declined
	8I71.00	Warfarin not tolerated
	8I7R.00	Dabigatran not tolerated
	8IES.00	Dabigatran declined
	9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
	TJ42.00	Adverse reaction to anticoagulants
	TJ42100	Adverse reaction to warfarin
	TJ42200	Adverse reaction to nicoumalone
	TJ42300	Adverse reaction to phenindione
	TJ42z00	Adverse reaction to anticoagulants NOS
	U604200	[x]anticoagulant causing adverse effects in therapeutic use
	U604211	[x] adverse reaction to anticoagulants
	U604212	[X] Adverse reaction to heparin
	U604213	[x] adverse reaction to warfarin sodium
	U604214	[X] Adverse reaction to acenocoumarol
	U604215	[X] Adverse reaction to phenindione
	U604216	[x] adverse reaction to anticoagulants NOS
	ZV14A00	Personal history of allergy to warfarin
Antihypertensive drugs	8I3N.00	Hypertension treatment refused
	TJC7z00	Adverse reaction to antihypertensives NOS
Lipid lowering drugs	8I27.00	Statins contraindicated
	8I27000	Simvastatin contraindicated
	8I2C.00	Lipid lowering therapy contraindicated
	8I3C.00	Statin declined
	8I3J.00	Lipid lowering therapy declined
	8I76.00	Statin not tolerated
	TJC2.00	Adverse reaction to antilipaemic/anti-arteriosclerotic drugs
	TJC2400	Adverse reaction to simvastatin
	TJC2500	Adverse reaction to pravastatin
	TJC2z00	Adverse reaction to antilipaemic/antiarterioscler drugs NOS

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	Read codes	Description
Lipid lowering drugs	U60C600	[X]Antihyperlipidaem/antiarterioscl drug cause adv ef ther use
	U60C611	[X] Adverse react to antilipaemic & anti-arteriosclerot drug
	U60C615	[X] Adverse reaction to simvastatin
	U60C616	[X] Adverse reaction to pravastatin
	U60C617	[X] Adverse react to antilipaemic/antiarterioscler drugs NOS
	U60C900	[X]lipid-lowering drug adverse reaction
	U60CA00	[X]statin causing adverse effect in therapeutic use
White coat hypertension	246M.00	White coat hypertension

Appendix 5: Read codes indicating lifestyle interventions

Read code	Description
Alcohol	
6792.00	Health ed. Alcohol
67H0.00	Lifestyle advice regarding alcohol
8BA8.00	Alcohol detoxification
8CAM.00	Patient advised about alcohol
8CAM000	Advised to abstain from alcohol consumption
8CAv.00	Advised to contact primary care alcohol worker
8CE1.00	Alcohol leaflet given
8G32.00	Aversion therapy – alcoholism
8H35.00	Admitted to alcohol detoxification centre
8H7p.00	Referral to community alcohol team
8HHe.00	Referral to community drug and alcohol team
8HkG.00	Referral to specialist alcohol treatment service
8HkJ.00	Referral to alcohol brief intervention service
9k14.00	Alcohol counselling by other agencies
9k1A.00	Brief intervention for excessive alcohol consumption completed
9k1B.00	Extended intervention for excessive alcohol consumption completed
9NN2.00	Under care of community alcohol team
Z191.00	Alcohol detoxification
Z191100	Alcohol withdrawal regime
Z191200	Planned reduction of alcohol consumption
Z191211	Alcohol reduction programme
Z191400	Self-monitoring of alcohol intake
Z4B1.00	Alcoholism counselling
ZC22200	Advice to change alcoholic drink intake
ZC2H.00	Advice to change alcohol intake
ZG23100	Advice on alcohol consumption
ZR1E.00	Alcohol dependence scale
Diet	
13A3.00	Weight reducing diet
66C3.00	Understands reducing diet
66C4.00	Has seen dietician – obesity
66C6.00	Treatment of obesity started
66CR.00	Interview risk health assessment overweight obesity advice about diet physical activity
66CS.00	Interview risk health overweight obesity advice diet physical activity consider drugs
66CT.00	Interview risk health overweight obesity advice diet physical activity consider drugs consider surgery

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Read code	Description
6799.00	Health ed. Diet
8B57.00	Weight reducing diet
8B5C.00	Calorie restricted diet
8B5C.11	Low calorie diet
8B5C011	Very low calorie diet
8CA4000	Pt advised re weight reducing diet
8CA4011	Patient advised to lose weight
8H4n.00	Referral to weight management special interest GP
ZC1..00	Actions to lose weight
ZC14.00	Attending slimming club
ZC2C700	Patient advised about weight reducing diet
ZC2C711	Dietary advice for weight reduction
ZC2CO00	Dietary advice for weight loss
ZC2F.11	Advice to change high calorie food intake
Exercise	
1384.00	Enjoys moderate exercise
1385.00	Enjoys heavy exercise
1389.00	Aerobic exercise 1 time/week
67H2.00	Lifestyle advice regarding exercise
6798.00	Health ed. – exercise
138A.00	Aerobic exercise 2 times/week
138B.00	Aerobic exercise 3+ times/week
138D.00	Anaerobic exercise 1 time/week
138E.00	Anaerobic exercise 2 times/week
138F.00	Anaerobic exercise 3+ times/week
138G.00	Attends exercise classes
138H.00	Enjoys intermediate exercise
138P.00	Aerobic exercise three times a week
138Q.00	Aerobic exercise four times a week
138R.00	Aerobic exercise five times a week
13CR.00	Physical activity target light exercise
13CS.00	Physical activity target moderate exercise
13CT.00	Physical activity target strenuous exercise
67H2.00	Lifestyle advice regarding exercise
8BAH.00	Exercise on prescription
8CA5.00	Patient advised re exercise
8CA5000	Advice about aerobic exercise
8CA5100	Advice about muscle strengthening exercise
8CAn.00	Pt given written advice on benefits of physical activity
8E79.00	Home exercise programme
8E7A.00	Group exercise programme

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Read code	Description
8E7B.00	Graded exercise therapy
8E7C.00	Aerobic exercises
8E7D.00	Exercise circuits
8H7q.00	Referral for exercise therapy
8H7q000	Referral for graded exercise therapy
8H7s.00	Referral to physical activity programme
8HHc.00	Referred for exercise programme
8HkX.00	Referral to exercise on referral programme
Z4G1400	Giving encouragement to exercise
Z4G1411	Offering encouragement to exercise
Z4M1200	Reassuring about exercise
Z65..00	Exercise therapy
Z658.00	Aerobic exercises
Z65A.00	Exercise circuits
Z65B.00	Home exercise programme
Z67..00	Exercise class
Z67..11	Group exercise
Z68..00	Exercises
Z6D3.00	Cardiovascular exercises in water
Z6D3100	Aquaerobic exercises
ZC17.00	Exercising to lose weight
ZG12.00	Advice to undertake activity
ZG16.00	Advice about exercise
ZG16100	Advice to exercise
Smoking	
67H1.00	Lifestyle advice regarding smoking
6791.00	Health ed. smoking
137b.00	Ready to stop smoking
137c.00	Thinking about stopping smoking
137G.00	Trying to give up smoking
13p0.00	Negotiated date for cessation of smoking
13p5.00	Smoking cessation programme start date
13p5000	Practice based smoking cessation programme start date
67H6.00	Brief intervention for smoking cessation
745H.00	Smoking cessation therapy
745H000	Nicotine replacement therapy using nicotine patches
745H100	Nicotine replacement therapy using nicotine gum
745H200	Nicotine replacement therapy using nicotine inhalator
745H300	Nicotine replacement therapy using nicotine lozenges
745H400	Smoking cessation drug therapy
745Hy00	Other specified smoking cessation therapy

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Read code	Description
745Hz00	Smoking cessation therapy NOS
8B2B.00	Nicotine replacement therapy
8B3f.00	Nicotine replacement therapy provided free
8B3Y.00	Over the counter nicotine replacement therapy
8BP3.00	Nicotine replacement therapy provided by community pharmacist
8CAg.00	Smoking cessation advice provided by community pharmacist
8CAL.00	Smoking cessation advice
8CdB.00	Stop smoking service opportunity signposted
8H7i.00	Referral to smoking cessation advisor
8HBM.00	Stop smoking face to face follow-up
8HBP.00	Smoking cessation 12 week follow-up
8HkQ.00	Referral to NHS stop smoking service
8HTK.00	Referral to stop smoking clinic
8T08.00	Referral to smoking cessation service
9kc..00	Smoking cessation - enhanced services administration
9kc0.00	Smoking cessation monitor template completed - enhanced service admin
9kc0.11	Smoking cessation ESA monitoring template completed
9N2k.00	Seen by smoking cessation advisor
9Ndf.00	Consent given for follow-up by smoking cessation team
9NdV.00	Consent given follow-up after smoking cessation intervention
9NS0200	Referral for smoking cessation service offered
9OO..00	Anti-smoking monitoring admin.
9OO..11	Stop smoking clinic admin.
9OO..12	Stop smoking monitoring admin.
9OO1.00	Attends stop smoking monitor.
9OO3.00	Stop smoking monitor default
9OO4.00	Stop smoking monitor 1st letter
9OO5.00	Stop smoking monitor 2nd letter
9OO6.00	Stop smoking monitor 3rd letter
9OO7.00	Stop smoking monitor verbal inv.
9OO8.00	Stop smoking monitor phone inv.
9OOA.00	Stop smoking monitor check done
9OOB.00	Stop smoking invitation short message service text message
9OOB000	Stop smoking invitation first SMS text message
9OOB100	Stop smoking invitation second SMS text message
9OOB200	Stop smoking invitation third SMS text message
9OOZ.00	Stop smoking monitor admin. NOS
ZG23300	Advice on smoking
Weight	
13A3.00	Weight reducing diet
66C4.00	Has seen dietician – obesity

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Read code	Description
66C5.00	Treatment of obesity changed
66C6.00	Treatment of obesity started
66C9.00	Target weight discussed
66C9.11	Weight loss advised
66CA.00	Ideal weight discussed
66CC.00	Wants to lose weight
66CG.00	Weight management programme offered
66CH.00	Weight management plan started
67H7.00	Lifestyle advice regarding diet
67H8.00	Lifestyle advice regarding hypertension
679P.00	Health education - weight management
67I9.00	Advice about weight
67K9.00	Cycle of change stage, weight management
6B4..00	Counterweight weight management programme
6B4..11	Counterweight programme
8B57.00	Weight reducing diet
8B5B.00	Weight gain diet
8CA4011	Patient advised to lose weight
8Cd7.00	Advice given about weight management
8CdC.00	Weight management service opportunity signposted
8CP5.00	Discussion about weight management programme
8H4n.00	Referral to weight management special interest GP
8HHH.00	Refer to weight management programme
8HHH000	Referral to local authority weight management programme
8HHH100	Referral to residential weight management programme
9NS0300	Referral to weight management service offered
ZC1..00	Actions to lose weight
ZC17.00	Exercising to lose weight
ZC2C700	Patient advised about weight-reducing diet
ZC2C711	Dietary advice for weight reduction
ZC2CM00	Dietary advice for obesity
ZC2CN00	Dietary advice for weight gain
ZC2CO00	Dietary advice for weight loss
ZG53.00	Advice about weight
ZG53100	Patient advised to lose weight
ZV65319	[V]dietary counselling in obesity

A1.2 Scientific Review Committee (SRC) approval

SRC Feedback

Researcher Name: Grace Turner
Organisation: University of Birmingham
SRC Reference Number: 13-023
Date: 31st May 2013
Study title: Missed opportunities for primary prevention of stroke and TIA in primary care
Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

We have approved it with minor comments for the researchers only.

Advice (General advice for the researchers as information only – No response required)
This is a very well thought out and important study. My only concern is that it potentially involves multiple comparisons of effects of variables on missed opportunities, especially when one considers the analysis by individual primary care practices and types of practice, and care will be needed to ensure that interpretation is appropriate to the number of comparisons made, and the power of the study for looking at any one of them. There is no power calculation provided and it would be beneficial to consider this at the outset - although one suspects there will be ample power for providing a precise estimate of the primary analysis of missed opportunities, there may be less power for analyses of some of the proposed modifying factors.

We are pleased to inform that you can proceed with the study as this is now approved. CSD Medical Research will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform CSD Medical Research in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla
Research Associate

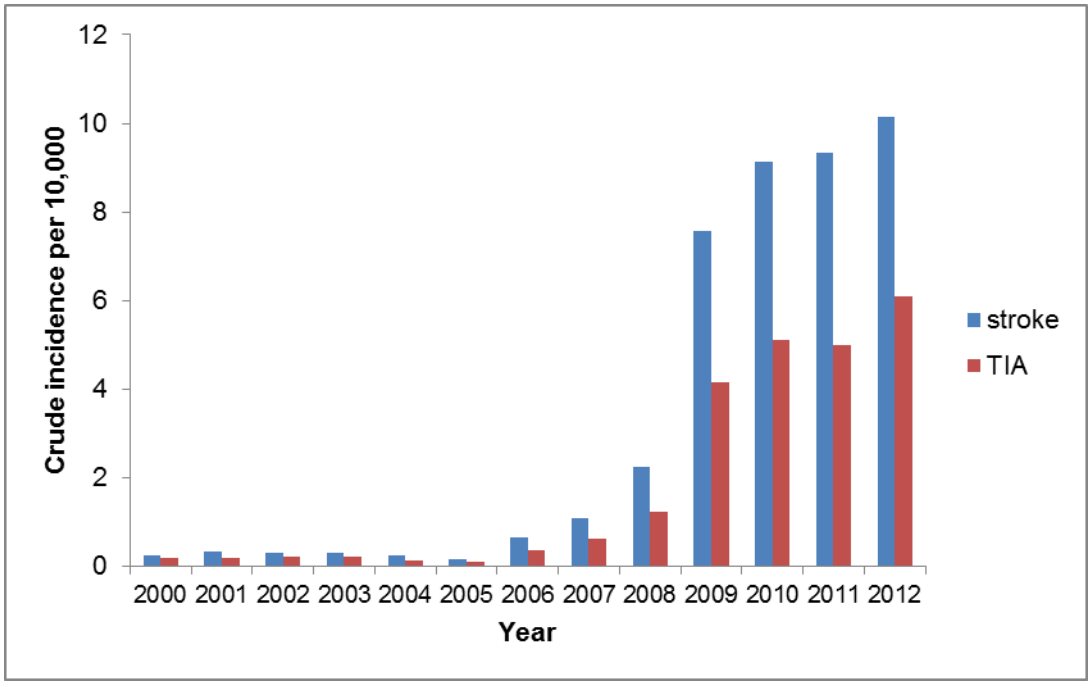
Appendix 2: Missed opportunities for stroke and TIA prevention: Lipid lowering drugs

A2.1 Supplementary material

eTable 1: Values outside clinically plausible ranges which were excluded.

Variable	Cut-off range
Height (m)	1 - 2.5
Weight (kg)	35 - 200
Body mass index (units)	10 - 60
Systolic blood pressure (mmHg)	60 - 260
Diastolic blood pressure (mmHg)	40 - 160
Total cholesterol (mm/L)	1 - 12
High-density lipoprotein (HDL) cholesterol (mm/L)	0.1 - 12

eFigure 1: Crude incidence of stroke and transient ischaemic attack (TIA) recorded in The Health Improvement Network (THIN) database.



eTable 2: Summary of logistic regression predictor variables. All variables were categorical unless otherwise stated.

Predictor variable		Total	Included in final regression model?
Age	<45	115	Y
	45-49	221	Y
	50-54	494	Y
	55-59	811	Y
	60-64	1,489	Y
	65-69	2,049	Y
	70-74	2,638	Y
	75-79	2,329	Ref
	80-84	2,514	Y
	85-89	2,068	Y
	90-94	1,012	Y
	≥95	288	Y
Sex	Male	8,941	Ref
	Female	7,087	Y
Deprivation	1 (least deprived)	3,709	Ref
	2	3,497	N
	3	3,210	N
	4	3,047	N
	5 (most deprived)	2,187	N
	Missing	378	N
Rurality*	Rural	5,997	Ref
	Urban	10,021	N
BMI	Healthy	4,655	Ref
	Underweight	339	Y
	Overweight	5,995	Y
	Obese	4,172	Y
	Missing	867	Y
Smoking	Non	3,927	Ref
	Ex	7,910	Y
	Current	3,716	Y
	Missing	475	Y

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Predictor variable		Total	Included in final regression model?
Alcohol	Never	2,093	Ref
	Light	2,855	N
	Moderate	1,859	N
	High	4,633	N
	Missing	4,588	N
Lifestyle intervention: Any	N	9,310	Ref
	Y	6,718	N
Lifestyle intervention: Alcohol	N	15,437	Ref
	Y	591	N
Lifestyle intervention: Diet	N	15,222	Ref
	Y	806	N
Lifestyle intervention: Exercise	N	14,161	R
	Y	836	N
Lifestyle intervention: Smoking	N	10,798	Ref
	Y	5,230	Y
Lifestyle intervention: Weight	N	14,964	Ref
	Y	1,064	Y
Year of event†	2009	2,777	N
	2010	3,213	
	2011	3,149	
	2012	3,482	
	2013	3,407	
Health authority/ Country	West Midlands	1,422	Ref
	East Midlands	453	Y
	East of England	952	Y
	London	1,100	Y
	North East	546	Y
	North West	1,738	Y
	South Central	1,977	Y
	South East Coast	1,409	Y
	South West	1,926	Y
	Yorkshire & Humber	381	Y
	Northern Ireland	692	Y
	Scotland	2,242	Y
	Wales	1,119	Y
	Missing	71	Y

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Predictor variable		Total	Included in final regression model?
Number of comorbidities†	0	1,318	N
	1	2,441	
	2	3,727	
	3	3,681	
	4	2,539	
	5	1,354	
	6	652	
	7	229	
	8	87	
Atrial fibrillation	N	13,636	Ref
	Y	2,392	N
Asthma	N	14,304	Ref
	Y	1,724	N
Cancer	N	14,117	Ref
	Y	1,911	N
CHD	N	10,485	Ref
	Y	5,543	Y
CKD	N	10,254	Ref
	Y	5,774	Y
COPD	N	14,558	Ref
	Y	1,470	N
Dementia	N	15,291	Ref
	Y	737	N
Depression	N	12,608	Ref
	Y	3,420	N
Diabetes	N	11,542	Ref
	Y	4,486	Y
Epilepsy	N	15,741	Ref
	Y	287	N
Heart failure	N	14,690	Ref
	Y	1,338	N
Hypertension	N	6,362	Ref
	Y	9,666	Y
Hypothyroidism	N	14,304	Ref
	Y	1,724	N

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Predictor variable		Total	Included in final regression model?
Learning disability	N	15,974	Ref
	Y	54	N
Osteoporosis	N	14,763	Ref
	Y	1,265	N
PAD	N	14,597	Ref
	Y	1,431	Y
Palliative care	N	15,805	Ref
	Y	223	Y
Psychosis	N	15,766	Ref
	Y	262	N
Rheumatoid arthritis	N	15,634	Ref
	Y	394	N

*10 missing, missing category not included in the model as too few events

† Continuous variable

BMI: Body Mass Index, CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, N: No, PAD: Peripheral Artery Disease, Ref: Reference category, Y: Yes

Exploratory analyses

Methods

Exploratory analyses investigated the effect of duration of registration and consultation frequency in the year prior to stroke/TIA. The Framingham risk equation is only valid for patients between 30-74 years; therefore, we investigated the impact of defining all patients over 74 years as high risk as suggested by the guidelines.[1] The most recent UK dyslipidaemia guidelines (2014) lowered the definition of high CVD risk from ≥20% to ≥10% over 10 years;[2] therefore, the effect of lowering the CVD risk threshold was explored. In addition, the influence of the individual elements of the high CVD risk definition (CHD, CKD, PAD, diabetes mellitus and ≥40 years or 10-year CVD risk ≥20%) were analysed. To reflect the updated 2014 NICE lipid modification guidelines, where the QRISK2 risk calculation was recommended over the Framingham risk equation,[2] sensitivity analysis investigated the impact of using QRISK2-2014 to calculate CVD risk. The difference in variables included in the Framingham and QRISK2-2014 equations are presented in eTable 3.

eTable 3: Variables included in Framingham and QRISK2-2014 equations.

Variable	Framingham	QRISK2-2014
Age	✓	✓
Sex	✓	✓
Ethnicity		✓
BMI		✓
Deprivation score		✓
Systolic blood pressure	✓	✓
Total cholesterol	✓	✓
HDL cholesterol	✓	✓
Family history of CHD/Stroke		✓
Smoking status	✓	✓
Treated hypertension		✓
Diabetes	✓	✓
ECG-LVH	✓	
Atrial fibrillation		✓
Rheumatoid arthritis		✓
Chronic kidney disease		✓

Results

In multivariable analysis, frequency of consultations in the year prior to stroke or TIA and duration of registration were not associated with lipid lowering drug prescribing. When entered into the regression model, a 10-year CVD risk ≥20% was associated with a statistically significant 2.4-fold increase in odds of having a missed opportunity. Given that CHD, CKD, PAD and diabetes were all protective in the regression model, we subsequently investigated the impact of not having a 'high risk comorbidity' (i.e. no CHD, CKD, PAD, diabetes or familial hypercholesterolemia). A variable for 'no high risk comorbidities' was entered into the regression model and associated with a 3-fold increase in odds of having a missed opportunity (OR 2.8; 95% CI 2.5, 3.2). There were 2,780 patients with a 10-year CVD risk ≥20% but no 'high risk comorbidities'; 81% (2,238/2,780) had a missed opportunity.

Further exploratory analysis investigated the impact of definitions of high risk: (i) original definition (CHD, CKD, PAD, diabetes and ≥40 years or 10-year CVD risk ≥20%); (ii) including all patients >74 years; (iii) lowering 10-year CVD risk to ≥10%; (iv) include all patients >74 years and lowering 10-year CVD risk to ≥10% (eTable 4). Considering all patients over the age of 74 years as high risk increased the number of patients eligible for lipid lowering medication from 16,028 to 22,077; 58% had a missed opportunity. Lowering the 10-year CVD risk threshold to ≥10% increased the number of eligible patients to 19,462, of which, 54% had a missed opportunity. Combining these two definitions of high risk, the number of eligible patients became 25,111 with 61% having a missed opportunity. When QRISK2 was used to calculate CVD risk, the number of eligible patients increased to 19,253 and 53% had a missed opportunity (10,237/19,253).

eTable 4: The impact of different definitions of high risk on proportion of eligible stroke and transient ischaemic attack (TIA) patients with a missed opportunity for lipid lowering primary prevention therapy.

	Definition of high risk	Missed opportunities	% missed opportunities
(i)	Original definition* (n=16,028)	7,836	48.9
(ii)	Include all patients >74 years (n=22,077)	12,739	57.7
(iii)	Lower 10-year CVD risk to ≥10% (n= 19,462)	10,575	54.3
(iv)	Include all patients >74 years and lower 10-year CVD risk to ≥10% (n=25,511)	15,478	60.7

* Original definition: Coronary Heart Disease (CHD), Chronic Kidney Disease (CKD), Peripheral Artery Disease (PAD), diabetes and aged ≥40 years or 10-year CVD risk ≥20%

References

1. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. Clinical Guideline 67. National Collaborating Centre for Primary Care and Royal College of General Practitioners. 2008
2. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline 181. National Clinical Guideline Centre; 2014.

eTable 5: Number of strokes that potentially could be prevented through prescribing lipid lowering drugs.

Age band	Number of strokes in the THIN sample		Estimated number of strokes that could be prevented in the THIN sample		Proportion of strokes that could be prevented in the THIN sample (%)		Number of strokes per year in UK		Estimated number of strokes that could be prevented in UK	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<35	115	124	1	1	1%	1%	0	0	0	0
35-44	301	258	8	7	3%	3%	1,469	896	39	23
45-54	841	652	57	23	7%	4%	2,453	1,097	165	39
55-64	1,669	1,034	182	50	11%	5%	6,712	4,413	731	212
65-74	2,462	1,903	289	133	12%	7%	18,817	12,744	2,208	889
75-84	2,613	2,925	167	188	6%	6%	14,656	20,001	939	1,287
≥85	1,232	2,468	115	281	9%	11%	9,747	16,677	913	1,899
All ages	18,597		1,502		8.1%		109,682		9,343	
<85	14,658		1,103		7.5%		83,258		6,531	

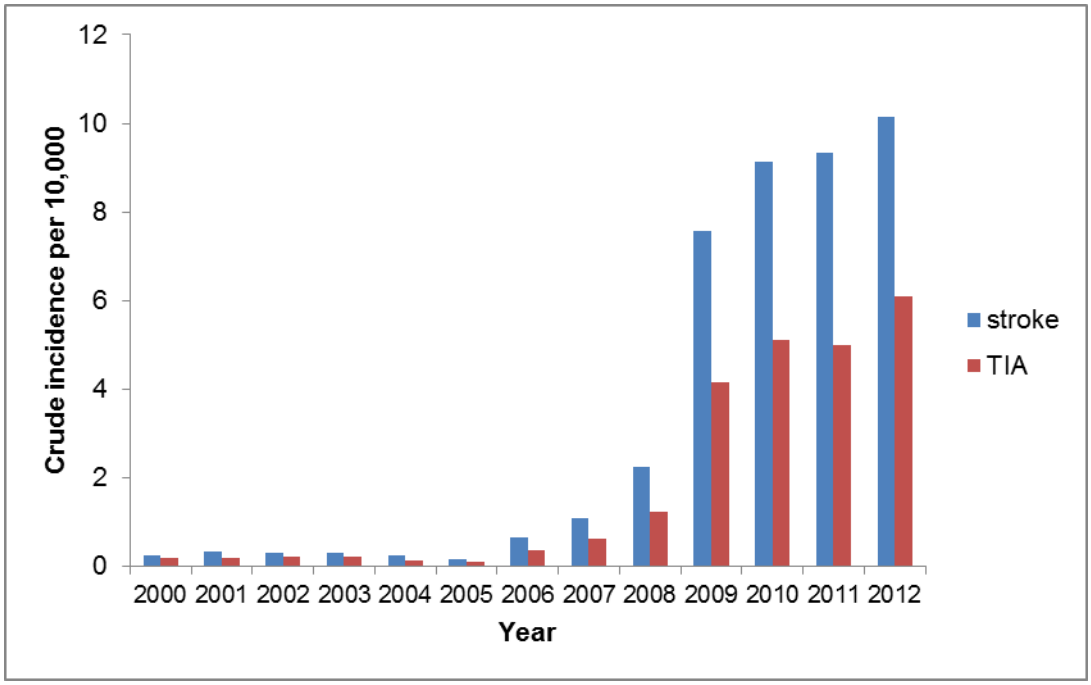
Appendix 3: Missed opportunities for stroke and TIA prevention: Anticoagulant and antihypertensive drugs

A3.1 Supplementary material

Supplementary Table S1: Values outside clinically plausible ranges which were excluded.

Variable	Cut-off range
Height (m)	1 - 2.5
Weight (kg)	35 - 200
Body mass index (units)	10 - 60
Systolic blood pressure (mmHg)	60 – 260
Diastolic blood pressure (mmHg)	40 - 160
Total cholesterol (mm/L)	1 – 12
High-density lipoprotein (HDL) cholesterol (mm/L)	0.1 – 12

Supplementary Figure S1: Crude incidence of stroke and transient ischaemic attack (TIA) recorded in The Health Improvement Network (THIN) database.



Supplementary Table S2: Summary of logistic regression predictor variables. All variables were categorical unless otherwise stated.

		Eligible for anticoagulant drugs		Eligible for antihypertensive drugs	
Predictor variable		**Total**	**Included in final regression model?**	**Total**	**Included in final regression model?**
Age	<45	6‡		69	Y
	45-49	9‡		109	Y
	50-54	15‡	Y	190	Y
	55-59	39	Y	311	Y
	60-64	70	Y	556	Y
	65-69	170	Y	832	Y
	70-74	291	Y	1,091	Y
	75-79	604	Ref	1,133	Ref
	80-84	760	Y	1,179	Y
	85-89	719	Y	974	Y
	90-94	399	Y	453	Y
	≥95	112	Y	111	Y
Sex	Male	1,469	Ref	3,440	Ref
	Female	1,725	Y	3,568	Y
Deprivation	1 (least deprived)	815	Ref	1,630	Ref
	2	763	N	1,582	N
	3	670	N	1,405	N
	4	528	N	1,323	N
	5 (most deprived)	347	N	900	N
	Missing	71	N	168	N

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Predictor variable		Eligible for anticoagulant drugs: Total	Eligible for anticoagulant drugs: Included in final regression model?	Eligible for antihypertensive drugs: Total	Eligible for antihypertensive drugs: Included in final regression model?
Rurality	Rural	1,236	Ref	2,555	Ref
	Urban	1,957	N	4,451	N
	Missing*	1	N	2	N
BMI	Healthy	1,108	Ref	1,953	Ref
	Underweight	98	Y	135	N
	Overweight	1,141	Y	2,599	N
	Obese	651	Y	2,010	N
	Missing	196	Y	311	N
Smoking	Non	886	Ref	1,626	Ref
	Ex	1,865	Y	3,702	N
	Current	335	Y	1,487	N
	Missing	108	Y	193	N
Alcohol	Never	391	Ref	902	Ref
	Light	649	N	1,282	N
	Moderate	376	N	809	N
	High	851	N	1,999	N
	Missing	927	N	2,016	N
Lifestyle intervention: Any	N	2,269	Ref	4,110	Ref
	Y	925	N	2,898	N
Lifestyle intervention: Alcohol	N	3,102	Ref	6,742	Ref
	Y	92	N	266	N

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Predictor variable		Eligible for anticoagulant drugs: Total	Eligible for anticoagulant drugs: Included in final regression model?	Eligible for antihypertensive drugs: Total	Eligible for antihypertensive drugs: Included in final regression model?
Lifestyle intervention: Diet	N	3,062	Ref	6,631	Ref
	Y	132	N	377	N
Lifestyle intervention: Exercise	N	3,027	Ref	6,599	Ref
	Y	167	N	409	N
Lifestyle intervention: Smoking	N	2,559	Ref	4,808	Ref
	Y	635	N	2,200	N
Lifestyle intervention: Weight	N	3,037	Ref	6,476	Ref
	Y	157	N	532	Y
Year of event	2009	532	Ref	1,322	Ref
	2010	634	Y	1,406	N
	2011	660	Y	1,374	N
	2012	731	Y	1,495	N
	2013	637	Y	1,411	N
Health authority/ Country	West Midlands	281	Ref	641	Ref
	East Midlands	90	N	210	N
	East of England	232	N	421	N
	London	196	N	481	N
	North East	108	N	206	N
	North West	332	N	776	N
	South Central	470	N	903	N
	South East Coast	287	N	584	N
	South West	390	N	927	N
	Yorkshire & Humber	69	N	152	N

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Predictor variable		Eligible for anticoagulant drugs: Total	Eligible for anticoagulant drugs: Included in final regression model?	Eligible for antihypertensive drugs: Total	Eligible for antihypertensive drugs: Included in final regression model?
Health authority/ Country	Northern Ireland	153	N	259	N
	Scotland	393	N	952	N
	Wales	185	N	464	N
	Missing	8*	N	32	N
Number of comorbidities†	0	0	N	364	Y
	1	136		1,230	
	2	535		1,872	
	3	830		1,649	
	4	739		1,036	
	5	477		501	
	6	287		252	
	7	137		73	
	8+	53		31	
Atrial fibrillation	N	0*	Ref	6,085	Ref
	Y	3,194	N	923	Y
Asthma	N	2,874	Ref	6,272	Ref
	Y	320	N	736	Y
Cancer	N	2,774	Ref	6,212	Ref
	Y	420	N	796	Y
CHD	N	2,111	Ref	4,985	Ref
	Y	1,083	N	2,023	Y

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		Eligible for anticoagulant drugs		Eligible for antihypertensive drugs	
Predictor variable		**Total**	**Included in final regression model?**	**Total**	**Included in final regression model?**
CKD	N	2,037	Ref	4,665	Ref
	Y	1,157	N	2,343	Y
COPD	N	2,885	Ref	6,461	Ref
	Y	309	N	547	N
Dementia	N	2,981	Ref	6,782	Ref
	Y	213	Y	226	Y
Depression	N	2,581	Ref	5,595	Ref
	Y	613	N	1,413	N
Diabetes	N	2,536	Ref	5,212	Ref
	Y	658	Y	1,796	Y
Epilepsy	N	3,147	Ref	6,891	Ref
	Y	47	N	117	N
Heart failure	N	2,543	Ref	6,571	Ref
	Y	651	Y	437	Y
Hypertension	N	897	Ref	1,767	Ref
	Y	2,297	N	5,241	Y
Hypothyroidism	N	2,754	Ref	6,253	Ref
	Y	440	N	755	Y
Learning disability*	N	3,188	Ref	6,992	Ref
	Y	6	N	16	N
Osteoporosis	N	2,822	Ref	6,430	Ref
	Y	372	N	578	N

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Predictor variable		Eligible for anticoagulant drugs: Total	Eligible for anticoagulant drugs: Included in final regression model?	Eligible for antihypertensive drugs: Total	Eligible for antihypertensive drugs: Included in final regression model?
PAD	N	2,978	Ref	6,432	Ref
	Y	216	N	576	Y
Palliative care	N	3,142	Ref	6,941	Ref
	Y	52	N	67	N
Psychosis	N	3,164	Ref	6,912	Ref
	Y	30	N	96	N
Rheumatoid arthritis	N	3,114	Ref	6,838	Ref
	Y	80	N	170	N

‡Categories combined

*Not included in regression model as too few events

† Continuous variable

BMI: Body Mass Index, CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, N: No, PAD: Peripheral Artery Disease, Ref: Reference category, Y: Yes

Exploratory analysis

Methods

Exploratory analyses investigated the effects of duration of registration and consultation frequency in the year prior to stroke/TIA. The impact of CHADS2 score on proportion of missed opportunities for anticoagulant prescribing was explored to investigate if level of risk was predictive of prescribing. The most recent UK atrial fibrillation guidelines recommend use of the CHA_2DS_2-VASc score to estimate stroke risk in patients with atrial fibrillation.[1] Therefore, sensitivity analysis investigated the impact of using this score to identify patients eligible for anticoagulants to reflect the updated guidelines. The difference between CHADS2 and CHA_2DS_2-VASc scores are presented in Table S3. The proportion of patients prescribed aspirin rather than anticoagulants was calculated. The impact of allowing a prescription of aspirin in patients with a CHADS2 score of 1 was explored in accordance with the 2006 atrial fibrillation guidelines.[2]

Supplementary Table S3: Comparison between the CHADS2 and CHA_2DS_2-VASc stroke risk scores.

CHADS2		CHA2DS2-VASc	
Variables	**Score**	**Variables**	**Score**
Congestive heart failure	1	Congestive heart failure	1
Hypertension	1	Hypertension	1
Age ≥75 years	1	Age ≥75 years	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke or TIA	2	Stroke or TIA	2
		Vascular disease	1
		Age 65-74 years	1
		Sex: female	1

Separate analyses were conducted for patients eligible for antihypertensive drugs because of high BP (≥160/100mmHg) or moderately high BP (≥140/100mmHg) with high cardiovascular disease (CVD) risk respectively. To reflect updated guideline recommendations where the QRISK2 CVD risk score has been recommended over the Framingham risk score,[2] QRISK2-2014 was used in exploratory analysis to calculate CVD risk. The difference in variables included in the Framingham and QRISK2-2014 equations are presented in Table S4. In addition, the influence of the individual elements of the high CVD risk definition (CHD, CKD, PAD, diabetes mellitus and ≥40 years or 10-year CVD risk ≥20%) were analysed.

Supplementary Table S4: Variables included in Framingham and QRISK2-2014 equations.

Variable	Framingham	QRISK2-2014
Age	✓	✓
Sex	✓	✓
Ethnicity		✓
BMI		✓
Deprivation score		✓
Systolic blood pressure	✓	✓
Total cholesterol	✓	✓
HDL cholesterol	✓	✓
Family history of CHD/Stroke		✓
Smoking status	✓	✓
Treated hypertension		✓
Diabetes	✓	✓
ECG-LVH	✓	
Atrial fibrillation		✓
Rheumatoid arthritis		✓
Chronic kidney disease		✓

Results

Anticoagulant prescribing

Exploratory analysis investigated the impact of using CHA_2DS_2-VASc to calculate stroke risk as recommended in the most recent atrial fibrillation guidelines published in 2014.[1] Using this stroke-risk score, the number of patients eligible for anticoagulant therapy increased by 280 and the proportion of missed opportunities became 50% (1,738/3,474). We investigated the proportion of missed opportunities by CHADS2 score and observed a general decrease in missed opportunities as CHADS2 score increased; however, the sample size was very small for the higher scores (Table S5). When entered into the regression model, duration of registration was not associated with anticoagulant drug prescribing; however frequency of consultations in the year prior to stroke or TIA was associated with a decrease in missed opportunities (OR 0.97 [per unit increase]; 95% CI 0.96, 0.98, P<0.01). Aspirin was prescribed in 71% (1,168/1,647) of patients with a missed opportunity for anticoagulant drug prescribing. Allowing patients with a CHADS2 score of 1 to be prescribed aspirin or anticoagulant drugs reduced the proportion of missed opportunities to 40% (1,277/3,194). Aspirin was still inappropriately prescribed in 62% (798/1,277) of patients with a missed opportunity under this definition (i.e. patients with CHADS2 ≥2).

Supplementary Table S5: CHADS2 score and the proportion of atrial fibrillation patients with a missed opportunity for prescription of anticoagulant drugs prior to stroke or transient ischaemic attack (TIA).

CHADS2 score	Missed opportunities (%)
1 (n= 986)	525 (53.2)
2 (n=1,431)	755 (52.8)
3 (n= 489)	226 (46.2)
4 (n= 226)	114 (50.4)
5 (n= 55)	25 (45.5)
6 (n= 7)	2 (28.6)

Antihypertensive prescribing

Missed opportunities for antihypertensive drug prescribing were recorded in 27% (540/2,038) of patients with high BP and 24% (1,484/6,272) of patients with moderately high BP and at high CVD risk (Table S6). Variables associated with having a missed opportunity for antihypertensive drug prescribing are presented in Tables S7 and S8 for patients eligible because of high BP or moderately high BP with high CVD risk, respectively.

Supplementary Table S6: Proportion of stroke and transient ischaemic attack (TIA) patients with a prior missed opportunity for antihypertensive drug prescribing in eligible patients (either BP ≥160/100mmHg or ≥140/90mmHg in patients at high cardiovascular disease (CVD) risk).

	Proportion of missed opportunities (frequency)	
	Untreated BP ≥160/100mmHg	**Untreated BP ≥140/90mmHg & high CVD risk**
Stroke	28.3 (348/1,232)	23.8 (802/3,376)
TIA	23.7 (154/649)	22.4 (444/1,984)
Stroke with previous TIA	24.2 (38/157)	26.1 (238/912)
Total	26.5 (540/2,038)	23.7 (1,484/6,272)

BP: Blood Pressure, CVD: Cardiovascular Disease, TIA: Transient Ischaemic Attack

Supplementary Table S7: Adjusted* odds ratios for effects of patient and demographic characteristics on having a missed opportunity for prescription of antihypertensive drugs prior to stroke or transient ischaemic attack (TIA) in patients with high BP (≥160/100mmHg).

		Odds Ratio	95% CI	P Value
Age	<45	1.75	0.82, 3.70	0.15
	45-49	1.40	0.72, 2.73	0.32
	50-54	1.61	0.90, 2.90	0.11
	55-59	2.12	1.27, 3.53	<0.01
	60-64	0.92	0.55, 1.52	0.74
	65-69	1.32	0.82, 2.12	0.26
	70-74	1.04	0.68, 1.59	0.86
	75-79	1.00		
	80-84	0.96	0.62, 1.50	0.87
	85-89	1.25	0.82, 1.91	0.30
	90-94	1.62	0.97, 2.72	0.07
	>95	5.23	2.39, 11.46	<0.01
Sex	Male	1.00		
	Female	0.85	0.67, 1.07	0.17
Rurality	Rural	1.00		
	Urban	1.32	1.04, 1.67	0.02
Comorbidities	CKD	0.72	0.51, 0.99	0.05
	Hypertension	0.14	0.10, 0.18	<0.01
	Atrial fibrillation	0.56	0.36, 0.86	0.01
	Diabetes	0.42	0.29, 0.62	<0.01
	CHD	0.49	0.34, 0.71	<0.01
	Dementia	2.39	1.24, 4.60	0.01

*Each odds ratio is adjusted for the other variables in the table.
CHD: Coronary Heart Disease, CI: Confidence Interval CKD: Chronic Kidney Disease

Supplementary Table S8: Adjusted* odds ratios for effects of patient and demographic characteristics on having a missed opportunity for prescription of antihypertensive drugs prior to stroke or transient ischaemic attack (TIA) in patients with moderately high BP (≥140/90mmHg) and high CVD risk.

		Odds Ratio	95% CI	P Value
Age	<45	1.81	0.70, 4.70	0.22
	45-49	1.54	0.83, 2.87	0.17
	50-54	1.62	1.07, 2.44	0.02
	55-59	1.53	1.10, 2.15	0.01
	60-64	1.18	0.87, 1.60	0.28
	65-69	1.30	0.98, 1.72	0.07
	70-74	1.17	0.92, 1.50	0.21
	75-79	1.00		
	80-84	0.95	0.74, 1.22	0.69
	85-89	1.27	0.95, 1.70	0.11
	90-94	1.68	1.21, 2.33	<0.01
	>95	3.23	1.86, 5.60	<0.01
Sex	Male	1.00		
	Female	0.87	0.75, 1.01	0.07
Comorbidities	Diabetes	0.46	0.38, 0.56	<0.01
	CHD	0.29	0.24, 0.36	<0.01
	Hypertension	0.10	0.09, 0.12	<0.01
	Heart failure	0.60	0.40, 0.90	0.01
	CKD	0.53	0.44, 0.65	<0.01
	PAD	0.68	0.53, 0.89	0.01
	AF	0.38	0.29, 0.50	<0.01
	Dementia	2.01	1.41, 2.87	<0.01
Multimorbidity	One unit increase	1.17	1.08, 1.27	<0.01
Lifestyle intervention	Weight	0.62	0.46, 0.82	<0.01

*Each odds ratio is adjusted for the other variables in the table.
AF: Atrial Fibrillation, CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, PAD: Peripheral Artery Disease

When entered into the regression model, duration of registration was not associated with antihypertensive drug prescribing; however frequency of consultations in the year prior to stroke or TIA was associated with a decrease in missed opportunities (OR 0.98 [per unit increase]; 95% CI 0.98, 0.99, P<0.01). The most recent guidelines, released 2014, regarding estimation of CVD risk recommend the use of QRISK2 over the Framingham risk equation.[3] When QRISK2-2014 was used to calculate 10-year CVD risk ≥20%, the number of patients eligible for antihypertensive drugs (moderately high BP with high CVD risk) increased to 7,759; the proportion of missed opportunities was similar 24.6% (1,912/7,759).

For patients eligible for antihypertensive drugs because of moderately high BP and high CVD risk (n=6,272), the impact of definitions of 'high CVD risk' was investigated (n=1,647). A 10-year Framingham risk of ≥20% was associated with increased odds of having a missed opportunities (OR 1.5; 95% CI 1.2, 1.9, P<0.01). The other components of the definition of high CVD risk (coronary heart disease, chronic kidney disease, peripheral artery disease and diabetes) were all protective in the regression model. Therefore, we entered the variable 'no high risk comorbidities' (i.e. no CHD, CKD, PAD, or diabetes) (n=1,076) into the regression which gave an odds ratio of 1.5 (95% CI 1.2, 1.9, P<0.01).

References

1. National Institute for Health and Care Excellence (NICE). Atrial fibrillation: the management of atrial fibrillation. Clinical Guideline 180. 2014.
2. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: the management of atrial fibrillation. Clinical Guideline 36. 2006.
3. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline 181. 2014.

Supplementary Table S9: Number of strokes that potentially could be prevented through prescribing anticoagulant drugs.

Age band	Number of strokes in the THIN sample		Estimated number of strokes that could be prevented in the THIN sample		Proportion of strokes that could be prevented in the THIN sample (%)		Number of strokes per year in UK		Estimated number of strokes that could be prevented in UK	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<35	115	124	0	0	0%	0%	0	0	0	0
35-44	301	258	0	0	0%	0%	1,469	896	0	0
45-54	841	652	1	1	0%	0%	2,453	1,097	4	3
55-64	1,669	1,034	7	3	0%	0%	6,712	4,413	28	14
65-74	2,462	1,903	20	21	1%	1%	18,817	12,744	154	140
75-84	2,613	2,925	70	102	3%	3%	14,656	20,001	394	698
≥85	1,232	2,468	58	151	5%	6%	9,747	16,677	460	1,022
All ages	18,597		436		2.3%		109,682		2,918	
<85	14,658		227		1.5%		83,258		1,435	

Supplementary Table S10: Number of strokes that potentially could be prevented through prescribing antihypertensive drugs.

Age band	Number of strokes in the THIN sample		Estimated number of strokes that could be prevented in the THIN sample		Proportion of strokes that could be prevented in the THIN sample (%)		Number of strokes per year in UK		Estimated number of strokes that could be prevented in UK	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<35	115	124	0	1	0%	1%	0	0	0	0
35-44	301	258	6	3	2%	1%	1,469	896	27	12
45-54	841	652	23	11	3%	2%	2,453	1,097	67	18
55-64	1,669	1,034	63	21	4%	2%	6,712	4,413	253	90
65-74	2,462	1,903	107	55	4%	3%	18,817	12,744	815	371
75-84	2,613	2,925	55	64	2%	2%	14,656	20,001	311	435
≥85	1,232	2,468	36	68	3%	3%	9,747	16,677	282	458
All ages	18,597		512		2.8%		10,9682		3,137	
<85	14,658		408		2.8%		83,258		2,398	

Supplementary Table S11: Combinations of stroke and TIA prevention drugs clinically indicated.

Number of prevention drug classes clinically indicated	Prevention drugs clinically indicated	Number of strokes and TIAs with prevention drugs clinically indicated (n (%))
0	None	11,363 (39.1)
1	Lipid lowering drugs	8,365 (28.8)
	Anticoagulants drugs	918 (3.2)
	Antihypertensive drugs	670 (2.3)
2	Lipid lowering and anticoagulant drugs	1,389 (4.8)
	Lipid lowering and antihypertensive drugs	5,451 (18.8)
	Anticoagulant and antihypertensive drugs	64 (0.2)
3	Lipid lowering, anticoagulant and antihypertensive drugs	823 (2.8)

Supplementary Table S12: Combinations of missed opportunities for different stroke and TIA prevention drugs.

Prevention drugs clinically indicated	Number of missed opportunities	Missed opportunities	Number of strokes and TIAs with missed opportunities (n)
Lipid lowering drugs only	0	None	4,231
	1	Lipid lowering drugs	4,134
Anticoagulants drugs only	0	None	408
	1	Anticoagulant drugs	510
Antihypertensive drugs only	0	None	427
	1	Antihypertensive drugs	243
Lipid lowering and anticoagulant drugs	0	None	429
	2	Both drugs missed	320
	1	Lipid lowering drugs only	286
		Anticoagulant drugs only	354
Lipid lowering and antihypertensive drugs	0	None	2,369
	2	Both drugs missed	1,036
	1	Lipid lowering drugs only	1,684
		Antihypertensive drugs only	362
Anticoagulant and antihypertensive drugs	0	None	25
	2	Both drugs missed	10
	1	Anticoagulants drugs only	27
		Anticoagulant drugs only	2
Lipid lowering, anticoagulant and antihypertensive drugs	0	None	212
	1	Lipid lowering drugs only	145
		Anticoagulant drugs only	209
		Antihypertensive drugs only	13
	2	Lipid lowering and anticoagulant drugs	170
		Lipid lowering and antihypertensive drugs	27
		Anticoagulant and antihypertensive drugs	13
	3	All three drugs missed	34

Appendix 4: Residual impairments after TIA: Systematic review protocol

A4.1 Supplementary material

Supplementary material published online for Publication 2 (presented as published):

Moran GM, Fletcher B, Calvert M, Feltham MG, Sackley C, Marshall T. A systematic review investigating fatigue, psychological and cognitive impairment following TIA and minor stroke: protocol paper. *Systematic Reviews* 2013; 2: 72. doi: 10.1186/2046-4053-2-72

Appendix: Search strategy for MEDLINE (via Ovid) 1993 to April 2013.

1. transient isch?emic attack$.mp. or exp Ischemic Attack, Transient/
2. TIA.mp.
3. TIAs.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. (transient adj (brain isch?emia$ or cerebral isch?emia$ or CVA$ or cerebral vasc$ or cerebro vasc$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. mini stroke.mp.
6. minor stroke$.mp.
7. mild stroke$.mp.
8. NDS.mp.
9. non$disabling stroke$.mp.
10. (minor adj (cerebrovasc$ accident$ or cerebrovasc$ stroke$ or CVA$ or brain isch?emia$ or cerebral stroke$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. Non$severe stroke$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. RIND or reversible isch?emic neurologic$ deficit$
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. "quality of life".mp. or exp "Quality of Life"/
15. exp Anxiety/ or exp Anti-Anxiety Agents/ or exp Anxiety Disorders/ or anxiety.mp.
16. exp Stress Disorders, Post-Traumatic/ or stress disorder$.mp.
17. (anxiety disorder$ or agoraphobia$ or obsessive$compulsive disorder$ or panic disorder$ or phobic disorder$ or distress$ or panic$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
18. (feel$ adj3 (apprehens$ or dread or disaster$ or fear$ or worry or worried or terror)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19. exp Depression/ or depress$.mp.
20. exp Antidepressive Agents/ or antidepress$.mp. or exp Depressive Disorder/
21. mood disorder$.mp. or exp Mood Disorders/

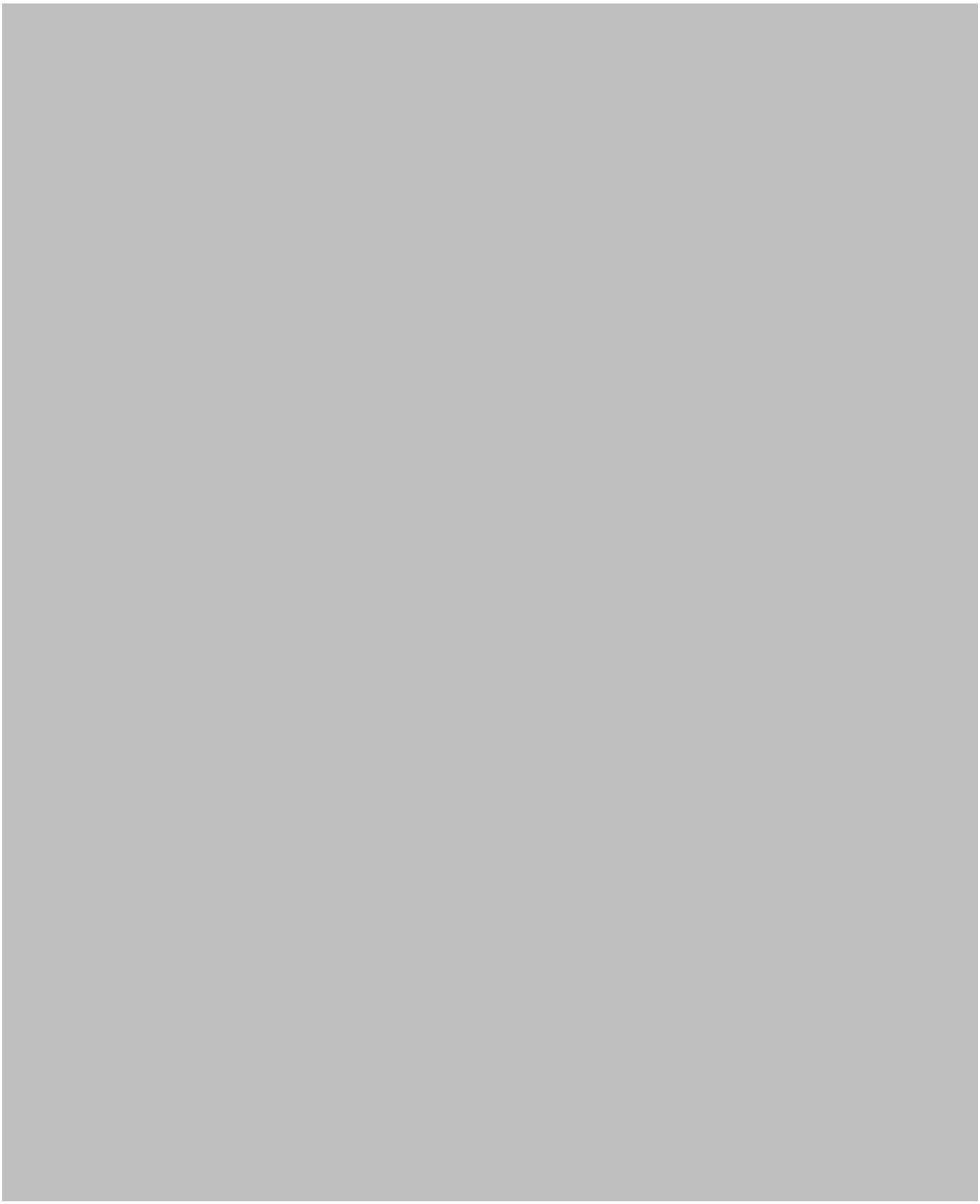
22. posttraumatic stress disorder$.mp.
23. post traumatic stress disorder$.mp.
24. PTSD.mp.
25. (flashback$ or avoidance$ or avoid$ or re$experience).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
26. exp Cognition Disorders/ or cognit$ disorder$.mp. or exp Cognition/
27. exp Attention/ or cognit$ impair$.mp.
28. (cognition or orientation or attention or perception or mental processing or problem solving or memory).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
29. exp Fatigue/ or exp Fatigue Syndrome, Chronic/ or fatigue.mp.
30. CFS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
31. (fatigue adj (chronic or syndrome$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
32. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 13 and 32
34. limit 33 to (humans and yr="1993 -Current")

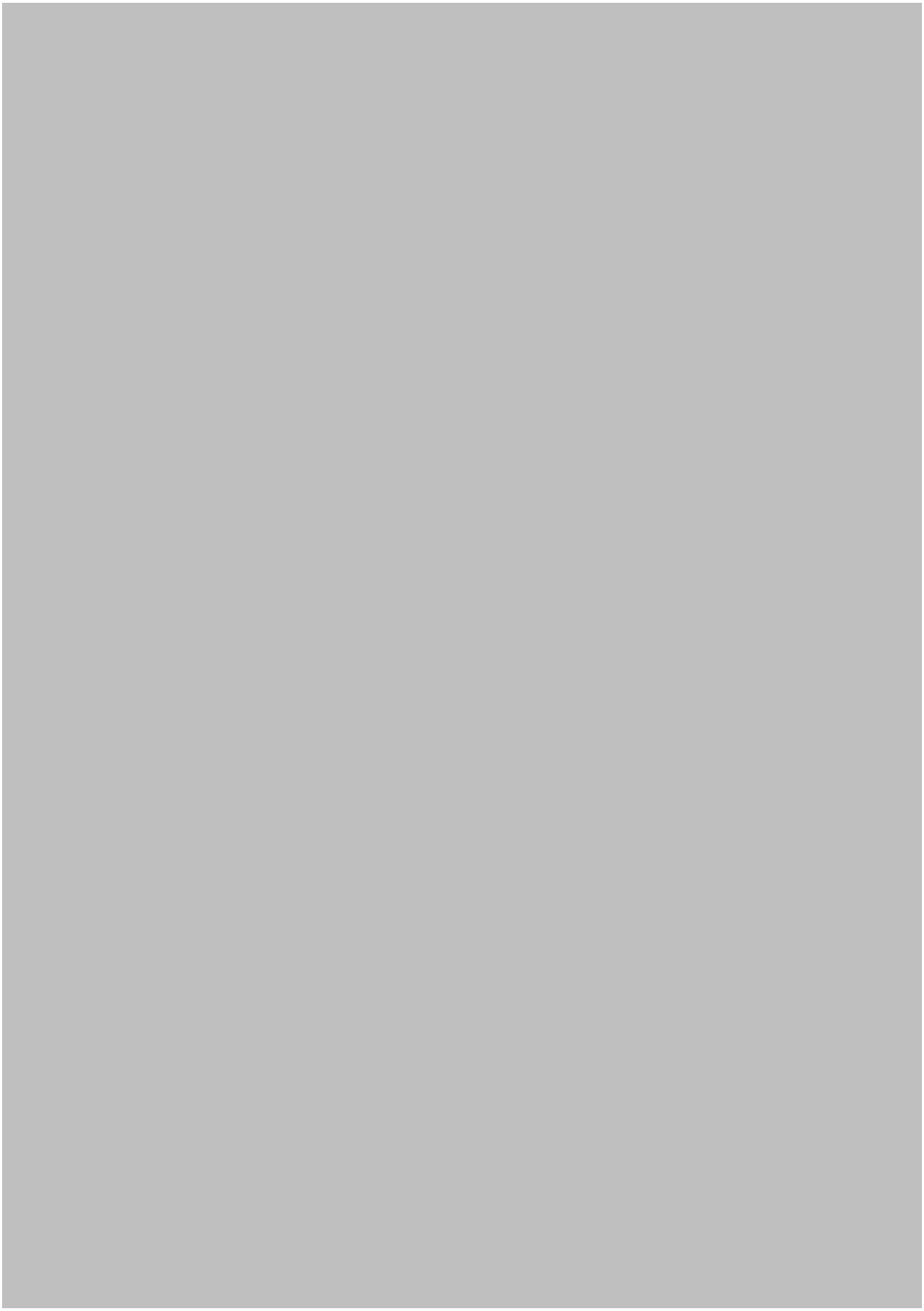
Appendix 5: Residual impairments after TIA: Systematic review results

A5.1 Supplementary material

Supplementary material published online for Publication 3 (presented as published):

Moran GM, Fletcher B, Feltham MG, Calvert M, Sackley C, Marshall T. Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: a systematic review. *European Journal of Neurology* 2014 21(10):1258-67. doi: 10.1111/ene.12469





A5.2: Criteria used by studies included in the systematic review to define TIA and minor stroke

Diagnosis	Definition	Number of studies
TIA	WHO criteria (a focal neurological deficit of sudden onset with a vascular cause, with resolution of focal symptoms within 24 hours)	5
	Diagnosis confirmed by neurologist/ stroke physician (criteria not defined)	5
	Diagnosis at discharge (criteria not defined)	1
	Symptoms of retinal or cerebral TIA	1
	Self-reported ("Have you ever experienced transient speech dysfunction, numbness/tingling, weakness/paralysis and resolved within 24 hours which people call TIA or 'mini stroke'?")	1
	Unclear	8
Minor stroke	SSS >45	1
	Barthel index 50-100 (one week after stroke onset)	1
	Diagnosis confirmed by neurologist/ stroke physician (criteria not defined)	2
	Direct discharge home within 3 weeks post-stroke	1
	Modified Rankin grade of ≥3	2
	NIHSS ≤3 at discharge	1
	NIHSS ≤5 at discharge	2
	NIHSS <6 at discharge	1
	NIHSS ≤6 at discharge from hospital and ≤3 after 6m, Rankin score <1 at 6m	1
	Pts showing no neurological symptoms or mild non-disabling symptoms (standard neurological examination) 3 weeks post stroke	1
	Self-reported and verified against mobility, self-care, pain, usual activities and depression scores	1
	able to walk 10m independently, living at home, independent in activities of daily living	1
	Unclear	2

NIHSS: National Institutes of Health Stroke Scale; SSS: Scandinavian Stroke Scale; TIA: Transient Ischaemic Attack; WHO: World Health Organisation

Appendix 6: Residual impairments after TIA: Retrospective cohort study protocol

A6.1 Supplementary material

Supplementary material published online for Publication 4 (presented as published):

Moran GM, Calvert M, Feltham MG, Ryan R, Marshall T. A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper. *BMJ Open* 2015;5:e008149. doi:10.1136/bmjopen-2015-008149

Appendix 1: Read and drug codes for: (a) fatigue, (b) anxiety, (c) depression, (d) anxiety and depression (e) post-traumatic stress disorder (PTSD) and (f) cognitive impairment.

a) Fatigue

Read code	Description
168..00	Tiredness symptom
168..11	Fatigue – symptom
168..12	Lethargy – symptom
168..13	Malaise – symptom
168..14	C/O "muzzy head"
1682.00	Fatigue
1683.00	Tired all the time
1683.11	C/O - "tired all the time"
1684.00	Malaise/lethargy
1684.11	C/O - debility – malaise
1684.13	C/O - postviral syndrome
1688.00	Exhaustion
168Z.00	Tiredness symptom NOS
1B3..12	Weakness symptoms
1B32.00	Weakness present
8HkW.00	Referral to chronic fatigue syndrome specialist team
8HlL.00	Referral for chronic fatigue syndrome activity management
8Q1..00	Activity management for chronic fatigue syndrome
E205.00	Neurasthenia - nervous debility
E205.11	Nervous exhaustion
E205.12	Tired all the time
Eu46011	[X]Fatigue syndrome
F286.00	Chronic fatigue syndrome
F286.11	CFS - chronic fatigue syndrome
F286.12	Postviral fatigue syndrome
F286.13	PVFS - post viral fatigue syndrome
F286.14	Post-viral fatigue syndrome
F286.15	Myalgic encephalomyelitis
F286.16	ME - myalgic encephalomyelitis
F286000	Mild chronic fatigue syndrome
F286100	Moderate chronic fatigue syndrome
F286200	Severe chronic fatigue syndrome
R007.00	[D]Malaise and fatigue
R007000	[D]Malaise
R007100	[D]Fatigue
R007200	[D]Asthenia NOS

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Read code	Description
R007211	[D]General weakness
R007300	[D]Lethargy
R007400	[D]Postviral (asthenic) syndrome
R007411	[D]Post viral debility
R007500	[D]Tiredness
R007600	[D]Post polio exhaustion
R007z00	[D]Malaise and fatigue NOS
R007z11	[D]Lassitude

CFS Chronic fatigue syndrome; ME Myalgic encephalomyelitis; NOS Not otherwise specified; PVFS Post viral fatigue syndrome; C/O Complaining of; [D] Diagnosis; [X] Cross referenced to specific ICD-10 codes (READ 2 relates to ICD-9)

b) Anxiety

Read code	Description
1466.00	H/O: Anxiety state
16ZB100	Feeling low or worried
173f.00	Anxiety about breathlessness
1B1H.00	Frightened
1B1H.11	Fear
1B1H.12	Apprehension
1B1T.00	Feeling stressed
1B1V.00	C/O - Panic attack
1BK..00	Worried
1P3..00	Compulsive behaviour
2253.00	O/E – Distressed
225J.00	O/E - Panic attack
225K.00	O/E - Fearful mood
67J..00	Stress counselling
8G94.00	Anxiety management training
8HHp.00	Referral for guided self-help for anxiety
9N54.00	Encounter for fear
E200.00	Anxiety states
E200000	Anxiety state unspecified
E200100	Panic disorder
E200111	Panic attack
E200200	Generalised anxiety disorder
E200400	Chronic anxiety
E200500	Recurrent anxiety
E200z00	Anxiety state NOS
E202.00	Phobic disorders
E202.11	Social phobic disorders
E202.12	Phobic anxiety
E202000	Phobia unspecified
E202100	Agoraphobia with panic attacks
E202200	Agoraphobia without mention of panic attacks
E202D00	Fear of death
E203.00	Obsessive-compulsive disorders
E203.11	Anancastic neurosis
E203000	Compulsive neurosis
E203100	Obsessional neurosis
E203z00	Obsessive-compulsive disorder NOS
E214.00	Compulsive personality disorders
E214000	Anankastic personality
E214100	Obsessional personality

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Read code	Description
E214z00	Compulsive personality disorder NOS
E28..00	Acute reaction to stress
E280.00	Acute panic state due to acute stress reaction
E281.00	Acute fugue state due to acute stress reaction
E282.00	Acute stupor state due to acute stress reaction
E283.00	Other acute stress reactions
E283z00	Other acute stress reaction NOS
E284.00	Stress reaction causing mixed disturbance of emotion/conduct
E28z.00	Acute stress reaction NOS
Eu05400	[X]Organic anxiety disorder
Eu4..00	[X]Neurotic, stress - related and somoform disorders
Eu40.00	[X]Phobic anxiety disorders
Eu40000	[X]Agoraphobia
Eu40011	[X]Agoraphobia without history of panic disorder
Eu40012	[X]Panic disorder with agoraphobia
Eu40100	[X]Social phobias
Eu40112	Social neurosis
Eu41.00	[X]Other anxiety disorders
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]
Eu41011	[X]Panic attack
Eu41012	[X]Panic state
Eu41100	[X]Generalized anxiety disorder
Eu41111	[X]Anxiety neurosis
Eu41112	[X]Anxiety reaction
Eu41113	[X]Anxiety state
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41y00	[X]Other specified anxiety disorders
Eu41y11	[X]Anxiety hysteria
Eu41z00	[X]Anxiety disorder, unspecified
Eu41z11	[X]Anxiety NOS
Eu42.00	[X]Obsessive - compulsive disorder
Eu42.11	[X]Anankastic neurosis
Eu42.12	[X]Obsessive-compulsive neurosis
Eu42100	[X]Predominantly compulsive acts [obsessional rituals]
Eu42y00	[X]Other obsessive-compulsive disorders
Eu42z00	[X]Obsessive-compulsive disorder, unspecified
Eu43.00	[X]Reaction to severe stress, and adjustment disorders
Eu43000	[X]Acute stress reaction
Eu43012	[X]Acute reaction to stress
Eu43y00	[X]Other reactions to severe stress
Eu43z00	[X]Reaction to severe stress, unspecified
Eu51511	[X]Dream anxiety disorder

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Read code	Description
Eu60511	[X]Compulsive personality disorder
Eu60513	[X]Obsessive-compulsive personality disorder
Eu63011	[X]Compulsive gambling
Z4I7.00	Acknowledging anxiety
Z4I7100	Recognising anxiety
Z4I7200	Alleviating anxiety
Z4I7211	Reducing anxiety
Z4L1.00	Anxiety counselling
Z522600	Flooding - obsessional compulsive disorder

C/O Complaining of; O/E On Examination; NOS Not otherwise specified; [X] Cross referenced to specific ICD-10 codes (READ 2 relates to ICD-9)

c) Depression

Read code	Description
13Y3.00	Manic-depression association member
1465.00	H/O: Depression
146D.00	H/O: Manic depressive disorder
1B17.00	Depressed
1B17.11	C/O - Feeling depressed
1B1U.00	Symptoms of depression
1B1U.11	Depressive symptoms
1BT..00	Depressed mood
1BT..11	Low mood
1BT..12	Sad mood
1JJ..00	Suspected depression
2257.00	O/E – Depressed
6659000	Antidepressant drug treatment started
8BK0.00	Depression management programme
8CAa.00	Patient given advice about management of depression
8HHq.00	Referral for guided self-help for depression
9H90.00	Depression annual review
9H91.00	Depression medication review
9H92.00	Depression interim review
9HA0.00	On depression register
9hC..00	Exception reporting: depression quality indicators
9hC0.00	Excepted from depression quality indicators: patient unsuitable
9hC1.00	Excepted from depression quality indicators: informed dissent
9k4..00	Depression - enhanced services administration
9k40.00	Depression - enhanced service completed
9kQ..00	On full dose long term treatment depression
9kQ..11	On full dose long term treatment for depression
9Ov..00	Depression monitoring administration
9Ov0.00	Depression monitoring first letter
9Ov1.00	Depression monitoring second letter
9Ov2.00	Depression monitoring third letter
9Ov3.00	Depression monitoring verbal invite
9Ov4.00	Depression monitoring telephone invite
E001300	Presenile dementia with depression
E002.00	Senile dementia with depressive or paranoid features
E002100	Senile dementia with depression
E002z00	Senile dementia with depressive or paranoid features NOS
E004300	Arteriosclerotic dementia with depression
E03y200	Organic affective syndrome
E11..00	Affective psychoses

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Read code	Description
E11..11	Bipolar psychoses
E11..12	Depressive psychoses
E112.00	Single major depressive episode
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E112000	Single major depressive episode, unspecified
E112100	Single major depressive episode, mild
E112200	Single major depressive episode, moderate
E112300	Single major depressive episode, severe, without psychosis
E112400	Single major depressive episode, severe, with psychosis
E112500	Single major depressive episode, partial or unspecified remission
E112600	Single major depressive episode, in full remission
E112z00	Single major depressive episode NOS
E113.00	Recurrent major depressive episode
E113.11	Endogenous depression – recurrent
E113000	Recurrent major depressive episodes, unspecified
E113100	Recurrent major depressive episodes, mild
E113200	Recurrent major depressive episodes, moderate
E113300	Recurrent major depressive episodes, severe, no psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E113500	Recurrent major depressive episodes, partial/unspecified remission
E113600	Recurrent major depressive episodes, in full remission
E113700	Recurrent depression
E113z00	Recurrent major depressive episode NOS
E115.00	Bipolar affective disorder, currently depressed
E115.11	Manic-depressive - now depressed
E115000	Bipolar affective disorder, currently depressed, unspecified
E115100	Bipolar affective disorder, currently depressed, mild
E115200	Bipolar affective disorder, currently depressed, moderate
E115300	Bipolar affect disorder, now depressed, severe, no psychosis
E115400	Bipolar affect disorder, now depressed, severe with psychosis
E115500	Bipolar affect disorder, now depressed, part/unspecified remission
E115600	Bipolar affective disorder, now depressed, in full remission
E115z00	Bipolar affective disorder, currently depressed, NOS
E116.00	Mixed bipolar affective disorder
E116000	Mixed bipolar affective disorder, unspecified
E116100	Mixed bipolar affective disorder, mild
E116200	Mixed bipolar affective disorder, moderate
E116300	Mixed bipolar affective disorder, severe, without psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis

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Read code	Description
E116500	Mixed bipolar affective disorder, partial/unspecified remission
E116600	Mixed bipolar affective disorder, in full remission
E116z00	Mixed bipolar affective disorder, NOS
E117.00	Unspecified bipolar affective disorder
E117000	Unspecified bipolar affective disorder, unspecified
E117100	Unspecified bipolar affective disorder, mild
E117200	Unspecified bipolar affective disorder, moderate
E117300	Unspecified bipolar affective disorder, severe, no psychosis
E117400	Unspecified bipolar affective disorder, severe with psychosis
E117500	Unspecified bipolar affect disorder, partial/unspecified remission
E117600	Unspecified bipolar affective disorder, in full remission
E117z00	Unspecified bipolar affective disorder, NOS
E118.00	Seasonal affective disorder
E11y.00	Other and unspecified manic-depressive psychoses
E11y000	Unspecified manic-depressive psychoses
E11y200	Atypical depressive disorder
E11y300	Other mixed manic-depressive psychoses
E11yz00	Other and unspecified manic-depressive psychoses NOS
E11z.00	Other and unspecified affective psychoses
E11z000	Unspecified affective psychoses NOS
E11z100	Rebound mood swings
E11z200	Masked depression
E11zz00	Other affective psychosis NOS
E130.00	Reactive depressive psychosis
E130.11	Psychotic reactive depression
E135.00	Agitated depression
E204.00	Neurotic depression reactive type
E211.00	Affective personality disorder
E211000	Unspecified affective personality disorder
E211200	Depressive personality disorder
E290.00	Brief depressive reaction
E290z00	Brief depressive reaction NOS
E291.00	Prolonged depressive reaction
E292400	Adjustment reaction with anxious mood
E2B..00	Depressive disorder NEC
E2B0.00	Postviral depression
E2B1.00	Chronic depression
Eu05300	[X]Organic mood [affective] disorders
Eu06y11	[X]Right hemispheric organic affective disorder
Eu20400	[X]Post-schizophrenic depression
Eu3..00	[X]Mood - affective disorders
Eu31.00	[X]Bipolar affective disorder

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Read code	Description
Eu31.11	[X]Manic-depressive illness
Eu31.12	[X]Manic-depressive psychosis
Eu31.13	[X]Manic-depressive reaction
Eu31300	[X]Bipolar affective disorder cur epi mild or moderate depression
Eu31400	[X]Bipolar affective disorder, current episode sever depress, no psychotic symptoms
Eu31500	[X]Bipolar affective disorder cur epi severe depression with psychotic symptoms
Eu31600	[X]Bipolar affective disorder, current episode mixed
Eu31700	[X]Bipolar affective disorder, currently in remission
Eu31800	[X]Bipolar affective disorder type i
Eu31900	[X]Bipolar affective disorder type ii
Eu31911	[X]Bipolar ii disorder
Eu31y00	[X]Other bipolar affective disorders
Eu31y11	[X]Bipolar ii disorder
Eu31z00	[X]Bipolar affective disorder, unspecified
Eu32.00	[X]Depressive episode
Eu32.11	[X]Single episode of depressive reaction
Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32000	[X]Mild depressive episode
Eu32100	[X]Moderate depressive episode
Eu32200	[X]Severe depressive episode without psychotic symptoms
Eu32211	[X]Single episode agitated depression without psychotic symptoms
Eu32212	[X]Single episode major depression without psychotic symptoms
Eu32213	[X]Single episode vital depression without psychotic symptoms
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32313	[X]Single episode of psychotic depression
Eu32314	[X]Single episode of reactive depressive psychosis
Eu32400	[X]Mild depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32700	[X]Major depression, severe without psychotic symptoms
Eu32800	[X]Major depression, severe with psychotic symptoms
Eu32y00	[X]Other depressive episodes
Eu32y11	[X]Atypical depression
Eu32y12	[X]Single episode of masked depression NOS
Eu32z00	[X]Depressive episode, unspecified
Eu32z11	[X]Depression NOS
Eu32z12	[X]Depressive disorder NOS

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Read code	Description
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.00	[X]Recurrent depressive disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.14	[X]Seasonal depressive disorder
Eu33.15	[X]SAD - seasonal affective disorder
Eu33000	[X]Recurrent depressive disorder, current episode mild
Eu33100	[X]Recurrent depressive disorder, current episode moderate
Eu33200	[X]Recurrent depress disorder current episode severe without psychotic symptoms
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33213	[X]Manic-depress psychosis, depressed, no psychotic symptoms
Eu33214	[X]Vital depression, recurrent without psychotic symptoms
Eu33300	[X]Recurrent depress disorder cur epi severe with psychotic symptoms
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33312	[X]Manic-depress psychosis, depressed type + psychotic symptoms
Eu33313	[X]Recurrent severe episodes/major depression + psychotic symptom
Eu33314	[X]Recurrent severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu33400	[X]Recurrent depressive disorder, currently in remission
Eu33y00	[X]Other recurrent depressive disorders
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33z11	[X]Monopolar depression NOS
Eu34.00	[X]Persistent mood affective disorders
Eu34011	[X]Affective personality disorder
Eu34100	[X]Dysthymia
Eu34111	[X]Depressive neurosis
Eu34112	[X]Depressive personality disorder
Eu34113	[X]Neurotic depression
Eu34y00	[X]Other persistent mood affective disorders
Eu34z00	[X]Persistent mood affective disorder, unspecified
Eu3y.00	[X]Other mood affective disorders
Eu3y000	[X]Other single mood affective disorders
Eu3y011	[X]Mixed affective episode
Eu3y100	[X]Other recurrent mood affective disorders
Eu3y111	[X]Recurrent brief depressive episodes

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Read code	Description
Eu3yy00	[X]Other specified mood affective disorders
Eu3z.00	[X]Unspecified mood affective disorder
Eu3z.11	[X]Affective psychosis NOS
Eu92000	[X]Depressive conduct disorder
ZV11100	[V]Personal history of affective disorder
ZV11111	[V]Personal history of manic-depressive psychosis
ZV11112	[V]Personal history of manic-depressive psychosis

C/O Complaining of; H/O History of; O/E On Examination; NEC Not elsewhere classified; NOS Not otherwise specified; SAD Seasonal affective disorder; [V] Correspond to the ICD-9 chapter that allows the recording of supplementary factors influencing health status or contact with health services other than for illness; [X] Cross referenced to specific ICD-10 codes (READ 2 relates to ICD-9)

d) Depression and anxiety

Read code	Description
E200300	Anxiety with depression
Eu34114	[X]Persistent anxiety depression
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression

[X] Cross referenced to specific ICD-10 codes (READ 2 relates to ICD-9)

e) PTSD

Read code	Description
E28..11	Combat fatigue
E29y100	Other post-traumatic stress disorder
E2A2.11	Post-traumatic brain syndrome
Eu43013	[X]Combat fatigue
Eu43100	[X]Post - traumatic stress disorder
E283100	Acute posttrauma stress state

[X] Cross referenced to specific ICD-10 codes (READ 2 relates to ICD-9)

f) Cognitive impairment

Read code	Description
1B1A.00	Memory loss – amnesia
1B1A.11	Amnesia symptom
1B1A.12	Memory loss symptom
1B1A.13	Memory disturbance
1BR..00	Reduced concentration
1BR0.00	Reduced concentration span
1BR0.11	Short attention span
1BW..00	Poor concentration
1S21.00	Disturbance of memory for order of events
28E..00	Cognitive decline
28E0.00	Mild cognitive impairment
28E1.00	Moderate cognitive impairment
28E2.00	Severe cognitive impairment
3A10.00	Memory: own age not known
3A20.00	Memory: present time not known
3A30.00	Memory: present place not known
3A40.00	Memory: present year not known
3A50.00	Memory: own DOB not known
3A60.00	Memory: present month not known
3A70.00	Memory: important event not known
3A80.00	Memory: important person not known
3A91.00	Memory: count down unsuccessful
3AA1.00	Memory: address recall unsuccessful
3AE1.00	GDS level 2 - very mild cognitive decline
3AE2.00	GDS level 3 - mild cognitive decline
3AE3.00	GDS level 4 - moderate cognitive decline
3AE4.00	GDS level 5 - moderately severe cognitive decline
3AE5.00	GDS level 6 - severe cognitive decline
3AE6.00	GDS level 7 - very severe cognitive decline
Eu80100	[X]Expressive language disorder
Eu80200	[X]Receptive language disorder
F481J00	Visual disorientation syndrome
R00z011	[D]Memory deficit
R00zX00	[D]Disorientation, unspecified
Ryu5.00	[X]Symptoms/signs involving cognition, percept, emotion state & behaviour
Ryu5100	[X]Other & unspecified symptom/signs involving cognitive function/awareness
Ryu5700	[X]Disorientation, unspecified
Z73..00	Cognitive intervention strategies

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Read code	Description
Z7A1.00	Cognitive skills training
Z7A1100	Concentration skills training
Z7A1300	Memory skills training
Z7A1400	Attention training
Z7A1500	Memory retraining
Z7A1600	Orientation training
Z7A1700	Reality orientation
Z7A1711	RO - reality orientation
Z7A1712	Reality orientation approach
Z7A1A00	Executive functions training
Z7A2100	Strategy training for cognitive skills
Z7A2200	Strategy training for perceptual skills
Z7A2300	Strategy training for executive skills
Z7C1.00	Impaired cognition
Z7C2200	Unable to recognise sounds
Z7C2600	Unable to recognise surroundings
Z7C2700	Mistakes people's identity
Z7C2900	Does not recognise self
Z7C2A00	Does not recognise photographs of self
Z7C2B00	Does not recognise self in mirror
Z7C2D00	Unable to recognise parts of own body
Z7C2F00	Unable to recognise own fingers
Z7C2H00	Unable to recognise objects
Z7C2J00	Unable to recognise objects by touch
Z7C2L00	Unable to recognise objects by sight
Z7C2L11	Unable to recognise objects visually
Z7C2N00	Unable to recognise warning sounds
Z7C2P00	Unable to recognise faces
Z7C2R00	Unable to recognise faces by sight
Z7C2T00	Unable to recognise familiar people
Z7C3200	Unable to reason
Z7C3300	Difficulty reasoning
Z7C3500	Unable to use verbal reasoning
Z7C3600	Difficulty using verbal reasoning
Z7C3800	Unable to use arithmetic reasoning
Z7C3900	Difficulty using arithmetic reasoning
Z7C3B00	Unable to use visuospatial reasoning
Z7C3C00	Difficulty using visuospatial reasoning
Z7C4200	Unable to process information
Z7C4300	Difficulty processing information
Z7C4600	Unable to process information accurately
Z7C4700	Difficulty processing information accurately

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Read code	Description
Z7C4900	Unable to process information at normal speed
Z7C4A00	Difficulty processing information at normal speed
Z7C4C00	Unable to analyse information
Z7C4D00	Difficulty analysing information
Z7C5100	Unable to concentrate
Z7C5111	Lack of concentration
Z7C5300	Reduced concentration span
Z7C5311	Reduced attention span
Z7C5312	Short attention span
Z7C5313	Short concentration span
Z7C6200	Unable to tell the time
Z7C6300	Difficulty telling the time
Z7C7200	Unable to write
Z7C7300	Difficulty writing
Z7C8200	Unable to read
Z7C8300	Difficulty reading
Z7C9200	Unable to perform logical sequencing
Z7C9300	Difficulty performing logical sequencing
Z7CC311	Orientation confused
Z7CC312	Orientation poor
Z7CC600	Disorientation for person
Z7CC700	Spatial disorientation
Z7CC800	Right-left disorientation
Z7CE400	Memory disturbance (& amnesia (& symptom))
Z7CE412	Memory loss symptom
Z7CE413	Memory loss – amnesia
Z7CE414	Memory disturbance
Z7CE415	Loss of memory
Z7CE611	Memory loss
Z7CE612	Memory gone
Z7CE614	Memory loss – amnesia
Z7CE615	Loss of memory
Z7CE616	LOM - loss of memory
Z7CEA11	Impairment of working memory
Z7CEA13	Impairment of primary memory
Z7CEB11	Loss of memory for remote events
Z7CEB12	Poor memory for remote events
Z7CEC11	Loss of memory for recent events
Z7CEC12	No memory for recent events
Z7CEF00	Temporary loss of memory
Z7CEG00	Transient memory loss
Z7CEH00	Memory impairment

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Read code	Description
Z7CEH11	Memory dysfunction
Z7CEH12	Memory deficit
Z7CEH13	Bad memory
Z7CEH14	Memory problem
Z7CEH15	Poor memory
Z7CEJ00	Memory lapses
Z7CEK00	Minor memory lapses
Z7CEL00	Mild memory disturbance
Z7CEM00	Distortion of memory
Z7CEN11	Invents experiences to compensate for loss of memory
Z7CF800	Poor short-term memory
Z7CF811	Short-term memory loss
Z7CFO00	Poor long-term memory
Z7CFO11	Long-term memory loss
Z7CFw00	Memory aided by use of diary
Z7CFx00	Memory aided by use of labels
Z7CFz00	Memory aided by use of lists
Z7CGP00	Delayed verbal memory
Z7CI100	Difficulty making plans
Z7CI200	Difficulty making decisions
Z7CI500	Unable to use decision-making strategies
Z7CI600	Difficulty using decision-making strategies
Z7CI900	Unable to make considered choices
Z7CIA00	Difficulty making considered choices
Z7CJ100	Difficulty solving problems

DOB Date of birth; GDS Global deterioration scale ; LOM Loss of memory; RO Reality orientation; [D] Diagnosis; [X] Cross referenced to specific ICD-10 codes (READ 2 relates to ICD-9)

Appendix 2: Read codes for (a) transient ischaemic attack (TIA) and (b) stroke.

a) TIA Read codes

Read code	Description
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G656.00	Vertebrobasilar insufficiency
G657.00	Carotid territory transient ischaemic attack
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
Fyu5500	[X]Other transient cerebral ischaemic attacks+related syndromes

b) Stroke Read codes

Read code	Description
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrhage from intracranial artery, unspecified
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accident due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
G62z.00	Intracranial haemorrhage NOS
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction – cerebral

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Read code	Description
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G671000	Acute cerebrovascular insufficiency NOS
G676000	Cerebral infarct due cerebral venous thrombosis, nonpyogenic
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G6W..00	Cerebral infarct due unspecified occlusion/stenosis precerebral arteries
G6X..00	Cerebral infarction due/unspecified occlusion or stenosis/cerebral arteries
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage

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Read code	Description
Gyu6300	[X]Cerebral infarction due/unspecified occlusion or stenosis/cerebral arteries
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6E00	[X]Subarachnoid haemorrhage from intracranial artery, unspecified
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cerebral infarct due unspecified occlusion/stenosis precerebral arteries
Fyu5600	[X]Other lacunar syndromes
Fyu5700	[X]Other vascular syndromes/brain in cerebrovasculr diseases

Appendix 3: Read codes for diagnoses including history of and resolved Read codes

Diagnosis	Read codes
Atrial fibrillation*	G573.% (excluding G5731, G5736)
Asthma*	H33..%, H3120, 173A.
Cancer*	B0... - B32z., B34.. -B6z0. (excluding B677.), Byu.. - Byu41, Byu5. - ByuE0, K1323, K01w1
CHD*	G3-G309, G30B-G330z (except G310), G33z-G3401, G342-G365X, G38-G3z, Gyu3% (except Gyu31)
CKD*	1Z12. -1Z16, 1Z1B. – 1Z1L., K053. - K055.
COPD*	H3…, H31..% (excluding H3101, H31y0, H3122), H32..%, H36.. - H3z.. (excluding H3y0., H3y1.), H5832
Dementia*	Eu02.%, E00..%, Eu01.%, E02y1, E012.%, Eu00.%, E041., Eu041, F110. – F112., F116.
Depression*	E0013, E0021, E112.%, E113.%, E118., E11y2, E11z2, E130., E135., E2003, E291., E2B.., E2B1., Eu204, Eu251, Eu32.% (excluding Eu32A, Eu32B, Eu329), Eu33.%, Eu341, Eu412
Diabetes mellitus*	C10.., C109J, C109K, C10C., C10D., C10E.%, C10F.% (Excluding C10F8), C10G.%, C10H.%, C10M.%, C10N.%, PKyP.
Epilepsy*	F25..% (excluding F2501, F2504, F2511, F2516, F256.%, F258. – F25A., F25y4, F25G., F25H.), F1321, SC200
Familial hypercholesterolemia	1W2.., C320.11, C3200, C3201, C3204, C3205
Heart Failure*	G58..%, G1yz1, 662f. – 662i., 585f., G5yy9
Hypertension*	G2..., G20..%, G24.. - G2z.. (Excluding G24z1, G2400, G2410, G27..), Gyu2., Gyu20
Hypothyroidism*	C03..%, C04..%
Learning disabilities*	E3…%, Eu7..%, Eu814 – Eu817, Eu81z, 918e
Osteoporosis*	N330.% (Excluding N3308, N3309), N3312, N3313, N3316, N3318 – N331B, N331H – N331M, NyuB0, NyuB1, NyuB8, N3314, N3315, N3746, NyuB2
PAD*	G73.., G73z.% (Excluding G73z1), Gyu74, G734., G73y.
Palliative care*	1Z01., 2JE.., 8B2a., 8BA2., 8Bae., 8BAP., 8BAS., 8BAT., 8BJ1., 8CM1.% (excluding 8CM15), 8CM4., 8CMb., 8CME., 8CMQ., 8CMW3, 8H6A., 8H7g., 8H7L., 8HH7., 8IEE., 9367, 9c0L0, 9c0M., 9c0N., 9c0P., 9EB5., 9G8.., 9K9.., 9Ng7., 9NgD., 9NNd., 9NNf0, ZV57C
Psychosis, schizophrenia, bipolar affective disease*	E10..%, E110.%, E111.%, E1124, E1134, E114. – E117z, E11y.% (excluding E11y2), E11z., E11z0, E11zz, E12..%, E13..% (excluding E135.), E2122, Eu2..%, Eu30.%, Eu31.%, Eu323, Eu328, Eu333, Eu32A, Eu329
Rheumatoid arthritis*	N040.%, N041., N042.% (excluding N0420), N047., N04X., N04y0, N04y2, Nyu11, Nyu12, Nyu1G, Nyu10, G5yA., G5y8.

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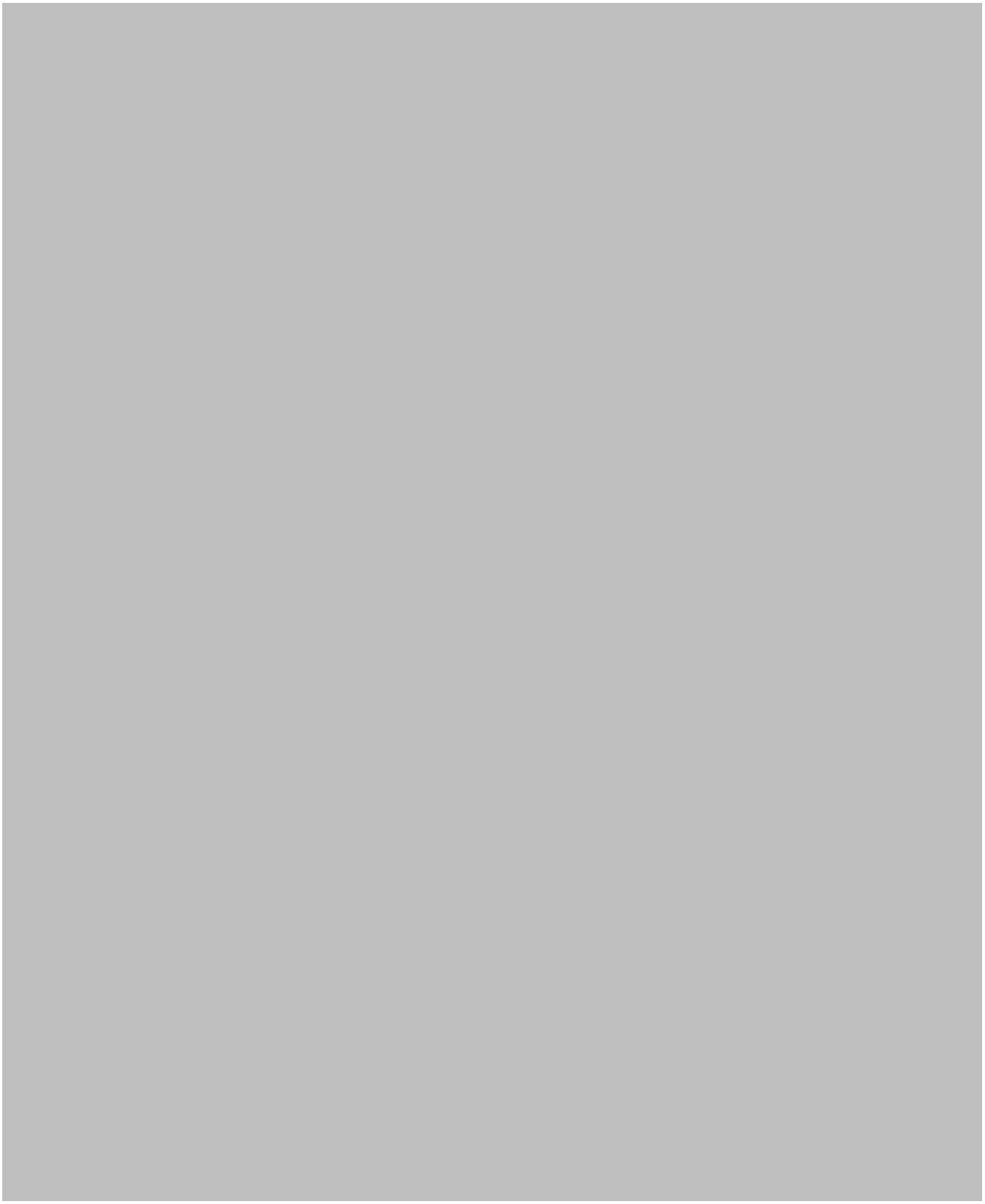
Read code	Description
History of Read codes	
Asthma	14B4.00
Atrial fibrillation	14AN.00
CHD	14A3.00-14A5.00, 14AH.00, 14AJ.00, 14AL.00, 14AT.00, 14AW.00, G32..12
COPD	14B3.12
Dementia	1461.00
Diabetes	1434.00
Epilepsy	1473.00
Heart failure	14A6.00, 14AM.00
Hypothyroidism	1432.00
Osteoporosis	14GB.00
Psychosis, schizophrenia	1464.00, 146H.00, ZV11000- ZV11112
Rheumatoid arthritis	14G1.00
Resolved Read codes	
Atrial Fibrillation	212R.00
Asthma	2126200, 212G.00
Depression	212S.00
Diabetes	2126300, 212H.00
Epilepsy	2126000, 212J.00
Heart failure	2126400
Hypertension	2126100, 212K.00
Osteoporosis	2126500
Psychosis, schizophrenia, bipolar affective disease	212T.00-212X.00, E100500, E101500, E102500, E103500, E105500, E107500, E110600, E111600, E114600, E115600, E116600, E117600, Eu22300, Eu26.00, Eu31700, Eu32900, Eu32A00

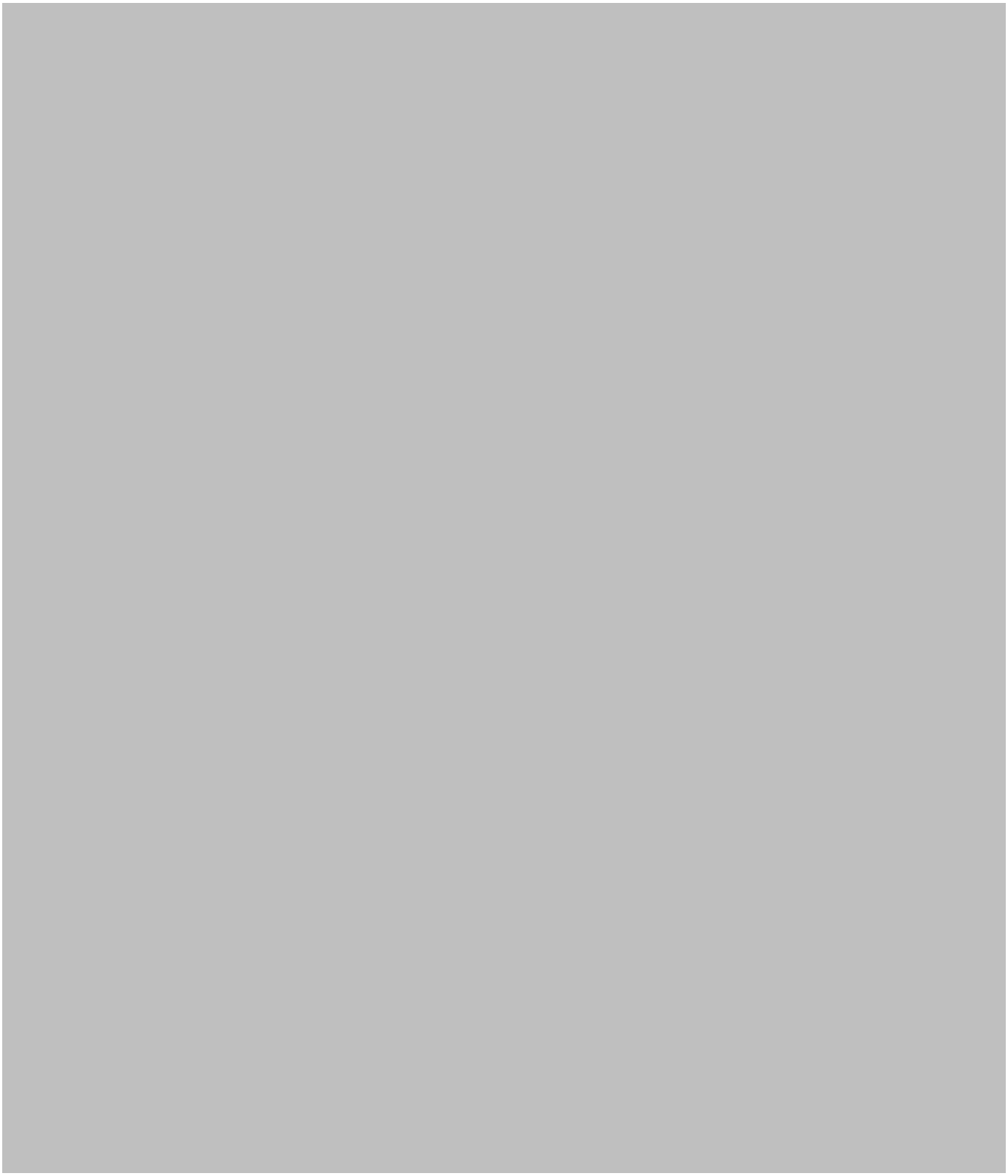
CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, PAD: Peripheral Arterial Disease

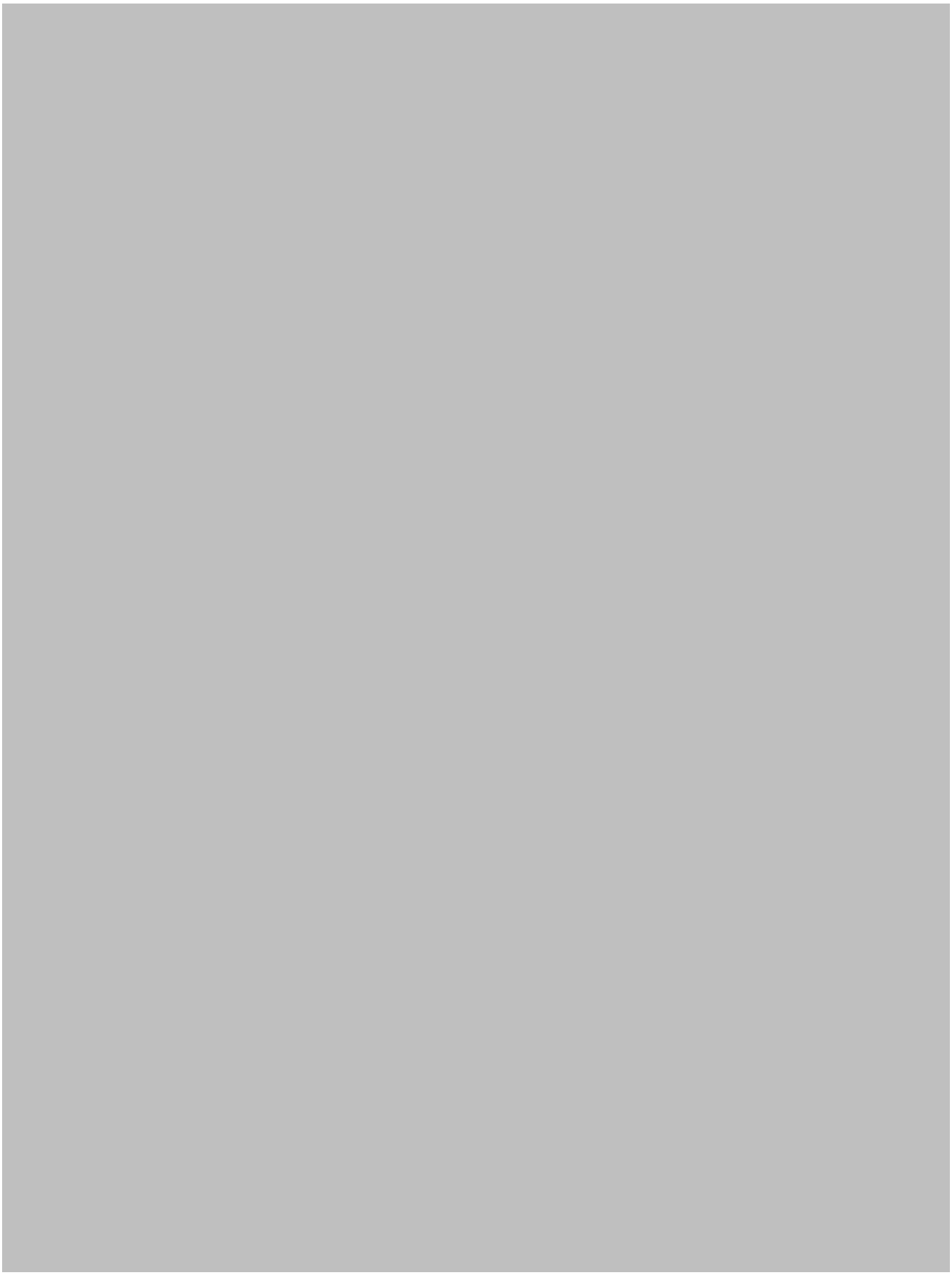
*QOF business rules version 27 (http://www.pcc-cic.org.uk/article/qof-business-rules-v27)

A6.2 Scientific Review Committee (SRC) approval

SRC Feedback







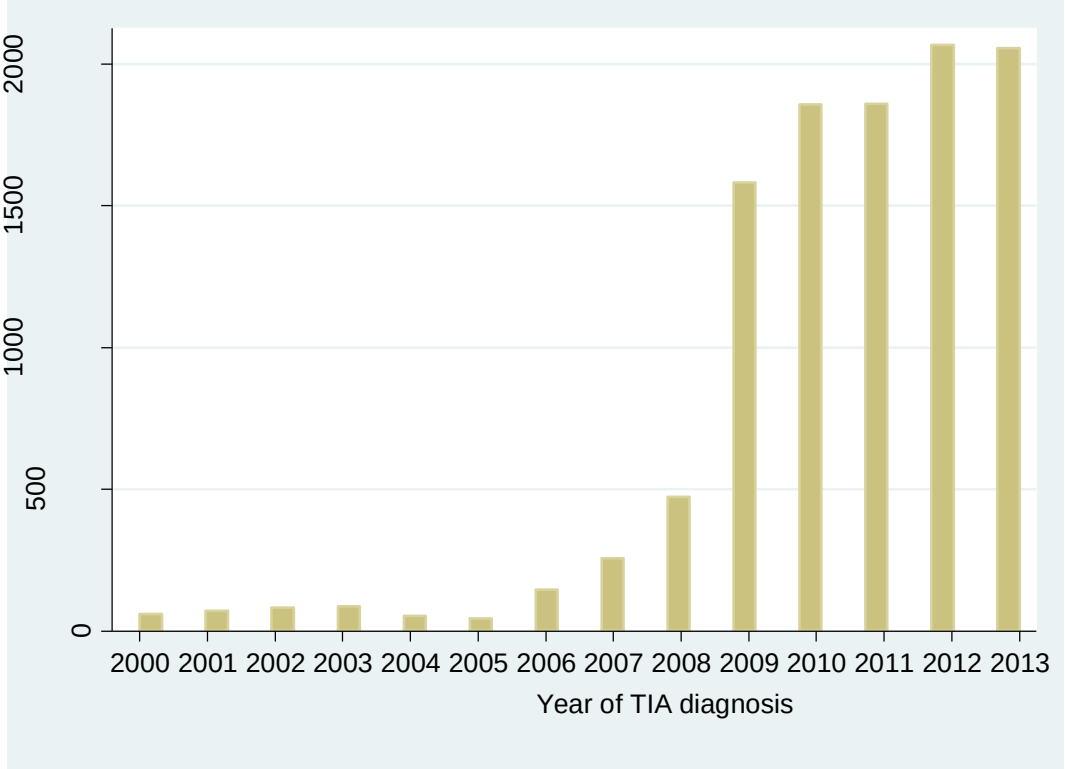
Appendix 7: Residual impairments after TIA: Retrospective cohort study results

A7.1 Supplementary material

Supplementary Table S1: Values outside clinically plausible ranges which were excluded.

Variable	Cut-off range
Height (m)	1 - 2.5
Weight (kg)	35 - 200
Body mass index (units)	10 - 60
Systolic blood pressure (mmHg)	60 – 260
Diastolic blood pressure (mmHg)	40 - 160
Total cholesterol (mm/L)	1 – 12
High-density lipoprotein (HDL) cholesterol (mm/L)	0.1 – 12

Supplementary Figure S1: Number of incident transient ischaemic attack (TIA) events recorded in The Health Improvement Network (THIN) database between 1st January 2000 and 31st December 2013.



Supplementary methods and results

Exploratory analyses

Methods

Sensitivity analyses explored the effect of excluding patients with a record of the outcome prior to the index date in matched sub-studies for each impairment. The composite outcome psychological impairment was analysed individually for anxiety, depression, and post-traumatic stress disorder (PTSD). Further exploratory analyses investigated the effects of excluding patients with no consultations post-index date or those who consulted for the outcomes within the first month of follow-up.

Results

Patients with presence of the outcome prior to their index date excluded

TIA patients had increased risk of consulting for fatigue, psychological and cognitive impairment compared to controls when adjusted for patient and demographic variables (Table S2-S4).

Supplementary Table S2: Adjusted* hazard ratios for the effects of patient and demographic characteristics on consultations for fatigue in TIA patients and controls with no history of fatigue prior to the index date.

		Hazard Ratio	P value	95% CI	
TIA/ control	TIA	1.75	<0.01	1.57	1.94
Age	<45	1.38	0.02	1.06	1.81
	45-49	1.02	0.89	0.75	1.39
	50-54	0.86	0.26	0.66	1.12
	55-59	1.04	0.76	0.82	1.32
	60-64	0.93	0.48	0.75	1.15
	65-69	0.99	0.95	0.81	1.22
	70-74	1.00			
	75-79	1.12	0.19	0.95	1.34
	80-84	1.39	<0.01	1.15	1.67
	85-89	1.26	0.02	1.04	1.52
	≥90	1.13	0.37	0.86	1.49
Sex	Female	1.13	0.02	1.02	1.25
Impairment prior to index date	Psychological impairment	1.16	0.01	1.04	1.31
Impairment post index date	Psychological impairment	1.64	<0.01	1.46	1.83
BMI	Healthy	1.00			
	Underweight	1.13	0.49	0.80	1.58
	Overweight	1.00	0.95	0.90	1.11
	Obese	0.93	0.26	0.82	1.05
	Missing	0.71	0.01	0.56	0.90
Alcohol intake	Never	1.00			
	Light	1.31	<0.01	1.11	1.55
	Moderate	1.32	0.01	1.09	1.61
	Heavy	1.30	<0.01	1.09	1.54
	Missing	1.35	<0.01	1.14	1.59
Comorbidities	CKD	0.85	0.03	0.74	0.98
	Dementia	0.68	0.01	0.51	0.91
	Multimorbidity	1.18	<0.01	1.14	1.23
Health authority	West Midlands	1.00			
	Yorkshire & Humber	0.87	0.43	0.61	1.24
	North West	1.07	0.64	0.81	1.41
	East Midlands	1.37	0.14	0.91	2.06
	North East	1.18	0.42	0.79	1.78
	East of England	1.20	0.20	0.91	1.59
	London	0.99	0.95	0.76	1.29
	South East Coast	0.89	0.44	0.67	1.19

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		Hazard Ratio	P value	95% CI	
	South Central	1.18	0.25	0.89	1.58
	South West	1.07	0.63	0.81	1.43
	Northern Ireland	1.39	0.02	1.05	1.85
	Scotland	1.29	0.06	0.99	1.69
	Wales	0.98	0.89	0.75	1.29

BMI: Body Mass Index, CI: Confidence Interval, CKD: Chronic Kidney Disease, TIA: Transient Ischaemic Attack

* Each hazard ratio is adjusted for the other variables in the table

Supplementary Table S3: Adjusted* hazard ratios for the effects of patient and demographic characteristics on consultations for psychological impairment in TIA patients and controls with no history of psychological impairment prior to the index date.

		Hazard Ratio	P value	95% CI	
TIA/ control	TIA	1.66	<0.01	1.50	1.84
Age	<45	1.20	0.17	0.93	1.56
	45-49	1.27	0.07	0.98	1.65
	50-54	1.06	0.64	0.83	1.36
	55-59	1.04	0.71	0.86	1.26
	60-64	0.98	0.86	0.81	1.19
	65-69	1.06	0.48	0.90	1.24
	70-74	1.00			
	75-79	1.11	0.17	0.96	1.29
	80-84	1.13	0.12	0.97	1.31
	85-89	1.23	0.01	1.05	1.45
	≥90	1.45	<0.01	1.20	1.75
Sex	Female	1.29	<0.01	1.18	1.41
Impairment prior to index date	Fatigue	1.43	<0.01	1.29	1.58
	Cognitive impairment	1.63	<0.01	1.37	1.93
Impairment post index date	Fatigue	1.73	<0.01	1.52	1.97
	Cognitive impairment	1.54	<0.01	1.29	1.86
Smoking status	Non	1.00			
	Ex	1.16	<0.01	1.06	1.27
	Current	1.20	0.01	1.04	1.39
	Missing	0.72	<0.01	0.60	0.86
Deprivation	1 (least deprived)	1.00			
	2	1.00	0.97	0.89	1.12
	3	1.08	0.21	0.96	1.21
	4	1.10	0.17	0.96	1.25
	5 (most deprived)	1.29	<0.01	1.11	1.51
	Missing	1.27	0.09	0.97	1.68
Comorbidities	Atrial fibrillation	0.86	0.04	0.75	0.99
	Asthma	0.77	<0.01	0.67	0.90
	CKD	0.74	<0.01	0.65	0.83
	Epilepsy	0.64	0.04	0.42	0.97
	Hypertension	0.84	<0.01	0.76	0.93
	Hypothyroidism	0.86	0.03	0.74	0.99
	PAD	0.77	0.03	0.61	0.97
	Multimorbidity	1.26	<0.01	1.20	1.32

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		Hazard Ratio	P value	95% CI	
Health authority	West Midlands	1.00			
	Yorkshire & Humber	1.73	<0.01	1.25	2.39
	North West	1.07	0.51	0.87	1.31
	East Midlands	0.82	0.17	0.63	1.09
	North East	0.96	0.73	0.78	1.19
	East of England	1.22	0.06	0.99	1.49
	London	1.00	0.98	0.78	1.27
	South East Coast	1.22	0.04	1.01	1.46
	South Central	1.24	0.02	1.03	1.49
	South West	1.26	0.01	1.07	1.48
	Northern Ireland	1.12	0.26	0.92	1.35
	Scotland	1.24	0.01	1.05	1.47
	Wales	1.07	0.54	0.86	1.32

CI: Confidence Interval, CKD: Chronic Kidney Disease, PAD: Peripheral Artery Disease, TIA: Transient Ischaemic Attack

* Each hazard ratio is adjusted for the other variables in the table

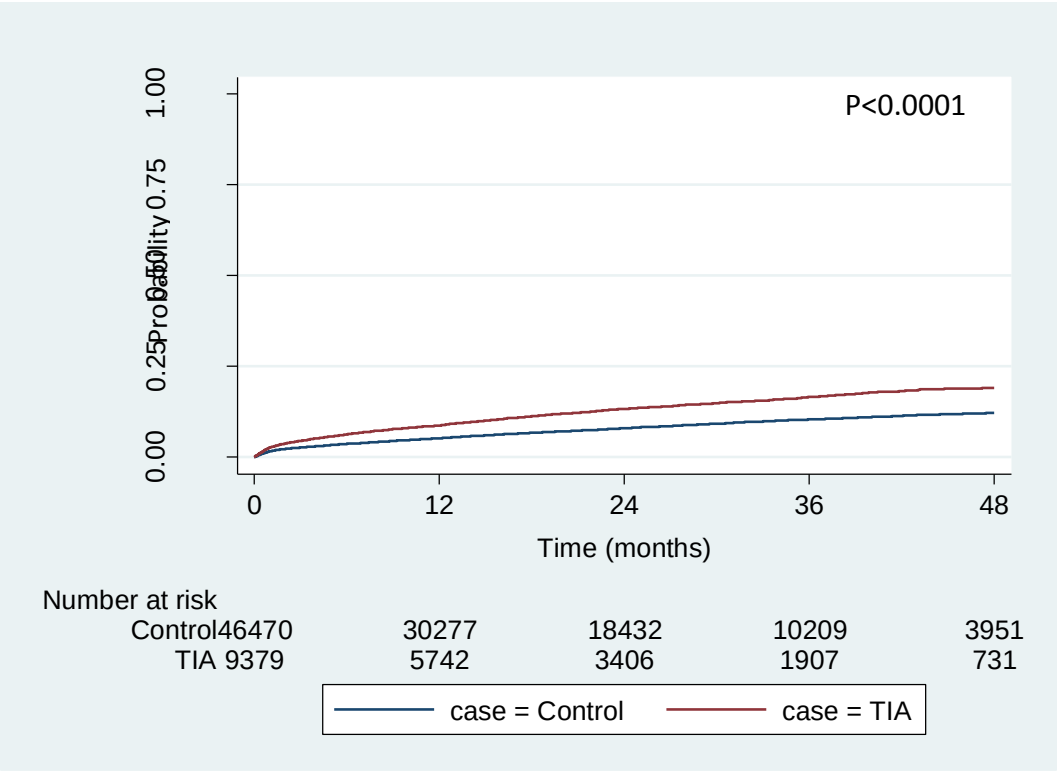
Supplementary Table S4: Adjusted* hazard ratios for the effects of patient and demographic characteristics on consultations for cognitive impairment in TIA patients and controls with no history of cognitive impairment prior to the index date.

		Hazard Ratio	P value	95% CI	
TIA/ control	TIA	1.54	<0.01	1.35	1.77
Age	<50	0.14	<0.01	0.08	0.26
	50-54	0.36	<0.01	0.23	0.56
	55-59	0.42	<0.01	0.28	0.62
	60-64	0.36	<0.01	0.25	0.52
	65-69	0.65	<0.01	0.49	0.86
	70-74	1.00			
	75-79	1.67	<0.01	1.34	2.07
	80-84	2.26	<0.01	1.83	2.80
	85-89	2.43	<0.01	1.95	3.02
	≥90	1.99	<0.01	1.49	2.66
Sex	Female	0.94	0.32	0.84	1.06
Impairment prior to index date	Fatigue	1.45	<0.01	1.26	1.66
Impairment post index date	Psychological impairment	1.83	<0.01	1.61	2.08
BMI	Healthy	1.00			
	Underweight	1.16	0.41	0.81	1.66
	Overweight	0.91	0.15	0.79	1.04
	Obese	0.78	0.01	0.65	0.93
	Missing	0.63	<0.01	0.49	0.82
Rurality	Urban	1.25	0.01	1.05	1.49
Comorbidities	Dementia	0.55	0.04	0.31	0.98
	PAD	0.70	0.03	0.51	0.97
Health authority	West Midlands	1.00			
	Yorkshire & Humber	0.49	0.08	0.22	1.09
	North West	1.18	0.23	0.90	1.54
	East Midlands	0.93	0.82	0.49	1.77
	North East	1.07	0.60	0.82	1.40
	East of England	1.07	0.69	0.78	1.46
	London	0.94	0.67	0.70	1.25
	South East Coast	0.94	0.63	0.72	1.22
	South Central	0.86	0.25	0.66	1.12
	South West	1.09	0.55	0.82	1.46
	Northern Ireland	1.46	0.04	1.02	2.10
	Scotland	1.52	<0.01	1.15	2.03
	Wales	0.98	0.94	0.67	1.45

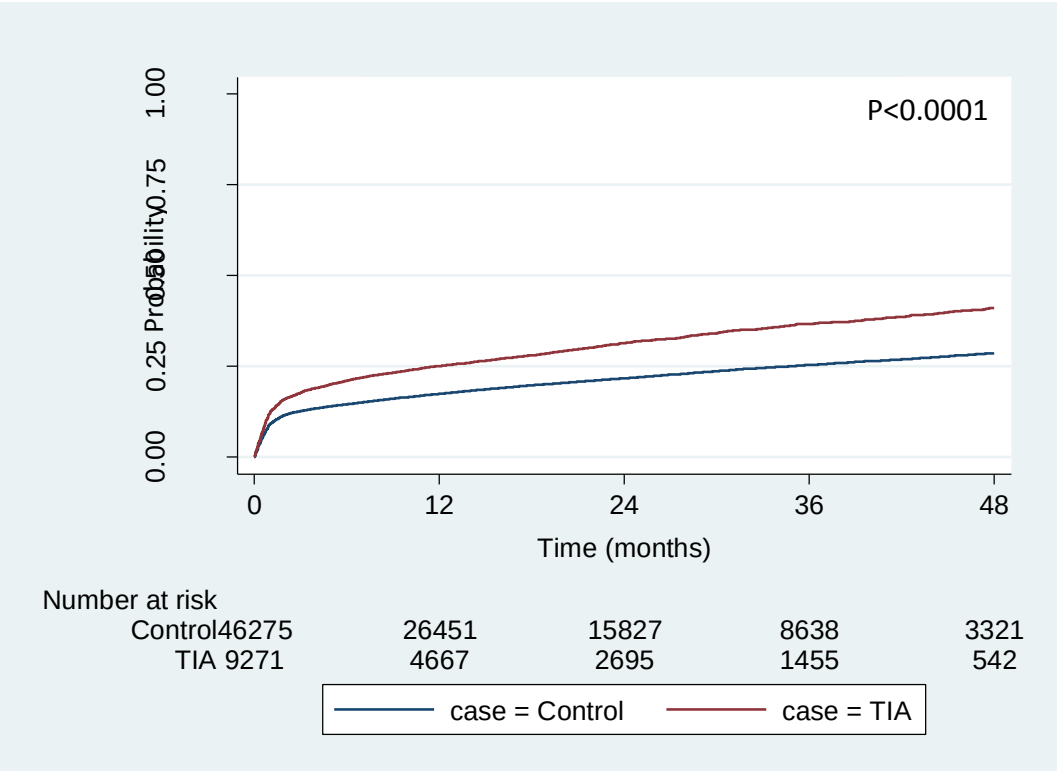
BMI: Body Mass Index, CI: Confidence Interval, PAD: Peripheral Artery Disease, TIA: Transient Ischaemic Attack. †BMI: Healthy (18.5-25.9 kg/m^2); Underweight (<18.5 kg/m^2); Overweight (26-30 kg/m^2); Obese (>30 kg/m^2). * Each hazard ratio is adjusted for the other variables in the table

Psychological impairment separated into anxiety, depression and PTSD sub-studies

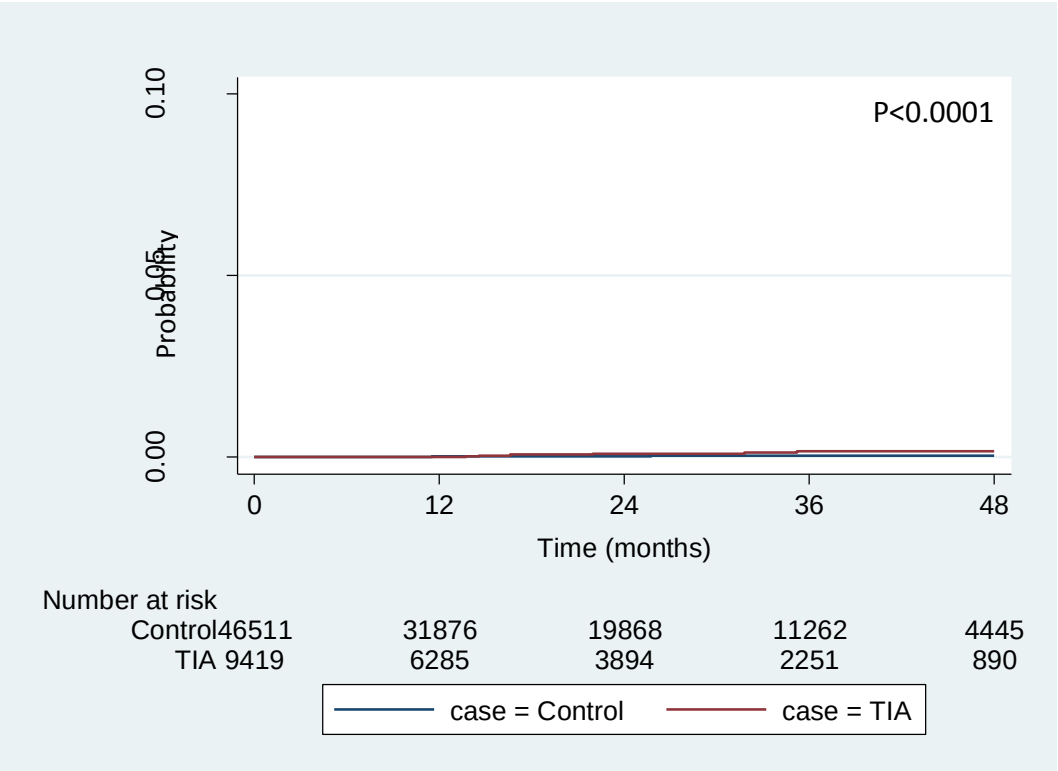
Psychological impairment was separated into three matched sub-studies comprised of anxiety, depression and PTSD. There were 55,849 patients included in the anxiety sub-study (9,379 TIA patients and 46,470 controls); 55,546 in the depression sub-study (9,271 TIA patients and 46,275 controls); and 55,930 in the PTSD sub-study (9,419 TIA patients and 46,511 controls). The K-M curves show that TIA patients consulted more for anxiety, depression and PTSD and the difference was statistically different ($P<0.01$; Figure S2-S4). Depression was further separated by time to clinical code for a diagnosis of depression and time to prescription for antidepressants to investigate the high failure rate after the index date for both TIA patients and controls. Figures S5 and S6 suggest that anti-depressant prescriptions account for this trend.



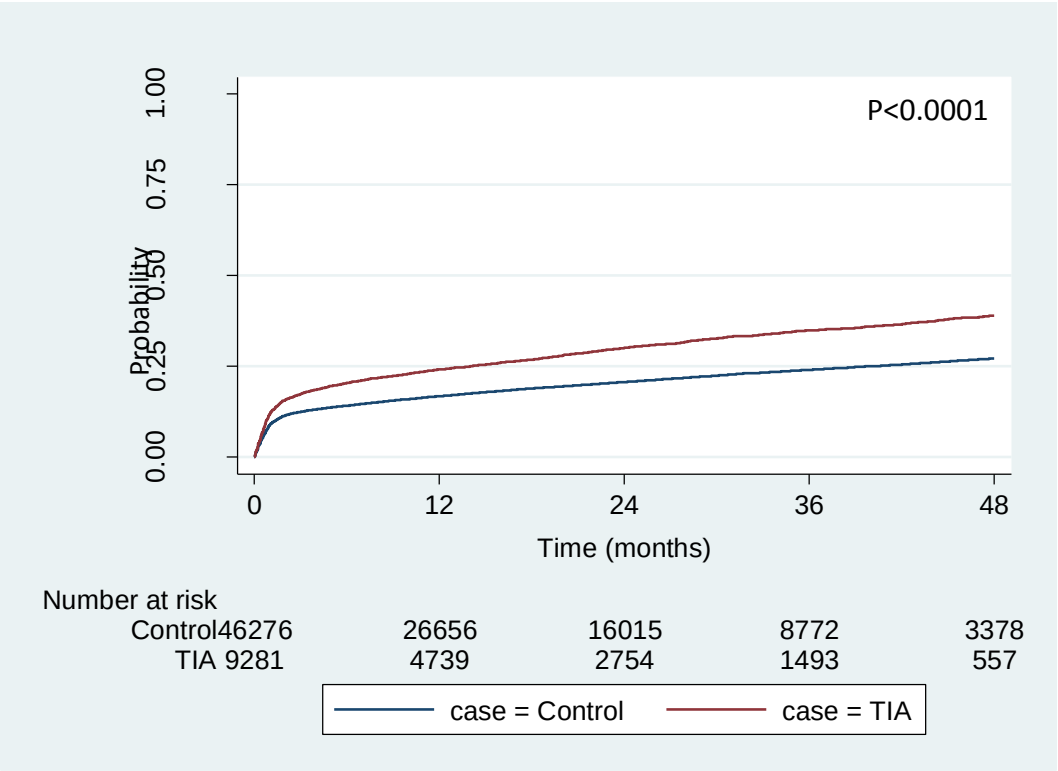
Supplementary Figure S2: Kaplan-Meier (K-M) failure estimates for TIA patients and controls consulting for anxiety.



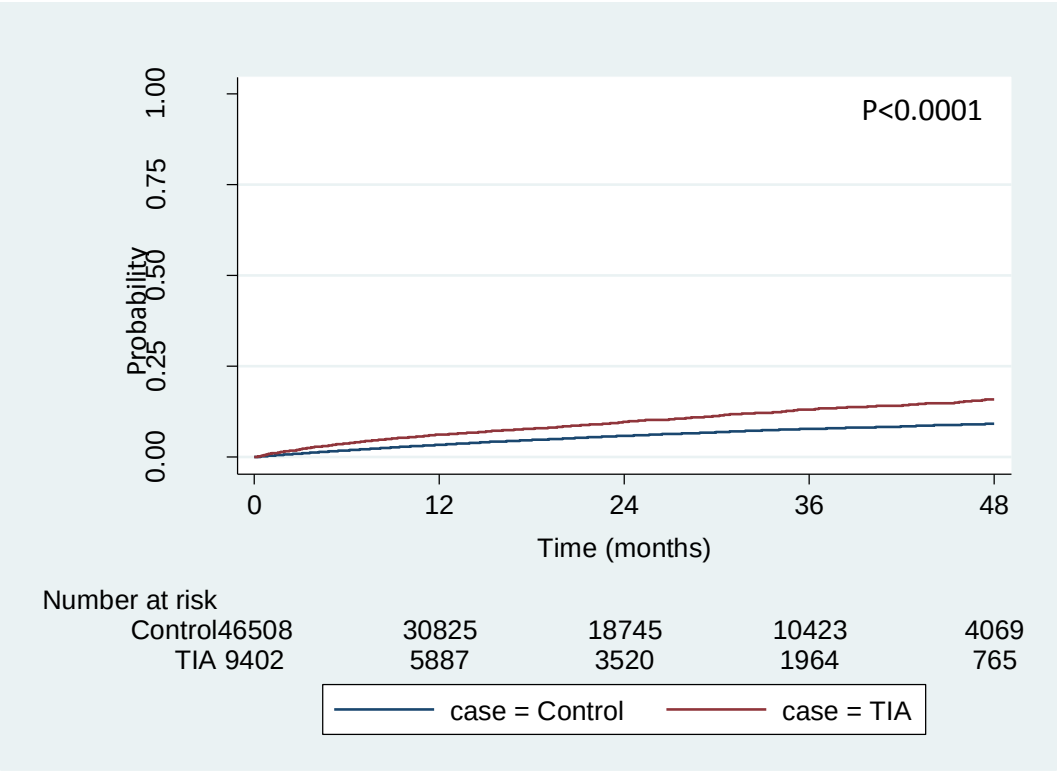
Supplementary Figure S3: Kaplan-Meier (K-M) failure estimates for TIA patients and controls consulting for depression.



Supplementary Figure S4: Kaplan-Meier (K-M) failure estimates for TIA patients and controls consulting for posttraumatic stress disorder (PTSD).



Supplementary Figure S5: Kaplan-Meier (K-M) failure estimates for TIA patients and controls consulting for depression with depression defined by prescription for anti-depressants.



Supplementary Figure S6: Kaplan-Meier (K-M) failure estimates for TIA patients and controls consulting for depression with depression defined by a clinical code for a diagnosis of depression.

Patients with consultation for outcome in the first month of follow-up excluded

Within the first month post-index date, 431 patients consulted for fatigue, 4,803 for psychological impairment, and 103 for cognitive impairment. Following the exclusion of these patients in exploratory analyses, a significant difference between TIA and control patients remained (P<0.0001).

Patients with no consultations in follow-up excluded

Number of consultations pre- and post-index date are summarised in Table S5. A significant difference remained between TIA patients and controls when patients with no consultations in follow-up were excluded for all three sub-studies (P<0.0001).

Supplementary Table S5: Summary of consultations pre- and post-index date for TIA patients and controls.

Consultations	TIA patients	Controls
In the year prior to index date (median [IQR])	9 [5,14]	6 [3,11]
In the year post index date (median [IQR])	10 [6,17]	5 [2,10]
Number with 0 consolations in follow up (frequency)	80	5,763

A7.2 Association between residual impairments post-TIA and stroke in follow-up

The second aim of the original protocol was to investigate if patients with TIA and who consult in primary care with residual impairments are more likely to experience subsequent stroke compared to TIA patients without impairments. Of the 55,930 TIA patients and controls included in the study, 440 had a stroke after the index date: 171 TIA patients and 269 controls. To test the association between residual impairments in TIA patients and subsequent stroke, a Kaplan-Meier (K-M) survivor function analysis was proposed to estimate time to stroke for TIA patients with impairment and TIA patients without impairment. However, there were unforeseen methodological issues regarding the identification of an index date for TIA patients without impairments. Therefore, the analysis could not be completed.