Ischaemic Stroke in South Asians

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Declaration of Authorship

I, Taylor Aurelius, hereby declare that this thesis and the work presented in it is entirely my own. Where I have consulted the work of others, this is always clearly stated.

Signed: 

Date: 10/03/2022

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Abstract (300 words)

South Asians make up the largest ethnic minority in the UK, however current research on ischaemic strokes within this demographic is limited. In this thesis, I explored differences in characteristics of ischaemic stroke in South Asians in the UK (BSA), India (ISA), and white British (WB) patients. I undertook a review of the limited literature available in which BSA reported earlier stroke onset compared to the WB population. BSA also presented with an increased mortality rate, and greater prevalence of cardiometabolic risk factors, including hypertension. These studies used small sample sizes while the only study reporting age was conducted +20 years ago.

To answer gaps within the literature I utilised the UK and Indian arms of the ongoing prospective international hospital-based study on South Asian stroke (BRAINS study). This database consists of 1650 BSA (men:1074, women:576), 1279 ISA (men:864, women:415) and 2291 WB (men:1296, women:995) ischaemic stroke patients. Both BSA and ISA suffered from stroke ~7 and ~20 years, respectively, earlier than their WB counterparts (BSA:64.3±15.1 years, vs. ISA:52.0±13.4 years, vs. WB:71.5±13.5 years, $P<0.001$). I found after adjusting for age, sex, atrial fibrillation, smoking history and central obesity in stepwise logistic regression, there was a ~2-fold increase in small vessel occlusion prevalence (BSA vs WB:1.65, 95%CI:1.15 – 2.38) and a ~30-60% decrease in large artery atherosclerosis (ISA vs WB:1.88, 95%CI: 1.44–2.44) classified stroke in both ISA and BSA, compared to WB patients.

Both BSA (OR=4.87, 95%CI: 3.80–6.25) and ISA (OR=1.96, 95%CI: 1.53–2.51) had an increased risk of having 3+ metabolic risk factors by ~4-6 fold compared to WB patients.

BSA has a lower risk of atrial fibrillation compared to their white British counterparts (OR:0.40, 95%CI:0.33-0.49). No ethnic-specific differences were reported in the use of anticoagulation at admission (*P*=0.93) or discharge (*P*=0.64).

Based on the results presented in this thesis, prevention and management strategies should consider distinct ethnic variations in ischaemic stroke age of onset, subtypes, and comorbidities. South Asian populations need more research on underlying mechanisms and potential interventions for reducing the stroke burden.

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Presentations

2019	I received a grant from the British Heart Foundation to present my work at the 25th annual International Stroke Genetics Consortium in 2019. Titled: First analysis of prevalence and risk factors in South Asians migrated to the UK and Qatar compared with UK Caucasians: the Bio-Repository of DNA in Stroke study (BRAINS) (Appendix 10.14)
2020	Presented an abstract and poster with a Q&A session for my work at the joint European Stroke Organisation and World Stroke Organisation Conference 2020. Titled: Differences in UK South Asians and European Ischaemic Stroke Patients: results from the Bio-Repository Of DNA In Stroke (Brains) Study

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Publications

- Aurelius, T, Maheshwari, A, Ken-Dror, G, et al. (2022) Ischaemic stroke in South Asians: The BRAINS study. Eur J Neurol. 2023; 30: 353- 361. doi: 10.1111/ene.15605

- Aurelius T, Ken-Dror G, Sharma SD, Amlani S, Gunathilagan G, et al. (2023) Atrial fibrillation in UK South Asian hospitalized ischemic stroke patients: The BRAINS study. PLOS ONE 18(2): e0281014. https://doi.org/10.1371/journal.pone.0281014

1 Content

1 Project Introduction 1

1.1 Research Context 1

1.1.1 Stroke globally 1

1.1.2 Stroke in the UK 1

1.1.3 Stroke in South Asians 2

1.2 Aims of this PhD 3

2 Ischaemic stroke in UK residing South Asians 5

2.1 Introduction 5

2.2 Methods 6

2.2.1 Study eligibility 6

2.2.2 Data collation and analysis 8

2.3 Epidemiology of Stroke 9

2.3.1 Literature search 9

2.3.2 Incidence, prevalence, and mortality 11

2.3.3 Age of onset of stroke 17

2.4 Cardiometabolic Risk Factors 18

2.4.1 Diabetes mellitus 21

2.4.2 Hypertension 22

2.4.3 Hyperlipidaemia, obesity, and body fat distribution 23

2.4.4 Atrial fibrillation 25

2.5 Migration and lifestyle risk factors 26
2.5.1 Psychosocial factors 27
2.5.2 Tobacco use 28
2.5.3 Diet 29
2.6 Summary 29
3 Research methods 30
3.1 Study design 30
3.2 BRAINS biorepository 32
3.3 Data Collection 36
3.4 Quality control and data analysis 39
3.4.1 Missing data 43
3.4.2 Recruitment bias 47
4 Age of Stroke Onset in South Asians 49
4.1 Introduction 49
4.2 Methods 50
4.3 Results 51
4.4 Discussion 59
4.5 Limitations 62
4.5.1 Limitations with the BRAINS dataset 62
4.5.2 Missing data 64
4.6 Summary 65

5 Ischaemic stroke subtype in South Asians 66

5.1 Introduction 66

5.2 Methods 68

5.3 Results 69

5.3.1 TOAST Stroke Subtype 71

5.4 Discussion 79

5.5 Limitations 82

5.6 Summary 83

6 Metabolic risk factors 84

6.1 Introduction 84

6.2 Methods 85

6.3 Results 86

6.4 Discussion 95

6.5 Limitations 97

6.6 Summary 99

7 Atrial Fibrillation in South Asian Ischaemic Stroke 100

7.1 Introduction 100

7.2 Methods 102

7.3 Results 103

7.3.1 Treatment 110

7.4 Discussion 116

7.5 Limitations 119

7.6 Summary 120

8 Conclusion 121

9 Bibliography 125

10 Appendix 154

10.1 – Ethical Approval confirmation. 154

10.2 - Percentage of the UK South Asian population per region. 156

10.3 – Example patient consent form. 157

10.4 – Example relative consent form. 158

10.5 – Example BRAINS questionnaire for the UK data collection. 159

10.6 – Example BRAINS questionnaire for the India data collection. 165

10.7 - Population characteristics stratified by missing values status. 172

10.8 - Comparison of the age of ischaemic stroke event in those with missing and complete data for each comorbidity, using chapter 4's selection criteria. 174

10.9 - Comparison of population characteristics of ISA and BSA with WB. 175

10.10 - Age of first-time stroke event between those with missing and complete for each comorbidity, using chapter 5's selection criteria. 176

10.11 - Age of first-time stroke event between those with missing and complete for each comorbidity, using chapter 6's selection criteria. 177

10.12 – Number of metabolic risk factors with complete data, stratified by ethnicity. 178

10.13 - Age of stroke event between those with missing and complete data for each comorbidity, using chapter 7's selection criteria. 179

10.14 – Metabolic Syndrome poster presentation given to the European and World stroke conference, using preliminary data from the BRAINS database in 2018. 180

List of tables

Table 2-1: Summary of studies which report incidence rate……..……..13

Table 1-2: Age-adjusted mortality rate per 100,000 total strokes (CI 95%) in England and Wales, by country of birth among those aged 30–69 years ……..……...16

Table 2-3: Summary of the prevalence of cardiometabolic risk factors in South Asians, compared to white British patients with total and ischaemic stroke only……20

Table 3-1: Recruitment site location for the BRAINS database…….……34

Table 3-2: Breakdown of ethnic groups for South Asians and white British ischaemic stroke patients in the UK and India BRAINS database……...…….. 37

Table 3-3: Questionnaire data coded……...41

Table 3-4: Comparison of the age of ischaemic stroke event in those with missing and complete data……46

Table 4-1: Population characteristics stratified by ethnicity…….……...…52

Table 4-2: Comparison of population characteristics between ethnic groups, by sex…….54

Table 4-3: Stepwise multivariable linear regression analysis predicting age of onset of ischaemic stroke (years) with traditional risk factor……....56

Table 4-4: Simple linear regression analysis predicting age of onset of ischaemic stroke (years) adjusting for each traditional risk factor……..58

Table 5-1: Population Characteristics stratified by ethnicity…….…..70

Table 5-2: Population characteristics stratified by ethnicity and TOAST classification…….72

Table 5-3: Age and sex adjusted comparison of stroke subtypes in BSA and ISA with the WB stroke populations……...…….76

Table 5-4: Logistic regression model to assess the risk of various ischaemic stroke subtypes (TOAST) in ISA and BSA……...78

Table 6-1: Population characteristics, stratified by ethnicity and sex….……..…87

Table 6-2: Prevalence of cumulative metabolic risk factors related components, stratified by ethnicity and sex……...89

Table 6-3: Population characteristics stratified by location, among those with 3+ metabolic risk factors……92

Table 6-4: Logistic regression model to assess the risk of cumulative metabolic risk factors in ISA and BSA ischaemic stroke patients compared with those of WB descent (reference group), stratified by sex……94

Table 7-1: Ischaemic stroke population characteristics stratified by Atrial Fibrillation (AF) status……...106

Table 7-2: Population characteristics with confirmed atrial fibrillation status stratified by ethnicity……..108

Table 7-3: Associations of the age of stroke event and other predictors with atrial fibrillation……...109

Table 7-4: Antiplatelet treatment at admission and discharge stratified by ethnicity and cardiovascular disease……115

List of figures

Figure 2-1: Flow chart of search strategy……10

Figure 1-1: Distribution of UK recruitment sites……33

Figure 5-1: Selection criteria for chapter 5……..69

Figure 5-2: Stroke subtypes in South Asian and white British ischaemic stroke cases……...73

Figure 5-3: Distribution of stroke subtype using the TOAST classification, stratified by ethnicity……75

Figure 6-1: Average age of onset (years) in the presence of varying metabolic risk factors, stratified by ethnicity and sex……...90

Figure 7-1: Flow diagram of the selection process for chapter 7……...104

Figure 7-2: Distribution of anticoagulation and antiplatelet status in confirmed atrial fibrillation cases, stratified by ethnicity, at admission……...111

Figure 7-3: Distribution of anticoagulation and antiplatelet status in confirmed atrial fibrillation cases, stratified by ethnicity, at discharge. …….…….112

Figure 7-4: Changes in anticoagulation treatment from admission to discharge in confirmed atrial fibrillation cases, stratified by ethnicity……114

List of Abbreviations

BRAINS	Bio-Repository of DNA in stroke
UK	United Kingdom
WB	White British
BSA	UK residing South Asians
ISA	Indian South Asians
CPRD	Clinical Practice Research Datalink
DM	Diabetes Mellitus
AF	Atrial Fibrillation
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
BMI	Body Mass Index
HDL	High-Density Lipoprotein
NOAC	Novel Oral Anticoagulants
MCAR	Missing Completely at Random
ANOVA	Analysis of Variance

1 Project Introduction

1.1 Research Context

1.1.1 Stroke globally

Globally, there are ~12 million new stroke cases each year: with 53% of these being in women and 47% in men(1). Stroke is one of the highest causes of death (10.2%) and disability (5.2%) in the world (2). Among the new stroke cases over 62% of all incident strokes are ischaemic strokes (1). Stroke incidence has been transitioning between high-income and low to middle-income countries. Between 1970 to 2008 there has been a 42% decrease in stroke incidence in high-income countries and over a 100% increase in stroke incidence in low to middle-income countries (3). Little is known about its epidemiology in lower- and middle-income countries.

1.1.2 Stroke in the UK

In the United Kingdom (UK), stroke occurs more than 100,000 times a year and is responsible for over 35,000 deaths annually (4,5). Similar to most high-income Western countries, the incidence of stroke among the general UK population has reduced from 1.48 per 1000 person-years in 1999 to 1.04 per 1000 person-years in 2008 (6). However, data on the trends in stroke over the years has not been well documented among UK ethnic minorities. It is well established that wealth and health inequalities exist between ethnic groups due to socioeconomic disparities and several environmental stresses (7,8). Mortality data reported by the Office of National Statistics demonstrates that each ethnic group suffers from stroke differently, with the highest rate of stroke mortality being considerably higher in South Asians compared to all other ethnic groups in the UK (9).

1.1.3 Stroke in South Asians

Stroke is among several chronic conditions where there is an excessive number of sufferers from a South Asian background (10–12). Since the mid-20th century, there has been a large influx of migrants from these countries into the West. The UK has 9% of its population with a nationality of a different country, with the largest being South Asian (Indian, Pakistani, Bangladeshi, etc). Before WWII, this population within the UK was relatively small at just over 7000 individuals in 1932 (13). This has since continued to grow to over 3 million. Of this, over 1.5 million UK South Asians were born in South Asian regions, with Indians making up the largest proportion followed by Pakistanis as of 2011 (14).

Compared to other ethnic minority groups, South Asians are inadequately represented in health research and thus the current understanding of stroke could also be misguided when applied to South Asians (15,16). Many of the traditional stroke risk factors such as hypertension, diabetes mellitus etc, were identified in a primarily Caucasian population during the Framingham Heart Study (17). There is considerable evidence to suggest that risk factors themselves are not uniform across ethnic populations, with South Asians displaying an adverse risk profile. These health inequalities not only affect South Asians but also black and other ethnic minority groups in the UK (18,19).

The expenses associated with caring for stroke patients encompass both direct and indirect costs, arising from medical interventions and decreased productivity, respectively. Direct costs involve hospitalization, primary care, medication, rehabilitation, and social services such as home care and nursing home care for those who have difficulty with daily activities due to stroke. The initial cost of a newly occurring stroke is estimated at £45,409 (95% CI

42,054-48,763) within the first year, followed by a subsequent cost of £24,778 (£20,234-£29,322) in the years thereafter. The total societal cost of stroke, including both the National Health Service (NHS) and social care expenses, amounts to £26 billion annually, with NHS and social care costs accounting for £8.6 billion of the total (20). Current management guidelines for stroke do not appropriately account for ethnicity and could add to these costs. The national clinical guidelines for stroke in the UK aim is to establish a standardised level of care for all stroke patients. However, the latest guidelines do not account for the variability of risk factors, including cultural and physiological factors, among individuals from different ethnic backgrounds (21). It has been reported that preventative measure for stroke including cholesterol monitoring and thus treatment is less likely to occur in UK South Asians compared to white British individuals (22). This oversight raises concerns about whether the guidelines are truly optimal for all stroke patients and highlights the need for further research and consideration of how to tailor stroke care to address the unique needs of diverse patient populations.

1.2 Aims of this PhD

The purpose of my research is to better understand differences in ischaemic stroke between South Asians in the UK and India with the white British population. This will include using the age of stroke onset as a gauge to determine if South Asians are at a greater risk of stroke and how traditional stroke risk factors influence this. To do this I utilised the data from the ongoing prospective large BRAINS (Bio-Repository of DNA in Stroke) study, which has recruited patients from 21 secondary healthcare sites across the UK and 2 in India. To the best of my knowledge, this is the largest such stroke study in UK South Asians.

The following report is organised into seven sections detailing my review of the current literature available, the overall methodology I have used, as well as showcase the results I have obtained. The second chapter, the literature review, will focus on ischaemic stroke data in the UK South Asian community. I will explore the traditional risk factors of stroke whilst also presenting how the effect of migration and acculturation can too be risks. Chapter three will focus on the overall methodology for the study of BRAINS including the initial quality control of the dataset. Chapter four aims to look at age of onset of ischaemic stroke in South Asians, and how much traditional risk factors can explain the difference. Chapter five will dive deeper into ischaemic stroke by looking at the breakdown of its subtype. The metabolic characteristics of South Asians and white British patients are reported in chapter six. In chapter seven I focus on atrial fibrillation prevalence and treatment. The BRAINS database has collected extensive data on treatment therapies used by each stroke patient prior to admission and at discharge. For this reason, I have focused on the prevalence of atrial fibrillation among this population and potential treatment inequalities. The last chapter, eight, of my report will summarise my PhD thesis, highlighting the key findings of my work along with its implications.

2 Ischaemic stroke in UK residing South Asians

2.1 Introduction

In this section, previous studies have been summarised, reviewed and differences explained where possible. Studies which focus on UK-residing South Asians are often overlooked especially on the most common type of stroke, ischaemic. For this reason, I wanted this review to focus on differences in ischaemic stroke within the UK South Asian and white British communities.

Due to its multi-ethnic demographic, the UK is one of the best locations for studying South Asian migrant populations. As per the 2011 census, individuals who identified as 'non-White' made up 13% of the UK's total population, of which 8% were categorised as Asian or British Asian (14). Only one review of the literature has been conducted previously by Gunarathne *et al* in 2009 (23). In this review, 33 articles were found in the search period from 1990 to 2005. Though this review intended to focus on the UK specifically, it expanded to include South Asian populations globally. According to the review, there was a noticeable rise in both the incidence and prevalence of ischaemic stroke, and it also highlighted that South Asians have a comparatively poorer cardiovascular risk profile when compared to the white British population.

As Gunarathne *et al* conducted their search up until 2005, newer primary studies are available to update current knowledge. My narrative review aims to describe the current understanding of ischaemic stroke prevalence, incidence, and mortality in UK-residing South Asians.

Further, I wanted to describe cardiometabolic risk factors, focusing on the prevalence of traditional stroke risk factors, whilst also trying to discuss the possible reasoning behind surprising differences. The last section, which includes migration and lifestyle risk factors, provides insight into novel risk factors such as acculturation and how this can influence lifestyle factors.

2.2 Methods

To assess the availability of data from studies focusing on ischaemic stroke in UK-residing South Asians, I generated search terms for use in Pubmed, and Embase. The search strategies were designed to include the search domains of "South Asian," which encompassed the populations of interest such as Indians, Pakistanis, and Bangladeshis, as well as "Stroke" and "Cardiovascular disease/Cerebrovascular accidents.". The search terms used across both databases were ((South Asians) OR (Indians) OR (Sri Lankans) OR (Bangladeshi) OR (Pakistani) OR (Nepalese)) AND ((Stroke) OR (Ischaemic Stroke) OR (Ischemic Stroke) OR (Cerebrovascular Accidents)) AND ((UK) OR (U.K.) OR (England) OR (Wales) OR (Scotland) OR (Northern Ireland)). Electronic databases were thoroughly searched using synonyms of the terms. Of the studies identified, I reviewed their references to ensure all studies were considered.

2.2.1 Study eligibility

Early on in the review process, I recognised the lack of population-based studies relating to ischaemic stroke in the UK-residing South Asian population, with only one study found

describing ischaemic stroke only in this population. For this reason, I decided to expand my search. I identified two routes I could use to expand this search. Firstly, I could expand the search to include the South Asian population globally, similarly to the previous study by Gunarathne *et al* (23). This would bring the benefit of an increased study pool to identify studies from however it could dilute the picture of ischaemic stroke in the UK for South Asians as each country has a different healthcare system and socioeconomic condition. Alternatively, during the initial search, studies focusing on UK South Asians with total stroke events, rather than ischaemic only, were more substantial. As ischaemic stroke is the most prevalent type of stroke in white British and South Asian populations (greater than 80% of all strokes are ischaemic) I chose to report ischaemic-only studies and total stroke only studies.

Following this, the inclusion criteria for this review is to include stroke (total or ischaemic) conducted in the UK where the study population comprises South Asians (Bangladeshi, Indian and Pakistani). This review included those studies that compared mortality, prevalence and/or incidence of stroke and stroke risk factors.

The exclusion criteria I followed in my search were:

- Studies that are not written in English, as well as unpublished research (such as dissertations and theses), reviews, systematic reviews, case reports, editorials, and letters.
- Studies which focus on haemorrhagic stroke or transient ischaemic attack only.
- Studies not conducted in the UK population.
- Studies not conducted on humans.

2.2.2 Data collation and analysis

Studies identified by the literature search were collated into tables by stroke incidence, mortality and cardiovascular risk profile. Within each table, I stratified the studies by the type of stroke reported, either total stroke or ischaemic stroke only. Total stroke is defined as the collective occurrence of both ischemic and haemorrhagic stroke. Studies under the total stroke group describe the overall burden of stroke in a population.

In my review, I will refer to prevalence, incidence, risk factors, and comorbidity. For prevalence, I am using the Gordis Epidemiology definition: 'the number of affected persons present in the population at a specific time divided by the number of persons in the population at that time' (24). Incidence is defined as the number of new cases of disease (stroke events) during a specified time interval. Comorbidity is defined as the co-occurrence of two or more long-term conditions in an individual (25). A risk factor is any exposure or behaviour that increases the likelihood of an individual developing a particular disease or health condition (26).

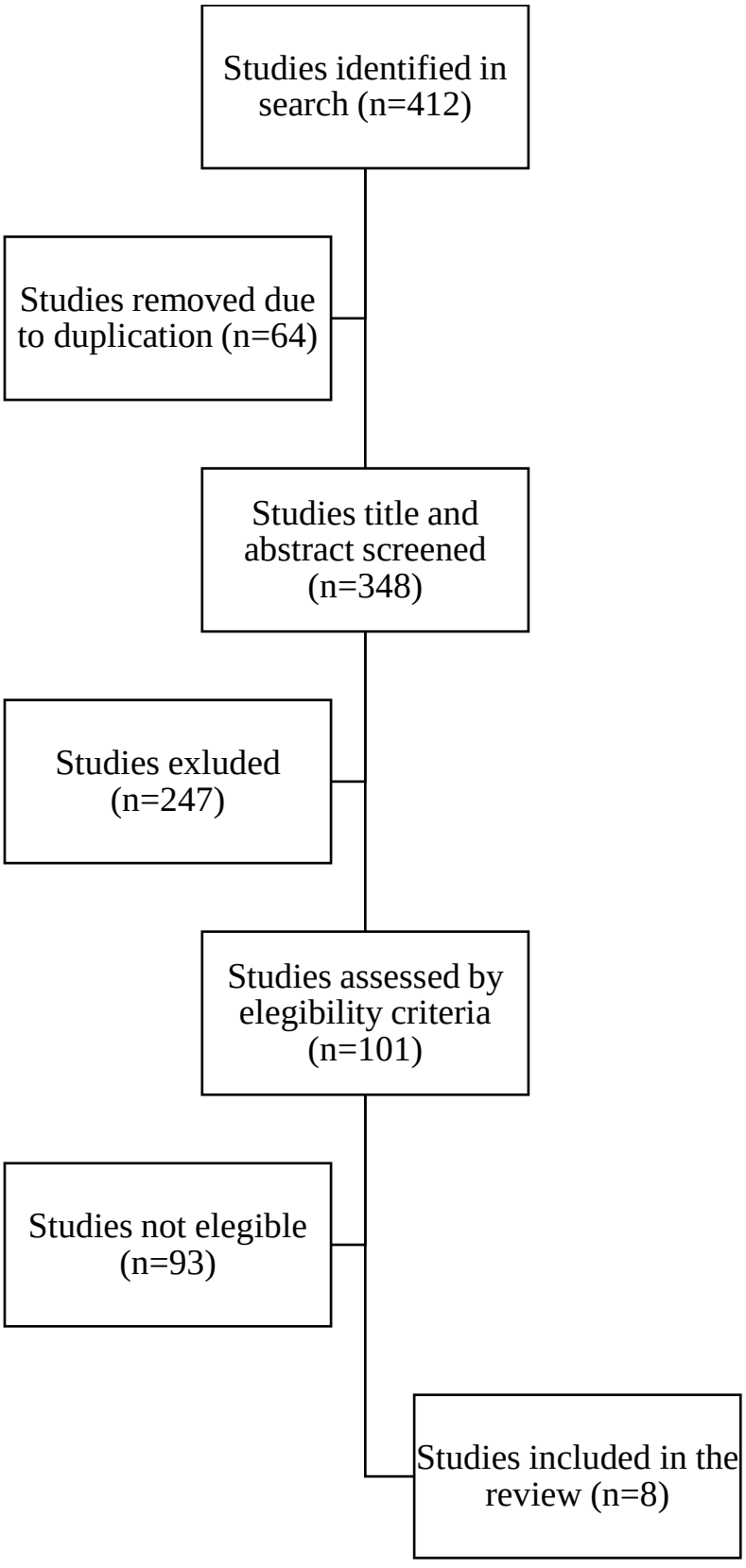
As the included studies in this review have differing stroke type included and populations, a meta-analysis was not conducted. In studies which report total stroke only, I will attempt to describe the breakdown of stroke subtype, with the assumption that ischaemic makes up the greatest proportion (>80%) of all total strokes. Where differences between South Asians and white British subjects are reported, I also attempted to report possible explanations of this outside of stroke, if any exist.

2.3 Epidemiology of Stroke

2.3.1 Literature search

The outcome of the literature search for total and ischaemic stroke-focused studies is described in Figure 2-1. In total, 412 (PubMed: 255, Embase:157) studies were identified using the search terms and 8 studies were identified using the inclusion criteria described in chapter 2.2.1. Of these, 3 studies reported incidence rate, 3 studies reported mortality rate, 2 studies reported age of event, and 4 studies reported the prevalence of cardiovascular risk factors.

Figure 2-1: Flow chart of the search strategy.



2.3.2 Incidence, prevalence, and mortality

The lack of population-based studies focused on ischaemic stroke in the UK South Asian community highlights the inequality of data available, resulting in the restricted publication of stroke incidence and prevalence. Data available relating to incidence is based on two studies, which have reported combined hemorrhagic and ischaemic stroke only (27,28) and one study reporting both total stroke and ischaemic stroke only (29).

Hsu *et al* in 1996, conducted a stroke study in Leicestershire involving 23 general practices, which focused on the South Asian population. The study aimed to compare the stroke incidence rates between "high Asian" general practices (with 80% or more South Asians) and "low Asian" general practices (with less than 2% South Asians). Recruitment started in 1996 however no end date was given. The study reported similar age-specific and crude incidence rates of combined stroke in these two ethnicities, though this is likely due to a low migrant South Asian (n=76) sample size and indirect sampling method (27). This study only reported incidence in total stroke, however breakdown of stroke type is not reported.

Tillin *et al* (SABRE study) reported age and sex-stratified incidence rates of combined ischaemic and hemorrhagic stroke among South Asians. The SABRE study is a prospective population-based study collecting data from 1988 to 2011. This study found higher incidences in both South Asian men and women at an earlier age (<55 and 56–70 years). Of interest is the reduction in difference among men in the 70+ year group (South Asian: 1290/100000 person-years vs white British 1260/100000 person-years) whereas South Asian women continue to an increased rate (28). This study only reported incidence in total stroke, however breakdown of stroke type is not reported.

Ramadan *et al* (29) was the only study to report the incidence of stroke in both first-time total stroke and ischaemic stroke only. This cohort study recruited Pakistani and white British patients at Bradford Teaching Hospitals NHS Foundation Trust between 01/05/2013 and 30/04/2014. After adjusting for age, standardised to the WHO world population, South Asians had a greater incidence of both total stroke and ischaemic stroke compared to the white British population. In this study, 81.5% of stroke events were ischaemic in white British (ischaemic: 351, total stroke: 438) and 84.3% in Pakistanis (ischaemic: 70, total stroke: 83).

Table 2--1: Summary of studies which report incidence rate.

Studies	Study period	Type of study	Sample size		Incidence	
			White British	South Asian	White British	South Asian
Total stroke						
Ramadan *et al* (29) [+]*	2014-2015	Cohort	438	83 (Pakistani)	101 per 100,000 person-years	155 per 100,000 person-years
Hsu *et al* (27)	1996	Cohort	No data	66,555	No data	114.2 per 100,000 persons
Tillin *et al* (28)*	1988-2011	Cohort	M:1564 F:485	M:1259 F:258	**Men** <55 years: 300 56-70 years: 340 70+ years: 1260 **Women** <55 years:0 56-70 years: 310 70+ years: 920	**Men** <55 years:120 56-70 years:540 70+ years:1290 **Women** <55 years: 80 56-70 years: 510 70+ years: 1690
Ischaemic only						
Ramadan *et al* (29)[+*]	2014-2015	Cohort	351	70 (Pakistani)	80 per 100,000 person-years	132 per 100,000 person-years

[+]Study population only included those with first-time stroke. *Incidence rates reported are age-adjusted.

The paucity of studies in this demographic has resulted in the data regarding the prevalence of stroke being low. The only data regarding the prevalence of stroke as a whole in the UK South Asian population originates from the 2004 UK census. From the last UK governmental report focusing on ethnic minority groups based in 2004, the prevalence of all types of strokes in the white British population has been reported to be 2.4% in men and 2.2% in women, which is higher than in UK residing Indian men (1.1%) and women (1.2%), Bangladeshi men (1.8%) and women (1.7%), and Pakistani men (1.8%) women (30). There has yet to be data specifically for ischaemic stroke prevalence for UK-residing South Asians.

These inverse ethnic differences in incidence and prevalence may be explained by differences in stroke outcomes, such as post-stroke complications leading to poorer survival rates among South Asians (31). Three studies identified reported mortality rates in those with total stroke only. No study has reported the mortality rate of UK South Asians with ischaemic stroke only. Hsu *et al* reported a crude mortality rate of South Asian high practices of 22.5 per 100,000 28 days after a stroke event (27). Another study by Conway and Lip took place between 1998-2000 in a hospital located in the inner-city of West Birmingham. The Indo-Asian population's age-adjusted all-cause mortality ratio was found to be 0.90 (95% CI: 0.65-1.27, p=0.56) compared to the white British (32).

Harding *et al* report mortality data obtained from the Office for National Statistics death data, stratified by the subjects country of birth (33). The authors reported age-adjusted mortality rates from three, 5-year intervals, 1979-1983, 1989-1993 and 1999-2003, which shows across all ethnic groups a decrease in mortality rate. The findings also demonstrate that even though there is a decrease, this is not equal across all ethnic groups with Bangladeshi men still

representing a greater mortality rate compared to those born in England and Wales (Table 2-2) (33). The poorer outcome of stroke seen in South Asians may only occur in the short term, with a 1-year ischaemic stroke mortality study finding South Asians more likely to survive in the long term compared to their white British counterparts (27).

Table 2-2: Age-adjusted mortality rate per 100,000 total strokes (CI 95%) in England and Wales, by country of birth among those aged 30–69 years (33).

Place of birth	Years 1979–1983		1989–1993		1999–2003	
	Total sample	Mortality rate per 100,000 total strokes	Total sample	Mortality rate per 100,000 total strokes	Total sample	Mortality rate per 100,000 total strokes
Men						
England and Wales	9,901,394	58.8 (58.1 - 59.4)	10,401,929	38.9 (38.4 - 39.5)	11,325,598	26.8 (26.4 - 27.3)
Indian	130,003	97.4 (88.7 - 106.2)	151,155	54.9 (49.5 - 60.4)	160,662	35.2 (31.4 - 39.1)
Pakistani	48,551	58.5 (43.2 - 73.8)	74,297	64.2 (54.3 - 74.1)	102,401	42.3 (35.7 - 48.9)
Bangladeshi	15,909	117.1 (79.8 - 154.5)	25,551	123.8 (99.2 - 148.4)	43,305	83.5 (68.3 - 98.8)
Women						
England and Wales	10,368,408	45.6 (45.1 - 46.2)	10,683,031	29.6 (29.2 - 30.0)	11,582,990	20.6 (20.2 - 21.0)
Indian	118,711	64.0 (56.8 - 71.3)	150,548	39.1 (34.4 - 43.8)	168,387	26.1 (22.8 - 29.5)
Pakistani	33,013	Not reported	65,538	47.1 (36.7 - 57.5)	96584	35.0 (28.7 - 41.3)
Bangladeshi		Not reported		Not reported		Not reported

Data originates from the Office for National Statistics death data and is presented in Harding *et al*. 2008 (33)**.** Total stroke includes ischaemic and haemorrhagic stroke.

It should be recognised that mortality is highly complex, arising from several other factors which tend to differ between ethnic groups. A study in 2007, which explored the possible causes of higher mortality in South Asians, revealed that diabetes mellitus was an independent predictor of mortality (*b*=1.76, 95% CI 1.14–2.70) (34). To gain further insights into the underlying aetiology of stroke in different ethnic groups, it is vital to examine other factors that variably contribute to stroke and related mortality.

2.3.3 Age of onset of stroke

There is a paucity of data on the age of stroke onset in South Asians. Of the available data, two studies report the age of stroke event, Banerjee *et al* (35) and Gunarathne *et al* (36). Gunarathne *et al* study collected patients between 1997–2005 for a cohort study in west Birmingham. This study reports South Asians ischaemic stroke onset occurred about 5 years earlier in South Asian men and 10 years earlier in South Asian women than in white British patients. Though the trend will likely be similar to the current day, data reported in this study were collected between 1997-2005 with only 420 South Asians.

Banerjee *et al* used a prospective database of all admissions to the St Mary's Hospital stroke unit (35). They focused only on ischaemic stroke between 2003 and 2007 and recruited 72 South Asians and 496 white British subjects. The breakdown of total stroke consisted of 89% ischaemic in white British (ischaemic: 441, total stroke: 496) and 81% in Bangladeshis (ischaemic: 58, total stroke: 72). This study reported the average age of stroke events in UK South Asians being 65 years compared to 73 years in white British. With a 17-year paucity, more current data is needed in a larger sample size to identify if the previous age of onset difference persists. Banerjee *et al* also reported stroke subtype using the Oxford Community

Stroke Project (OCSP) Classification. Of the subtype of ischaemic stroke occurring, small vessel occlusion appears to have a greater prevalence among South Asians (35), however, classification using the TOAST system has yet to be reported among this population.

In summary, there is a clear indication of ethnic differences in incidence and prevalence, and age of onset of stroke among South Asians and white British populations. To gain insights into the aetiology of these ethnic differences, I examined major risk factors for stroke including atrial fibrillation, cardiometabolic risk (diabetes mellitus, hypertension, dyslipidaemia, obesity and body fat distribution) as well as socioeconomic and lifestyle factors.

2.4 Cardiometabolic Risk Factors

The discrepancy in epidemiological traits of stroke in the two ethnicities can be, in part, associated with the difference in stroke risk factor prevalence. The last UK government report for ethnic minority health conditions was reported in 2004. This 18-year void of information has been partially filled with small sample size studies, thus, an update in this field is critical.

Cardiometabolic risk factors are one of the major areas in which prevalence discrepancies have been reported. Cardiometabolic risk is characterised as the risk of disease arising related to the cardiovascular system. These include hypertension, hypercholesteremia, diabetes mellitus and obesity. From the available literature, 2 studies reported total stroke and 2 reported ischaemic stroke only cardiometabolic risk factors (Table 2-3). As described in chapter 2.3.2, Ramadan *et al* conducted a prospective 12-month study consisting of 273,327 adults who are in the catchment area of the Bradford Teaching Hospitals NHS Foundation Trust (29). In this study, the authors described white British and Pakistani cardiovascular risk

factors in those with first-ever total stroke between 2014-2015 (Table 2-3). Total stroke is broken down to 80.1% ischaemic in white British (ischaemic: 351, total stroke:438) and 84.3% in Pakistanis (ischaemic: 70, total stroke: 83).

Bourke *et al* also only reports total stroke in Bangladeshi and white British patients recruited from the Royal London Hospital between 1997–2002. This study recruited 779 Bangladeshis and 186 white British patients with total stroke. Total stroke is broken down to 89% ischaemic in white British (ischaemic: 165, total stroke:186) and 86% in Bangladeshis (ischaemic: 68, total stroke: 79).

As described in chapter 2.3.3, Banerjee *et al* used a prospective database of all admissions to the St Mary's Hospital stroke unit between 2003-2007 (35). The authors identified 72 South Asians and 496 white British patients with total stroke. The breakdown of total stroke consisted of 89% ischaemic in white British (ischaemic: 441, total stroke: 496) and 81% in Bangladeshis (ischaemic: 58, total stroke: 72).

One study reported cardiovascular comorbidities in ischaemic stroke patients. As described in chapter 2.3.3, Gunarathne *et al* reports data recorded in West Midlands Regional Health Authority Hospital Activity Analysis register. The data reported was collected over a 9 year period between 1997–2005 and consisted of 420 South Asian and 1709 white British patients.

Table 2-3: Summary of the prevalence of cardiometabolic risk factors in South Asians, compared to white British patients with total and ischaemic stroke only.

Comorbidities	Study period	Type of study	Sample size		% prevalence	
			White British	South Asian	White British	South Asian
Diabetes mellitus						
Total stroke						
Ramadan *et al* (29)*[-]	2014-2015	Cohort	438	83	21	51
Bourke *et al* (22)[+]	1997–2002	Cohort	186	79	11	51
Banerjee *et al* (35)	2003-2007	Cohort	496	72	15	54
Ischaemic stroke						
Gunarathne *et al* (36)*	1997–2005	Cohort	1709	420	29.8	50.3
Hypertension						
Total stroke						
Ramadan *et al* (29)*[-]	2014-2015	Cohort	438	83	69	70
Bourke *et al* (22)[+]	1997–2002	Cohort	186	79	60	63
Banerjee *et al* (35)	2003-2007	Cohort	496	72	64	87
Ischaemic stroke						
Gunarathne *et al* (36)*	1997–2005	Cohort	1709	420	58.6	73.7
Hyperlipidaemia						
Total stroke						
Ramadan *et al* (29)*[-]	2014-2015	Cohort	438	83	81	88
Banerjee *et al* (35)	2003-2007	Cohort	496	72	45	70
Ischaemic stroke						
Gunarathne *et al* (36)*	1997–2005	Cohort	1709	420	9.2	10.8
Atrial fibrillation						
Total stroke						
Ramadan *et al* (29)*[-]	2014-2015	Cohort	438	83	29	10
Bourke *et al* (22)[+]	1997–2002	Cohort	186	79	13	4
Banerjee *et al* (35)	2003-2007	Cohort	496	72	23	12
Ischaemic stroke						
Gunarathne *et al* (36)*	1997–2005	Cohort	1709	420	34.8	11.8

Prevalence difference in South Asians, compared to white British patients.[-] Study whose South Asian group only consist of those who identify as Pakistani. [+] Study whose South Asian group only consist of those who identify as Bangladeshi. *population with first-time stroke event only.

2.4.1 Diabetes mellitus

Diabetes mellitus is one of the leading causes of increased stroke risk and poor outcomes. Among South Asians, the prevalence of diabetes mellitus has been reported in 3 studies to be higher (51-54%) compared to white British (8-29.8%) populations with total stroke (Table 2-3). Of these studies, only one reported the diagnostic criteria for diabetes which were Banerjee *et al*. Banerjee *et al* defined diabetes as fasting blood glucose >7.0 mmol/l or random blood glucose >11.1 mmol/l, on at least two occasions (at least two days post-admission), or on the basis of past medical history (self-reported or previously documented in case notes) or medication list on admission. Gunarathne *et al* reported the prevalence of diabetes in those with ischaemic stroke only, in which South Asians reported a similar prevalence as the total stroke studies (36). Gunarathne *et al* followed a slightly different definition compared to Banerjee *et al* of the presence of relevant clinical history and biochemical evidence of at least two measurements of fasting blood sugar readings >7.8 mmol/l (36).

It is postulated that the high prevalence of insulin resistance begins before birth, with this shown in one study where South Asians had ~10% higher umbilical cord insulin levels compared with white British umbilical cord samples, leading to a greater insulin tolerance at birth (37). Although stringent management of blood glucose later in life can reduce the risk of stroke, the lack of randomised control studies involving UK residing South Asians and diabetes mellitus management makes it hard to suggest the proportion of reduction in stroke risk that would occur.

2.4.2 Hypertension

Hypertension has been purported to have caused the largest increased risk of ischaemic stroke in both western and South Asian countries (38). Three studies reported hypertension prevalence in the total stroke population and 1 study in ischaemic only populations (Table 2-3). Definitions for hypertension are only reported in two studies, Banerjee *et al* and Gunarathne *et al* (35,36). Gunarathne *et al* defined hypertension as blood pressure >140/90 mm Hg on at least two separate readings (36). Banerjee *et al* defined hypertension as BP >140/90 on more than two occasions (at least two days post-admission), or based on past medical history (self-reported or previously diagnosis) or medication list on admission(35). In both total and ischaemic stroke only, South Asians report a marginally higher prevalence of hypertension compared to the white British population.

In the general population, this modifiable risk factor has had conflicting results regarding prevalence in UK residing South Asians (39–41). According to the latest minority report published by the UK government, hypertension in the general population is higher than that in South Asians (30). However, this is inconsistent with multiple smaller sample size studies reporting South Asians having a higher prevalence compared to the white British population (42,43). This inconsistency is likely to be down to heterogeneity within the South Asian population, with Indians generally possessing increased blood pressure, with Bangladeshi and Pakistanis having several pressures (44,45). Furthermore, the prevalence of this risk also seems to be increasing in South Asians (1997-99: 84.6% vs 2003-05: 88.9%), whilst no change was observed in the white British population, with prevalence staying at ~76.0% during the same period (46). This is further supported as South Asians have been found to have higher systolic (SBP) and diastolic blood pressure (DBP) compared with their white

British counterparts. Additionally, South Asian SBP and DBP were positively associated with stroke risk (P<0.001) when compared to their white British counterparts (47).

Of interest is the increased arterial stiffness reported in UK South Asians, resulting in adverse and disproportional impacts on mean arterial pressure, compared to the white British population (48,49). This is likely to be multifactorial, however genetic susceptibility along with the simultaneous presence of metabolic factors are likely to contribute to this. Partnering the increased stiffness with the inflammatory and oxidative stress promotes the pathological processes of atherosclerosis, leading to ischaemia.

2.4.3 Hyperlipidaemia, obesity, and body fat distribution

There is strong evidence that many ischaemic stroke risk factors, including dyslipidaemia and diabetes mellitus, are a consequence of obesity. One study, Ramadan *et al*, has reported obesity in a South Asian total stroke population however no definition of obesity is provided. The authors report obesity prevalence in those with first-time total stroke events to be greater in Pakistanis than in white British patients (South Asian:34% vs white British:26%) (29). General overweight/obesity prevalence in South Asians is lower compared to the white British population, with men seeing the largest prevalence difference of 16.3% and women only reporting a 1% difference (30), though prevalence has yet to be reported in those with ischaemic stroke. It has been observed that South Asian infants born in the UK have a lower birthweight, suggesting a genetic origin (50,51). With these seemingly promising metrics regarding overall obesity, it is worth noting the differences in fat distribution seen within the South Asian community. Multiple studies have reported South Asians having a greater accumulation of visceral fat and subcutaneous fat around the abdomen as well as increased

skinfold thickness compared to their white British counterparts (52–55). Increased central obesity in South Asians has already been identified to increase ischaemic stroke risk factors, such as raised C-reactive protein (CRP) concentration (56). Furthermore, it has been suspected that increased central obesity has resulted in the South Asian community having an atherogenic lipid profile (34,41).

Three studies reported hyperlipidaemia in the South Asian stroke population, two in the total stroke population and one reported in those with ischaemic stroke. Each study has a slightly different definition of hyperlipidaemia. Of the total stroke studies, Banerjee *et al* definition of hyperlipidaemia is as a total cholesterol >5.0 mmol/l, or defined by past medical history (self-reported or previously documented in case notes) or medication list on admission (35). Ramadan *et al* do not provide a definition of hyperlipidaemia. In both studies, South Asians report a greater prevalence of hyperlipidaemia (Table 2-3). Gunarathne *et al*, who reported ischaemic stroke only, defined hyperlipidaemia as a total cholesterol level >5.2 mmol/l (36). Compared to total stroke studies, the prevalence of hyperlipidaemia reported in both South Asians is considerably lower. Though the study does not provide a reason for this difference compared to other studies, a possible explanation is the recruitment period for subjects in this study, between 1997-2005, where the collection of cholesterol measurements might have been lower. Additionally, current treatment was not considered in the study and thus those on treatment are less likely to be diagnosed with hyperlipidaemia. Nonetheless, in this study, South Asians continue to present with a greater prevalence of hyperlipidaemia (Table 2-3). In studies which have not focused on stroke, similar or higher LDL and total cholesterol concentrations, regardless of sex, have been reported in South Asians when compared to their white British counterparts (57–59). Additionally, HDL-cholesterol has been reported to be lower in South Asians, with this not being linked to differences in diet (57,59). Among

ischaemic stroke cases, hyperlipidaemia prevalence appears to be significantly greater in South Asian stroke patients (36).

Though a UK based study has yet to report the origins of these differences, it could be found in the adipose tissue overflow hypothesis. This hypothesis posits that the increase in adiposity goes through layered stages, with the superficial subcutaneous being the primary site of growth followed by secondary sites of visceral and deep. Sniderman *et al* suggest that the primary site of adiposity is underdeveloped in South Asians compared to white British populations (60). This results in the primary site being overwhelmed at a quicker rate and thus increasing the propagation of deep and visceral adipose tissue.

2.4.4 Atrial fibrillation

Three studies reported atrial fibrillation prevalence in the total stroke population and one study in ischaemic only populations (Table 2-3). Two studies report the diagnostic criteria for atrial fibrillation, Banerjee *et al* and Gunarathne *et al* both require past medical history (self-reported or previously documented in case notes), and/or 12-lead electrocardiogram results since admission (35,36). In Ischaemic stroke populations, South Asians reported an 11% lower prevalence of atrial fibrillation compared to white British patients. Current studies focusing on those with ischaemic stroke have been small and mostly local with many not considering treatment data prior to admission. In the general population, South Asians present with up to a near six-fold lower prevalence of atrial fibrillation compared to the UK (61–63). There is no significant difference present between the sexes (61).

The exact cause of the disparity in the prevalence of atrial fibrillation has yet to be concluded, however, it was previously considered that atrial diameter influenced atrial fibrillation risk (64–66). It had already been determined that South Asians had smaller left atria compared to their white British counterparts, thus it was assumed to be the cause of the lower prevalence of atrial fibrillation (63,67). The smaller left atria can be linked to a broader, smaller stature in general when compared to the white British population (67–69). However, as Gillott *et al*. (2016) suggests, comorbidities such as hypertension, which has a greater prevalence in South Asians, would enlarge the left atria, thus increasing the risk with age (61). Furthermore, in mice studies, the administration of cholinergic agonists was able to continuously sustain an atrial fibrillation state, contradicting the hypothesis that the size of the atria affects the risk of atrial fibrillation (70). This leads to the suggestion that ethnic variation found in atrial electrophysiological parameters could cause a lower risk in South Asians (71). Ion channels, such as potassium and sodium, have been shown to have ethnic-specific polymorphisms (72). No confirmed South Asian specific genetic variants which could result in the protective effect seen have been identified (62).

2.5 Migration and lifestyle risk factors

As described above, the number of observational studies relating to South Asians with ischaemic stroke in the UK is low. This also translates when describing environmental factors such as migrations and lifestyle factors in this demographic. For this reason, I included papers which are related to the South Asian community in the UK rather than specifically in a stroke setting.

Migration acculturation has been characterised as the adoption of attitudes, values, beliefs, and behaviours which are prevalent in the host country. This was first theorised in 1953 by Social Science Research Council (73). More recently this theory has been used to explain the transition in health behaviours and risk factors (74). Furthermore, acculturation is dynamic, varying between ethnicities, sexes, and generations (75). Acculturation could consequently result in increased or reduced modifiable risk factors for stroke in South Asians. The level of physical activity is associated with an increased risk of diabetes mellitus. A meta-analysis to compare the physical activity of South Asians to white British found that, for both men and women, South Asians reported lower levels of physical activity, with Bangladeshis being found to have the lowest levels when compared to other South Asian groups (76). The associated lower physical activity could promote obesity-induced diabetes mellitus and thus further increase the risk of stroke.

2.5.1 Psychosocial factors

Psychosocial factors were identified, by the INTERSTROKE study, as one of the ten risk factors that 90% of global stroke is attributed (38). Migration, which can increase the risk of psychosocial factors, is an often-overlooked risk factor which likely influences South Asian stroke risk (77). Though it has not been studied in the UK South Asian population, it has been shown that prolonged stress was independently associated with increased ischaemic stroke risk (78) . Evidence suggests the white British population has a significantly higher average household income ($P<0.001$) and significantly lower social deprivation ($P<0.001$) compared to South Asians (79). It has been well reported that lower-income households have up to three-fold higher stroke prevalence when compared to the highest-income households (80). Family roles can also increase stress. South Asians were reported to have significantly greater

social crowding when compared to white British households ($P<0.001$). It has been discussed that although South Asians have a larger social network, this does not necessarily translate into a support network to combat stress (81).

2.5.2 Tobacco use

It has been well-studied that smoking and general tobacco use results in an increased risk of ischaemic stroke (82–85). Two studies, Banerjee *et al* and Ramadan *et al*, have reported smoking prevalence in a South Asian total stroke population. Banerjee *et al* report smoking prevalence as a dichotomous variable 'Smoking history' with no definition provided. The authors report that South Asians smoke less than white British subjects (South Asian:15% vs white British: 33%) (35). Ramadan *et al* report smokers as 'current smoker' or 'ex-smoker'. In both groups South Asians were less likely to be 'current' (South Asian:19% vs white British: 33%) and 'ex-smokers' (South Asian:11% vs white British: 29%) (29). In the South Asian community, it has been suggested that there is a low acceptance of tobacco use among the young and women, however, it is regarded as acceptable at social events (30). Furthermore, a lack of awareness of the health issues of tobacco use appears to be present (86). A breakdown of specific ethnic groups stratified by sex reveals Bangladeshi men had the higher percentage of current smokers (40%) followed by Pakistani (29%) and Indians (20%) (30). South Asians use a range of different tobacco-based products. These include chewing/pipe tobacco, chukka, chutta, chillum and bidi's (87). These types of tobacco are usually high in nicotine and tar (87). Chewing tobacco was most prevalent among the Bangladeshi demographic, with 9% of males and 16% of females reported (30). Furthermore, Bangladeshi women have the highest prevalence of tobacco use. For both types of tobacco use, under-reporting has been a major

problem which is difficult to quantify. Though South Asians report a lower prevalence, it should be considered that these studies solely rely on self-reporting (30,88).

2.5.3 Diet

UK residing South Asian diets, consisting of carbohydrate rich foods such as rice and bread, appears to remain unchanged from those living in South Asia (89). This di*et al*so includes higher fibre and lower sugar intake whilst the white British population has a more varied diet (90). Overall South Asians are more likely to be vegetarian, though this varies depending on religion and ethnicity (91). It has been shown that a vegetable and fruit-based diet decreases the risk of ischaemic stroke (92). Furthermore, salt intake also varies. The Health Survey for England in 2004 reported that 93-95% of South Asian men added salt during cooking when compared to the general population (56%). This was matched in women where the salt intake was ~40% higher (93). Salt intake has been shown to increase the risk of hypertension (94). However, greater salt has also been shown to directly increase the risk of stroke, independent of the effect salt has on blood pressure (95).

2.6 Summary

Although stroke incidence and mortality rates are declining in the UK, these reductions are ten-fold less in South Asians than in the white British population (96). With the UK South Asian population continuing to increase (97), the need to understand and investigate the greater burden of stroke in this community is becoming more evident. With current data, I hope to be able to fill in the epidemiological gaps.

3 Research methods

As shown in my literature review, there is a lack of current data available to effectively describe ischaemic stroke in this South Asian demographic. Specifically, no studies have been published in the last decade that reports on the mortality rate, incidence rate or prevalence rate of ischaemic stroke among the South Asian population. Furthermore, the age of onset of first-time ischaemic stroke, which is often a good indicator to represent how different ethnicities suffer from an ischaemic stroke, is not reported in recent studies.

3.1 Study design

To be able to report data such as incidence and mortality rates, a longitudinal cohort study would be needed. A cohort study is a type of observational study that follows a group of people (a cohort) and compares their outcomes (ischaemic stroke) based on their exposure to one or more risk/environmental factors over a period of time. In this case, the cohort would be composed of South Asians and white British people who are at risk of developing ischaemic stroke. The exposure would be defined as having certain medical conditions or lifestyle factors that increase the likelihood of having an ischaemic stroke, such as hypertension, diabetes, smoking, central obesity or atrial fibrillation. The outcome which I would measure is the occurrence of an ischaemic stroke, death from an ischaemic stroke or survival after an ischaemic stroke within the study period. With a cohort study, I could then compare the rates of these outcomes between South Asians and white British people and identify any differences or similarities between these ethnic groups. I would also be able to adjust for potential confounding factors that may influence the relationship between exposure and outcome, such as age, sex and diet. This could be conducted in a prospective or

retrospective manner. In a prospective cohort study, I would recruit patients who had not had a previous ischaemic stroke event and follow them over a fixed period of time to identify who suffers from an ischaemic stroke event. As it would be prospective, I would be able to pick specific variables to include in the study. This type of study would be costly and require patients to be followed over a long period of time. In a retrospective study, the data would already be collected and I would identify the population of interest, which would significantly decrease the cost. To do this I would need to identify a dataset which I would be able to access and that would include the specific variables of interest. An example of this is the Clinical Practice Research Datalink (CPRD) which collects anonymised patient data from primary and secondary care sources. With CPRD, I would have a large population within my data set to calculate the incidence and mortality rate of ischaemic stroke however, the cost associated with using this dataset would be too high for this study.

An alternative option is conducting a cross-sectional study, which is a type of observational study that analyses data from a population at a single point in time. A cross-sectional study approach to study ischaemic stroke in South Asians and white British patients would involve selecting a sample of patients with ischaemic stroke along with variables of interest, such as age, gender, ethnicity, risk factors, treatment options, etc. The data would be collected at one time point using surveys, interviews, medical records or other sources. The data would then be analysed to compare the differences and similarities between the two ethnic groups in terms of stroke prevalence, severity, outcomes, and associated factors. A cross-sectional study is more limited in the type of data it can report. This study type only collects data from a single point in time, so you are unable to report the incidence of ischaemic stroke or temporal changes. A cross-sectional study approach is typically used to provide a snapshot of the during the time of study period and is typically cheaper and quicker to conduct compared

to a prospective cohort study. For this reason, cross-sectional studies are usually conducted before a prospective cohort study, with any potential correlations identified being further investigated in longitudinal studies. With a cross-sectional study, you can either conduct the study yourself or use an existing data set. As discussed above, an example of an existing dataset includes CPRD, which requires a fee to use and as it is retrospective in its design, specific variables of interest, such as ischaemic stroke subtyping, are not always collected. A prospective dataset is needed to answer specific questions regarding ethnic differences in relation to ischaemic stroke. This was, in part, why the BRAINS prospective study was started, with an aim of collecting data related to stroke from multiple countries to identify epidemiological and genetic differences among differing ethnicities. For the reasons discussed above, including cost, length of the study period, and the data available, I chose to conduct my cross-sectional studies using BRAINS.

3.2 BRAINS biorepository

The BRAINS biorepository is an ongoing global (UK, Middle East, Sri Lanka, and India) repository of stroke in patients of South Asian and white British ethnicities. Patients admitted to the study were recruited at 21 secondary care sites across England (Figure 3-1) and two in India (Table 3-1). The BRAINS study meets all ethical and consent standards set by local institutional review boards at each of the participating sites (Riverside Research Ethics Committee 04/Q0401/40) (Appendix 10.1). The patient recruitment process was performed using the BRAINS protocol (98). The sites chosen (Table 3-1) included regions with large South Asian populations while also being representative of the white British population (Appendix 10.2) (99). The Indian arm screened stroke patients at two hospital sites located in

Kerala (Sree Chitra Tirunal Institute for Medical Sciences and Technology) and New Delhi (All India Institute of Medical Sciences, AIIMS).

Figure 3-1: Distribution of UK recruitment sites.

The green dot denotes the location of a UK recruitment site.

Table 3-1: Recruitment site location for the BRAINS database.

Location	Hospital/Trust	County	Ethnicity	
	UK		**South Asian***	**White British‡**
Southeast England	Ashford and St peter NHS Foundation Trust	Surrey	22	521
	Barts and The Royal London NHS Trust	London	211	169
	West Middlesex University	London	54	0
	Croydon University Hospital	London	77	0
	Northwick Park Hospital	London	336	4
	Newham University Hospital	London	93	0
	Hillingdon Hospital	London	116	0
	Charing Cross/Imperial Hospital	London	92	695
	Luton & Dunstable Hospital	Bedfordshire	113	2
	William Harvey Hospital	Kent	0	156
	Queen Elizabeth the Queen Mother Hospital	Kent	2	441
South England	Princess Royal Hospital	West Sussex	0	12
	Brighton and Sussex University Hospitals NHS Trust	East Sussex	2	268
West Midlands	Manor Hospital Walsall	West Midlands	26	0
	New Cross Hospital/ Wolverhampton	West Midlands	49	0
	Birmingham Heartlands Hospital	West Midlands	16	0

	City Hospital Birmingham (Sandwell General Hospital)	West Midlands	164	0
Northwest England	Queen's Park Hospital / Blackburn	Lancashire	23	0
North England	Bradford Teaching Hospital	West Yorkshire	193	0
	Airedale General Hospital	West Yorkshire	7	3
	Leeds General Infirmary	West Yorkshire	54	20
India				
South	Sree Chitra Tirunal Institute for Medical Sciences and Technology	Kerela	282	0
North	All India Institute of Medical Sciences, AIIMS	New Delhi	997	0

*South Asians are classified as self-reported Indian, Pakistani, Sri Lankan, or Bangladeshi origin. ‡ White British include those who self-reported as white British or white Irish.

3.3 Data Collection

Data was collected independently from my studies though I believe it's pertinent to describe relevant information. Each centre named above was chosen as it had a developed stroke service and a stroke physician/neurologist. Data was collected by a local trial coordinator and only once written consent was received (Appendix 10.3). For those unable to provide written consent, surrogate consent was taken (Appendix 10.4). As this is a non-interventional observational study, no extra testing was conducted for the specific use in the BRAINS dataset. All data collected for the BRAINS database occurred during the patient's hospital stay.

Detailed demographic data including age, sex, and ethnicity were collected during a nurse-led interview (Appendix 10.5 and 10.6). All those who were over 18 years of age at the time of the stroke event were considered for the study to ensure a representative sample. Ethnicity was obtained via self-identification. South Asians are classified as Indian, Pakistani, Sri Lankan, or Bangladeshi origin. White British patients include those who self-reported as white British or white Irish. The breakdown of the ethnicities recruited in BRAINS are summarised in Table 3-2. Ethnicity throughout the thesis is classified as South Asians living in India (ISA), UK residing South Asians (BSA), and white UK British (WB) stroke patients. All analyses in this study compared ISA and BSA with WB patients as the reference group.

Table 3-2: Breakdown of ethnic groups for South Asians and white British ischaemic stroke patients in the UK and India BRAINS database.

	UK		**India**	
	Men	**Women**	**Men**	**Women**
South Asian	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Indian	588 (64.8)	319 (35.2)	863 (67.5)	415 (32.5)
Pakistani	324 (63.2)	189 (36.8)	1 (100.0)	0 (0.0%)
Bangladeshi	120 (70.2)	51 (29.8)	-	-
Sri Lankan	42 (71.2)	17 (28.8)	-	-
Total South Asian	1074 (65.1)	576 (34.9)	864 (67.6)	415 (32.4)
White British	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
White British	1269 (56.5)	977 (43.5)	-	-
White Irish	27 (60.0)	18 (40.0)	-	-
Total white British	1296 (56.6)	995 (43.4)	-	-

n, sample size.

Clinical data was recorded via a standardised questionnaire. Brain imaging (CT and MRI scans) at each reporting site was used to determine and confirm a stroke event by an onsite stroke physician. TOAST subtyping criteria was used to assign a classification of each ischaemic stroke case (100). This classification was determined by clinical features and results of tests including brain imaging (CT, MRI), cardiac imaging (echocardiogram and electrocardiogram), extracranial vessel imaging (Doppler, MRA, CTA), and blood analysis. TOAST subtype classification consists of five categories: large artery atherosclerosis, small vessel occlusion, cardioembolism, stroke of other determined aetiology, and stroke of undetermined aetiology. Decisions on classifications were made by the reporting site, with

BRAINS not collecting diagnostic information used for the decision-making. Without the complete information to reassess the decision made at the reporting site, the TOAST classifications reported at each BRAINS site could vary. The potential variation in misclassification between sites would result in a nondifferential bias as possible misclassification would be expected to occur in all ethnic groups. Furthermore, as the sample size of those with TOAST classification data among the three ethnic groups is high, misclassification is not expected to affect the overall results.

This thesis relies on data from BRAINS, which only recorded the presence or absence of comorbidities/risk factors for stroke in a dichotomous form (yes/no). Furthermore, I did not have access to continuous data relating to included comorbidities and risk factors. For example, I did not have access to blood pressure measurements used to identify hypertension, cholesterol, or glycated haemoglobin among the patients included. Therefore, my results might not capture the full spectrum of comorbidities and risk factor profiles and their impact on stroke recovery. Risk factors for cases were defined as: hypertension diagnosed at discharge (≥140/90mmHg), previous diagnosis of hypertension or pre-stroke treatment with antihypertensive; hypercholesterolemia defined by a previous diagnosis or serum total cholesterol >5.2 mmol/L; diabetes mellitus classified from a previous diagnosis of type I or II diabetes mellitus; atrial fibrillation cases were diagnosed with an ECG throughout the hospital stay or from a pre-existing diagnosis. Previous diagnosis of ischaemic heart disease was collected from clinical records. Smoking and alcohol history was recorded if the patient had/does so on a regular basis. BMI (kg/m^2) was calculated using the height and weight data. Central obesity was defined by increased waist circumference (Men: >102cm, Women: >88 cm) or BMI (≥30) (101). Previous stroke history was collected via self-reporting or the patient's medical records.

Medication history included data on treatment before admission and following discharge. This data included antiplatelet (Aspirin, Clopidogrel, Dipyridamole), antihypertensives, statins and anticoagulant (Warfarin, Rivaroxaban, Apixaban, Dabigatran, Edoxaban) status.

BRAINS did not collect information relating to socioeconomic factors such as income or employment. For the UK arm of this project, I was able to link the data in BRAINS with the Index of Multiple Deprivation (IMD) data published by the UK government in 2019 using the recruiting hospital's location (102). The IMD is a measure of relative deprivation for small areas in England and Wales. The mean IMD is higher among BSA compared to WB (BSA: 21286.7, WB:17133.1) suggesting that BSA suffer from greater social deprivation. As this linkage was only possible for the UK participants and not based on the patient's specific location or socioeconomic factors, I did not use it for analysis. Instead, I focused on other variables that were more relevant and consistent across the BRAINS database.

3.4 Quality control and data analysis

My project is the first to use the UK and India arm of the BRAINS database and as such, quality control was needed. All data used in this study had been anonymised and analysed using SPSS v25.0 Statistical Software for Windows 11. Two versions of the UK database existed in separate Excel datasets. The first was data collected using a paper questionnaire which was subsequently inputted into an Excel file by research practitioners. Partnered with this were the scanned questionnaires which were digitalised for later reference. The paper questionnaire was utilised to record data from 2005-2015. The second dataset (2015-

onwards) utilises a digital version of the questionnaire accessed through a web portal. There were no differences in the questions asked or data collected between these two datasets. The Indian arm of BRAINS collected data using the paper version of the questionnaire, with a local trial coordinator converting the questionnaire data into a separate Excel file for each hospital. All four datasets were converted to an SPSS data file. Once in SPSS, I worked on standardising the variables imported as each original dataset was created by separate coordinators. This involved changing variable names to match across datasets, ensuring the coding used matched across datasets, and patients were not recorded multiple times between datasets. Duplicate cases were of concern as patients could be recorded twice during the transition from paper to electronic datasets.

Categorical data was standardised with the following coding system: 0=False, 1=True, 2=unknown at time of collection, 3=New Diagnosis (where applicable) as an example. The variables used in this study along with the data type and variable range or code are presented in Table 3-3.

Table 3-3: Questionnaire data coded.

Variable name	Variable type	Variable range or code
Age	Continuous	Range: 18 - 100
Location	Categorical	0 = White British 1 = BSA 2 = ISA
Sex	Categorical	0 = Women 1 = Men
Stroke subtype (TOAST)*	Categorical	1 = Large artery atherosclerosis 2 = Small vessel occlusion 3 = Cardioembolism 4 = Other determined aetiology 5 = Stroke of undetermined aetiology
Stroke history	Categorical	0 = Recurrent 1 = First stroke event 999 = Missing
Hypertension	Categorical	0 = False 1 = True 999 = Missing
Hypercholesterolemia	Categorical	0 = False 1 = True 999 = Missing
Diabetes mellitus	Categorical	0 = False 1 = True 999 = Missing
Ischaemic heart disease	Categorical	0 = False 1 = True 999 = Missing
Atrial fibrillation	Categorical	0 = False 1 = True 2 = New diagnosis 999 = Missing
Central Obesity	Categorical	0 = False 1 = True 999 = Missing
Smoking history	Categorical	0 = False 1 = True 999 = Missing
Alcohol history	Categorical	0 = False 1 = True 999 = Missing

TOAST, classification denotes five subtypes of ischaemic stroke (100).

I follow similar definitions as described in my review, prevalence, risk factors, and comorbidity. For prevalence, I am using Gordis Epidemiology definition: 'the number of affected persons present in the population at a specific time divided by the number of persons in the population at that time' (24). Comorbidity is defined as the co-occurrence of two or more long-term conditions in an individual (25). A risk factor is any exposure or behaviour that increases the likelihood of an individual developing a particular disease or health condition (26).

Quality control varied depending on the data type. Continuous variables were analysed using a mixture of descriptive statistics and data visualisations, including mean, median, standard deviation, minimum, maximum, quartiles, and histograms. Data normality was defined as normal if the Shapiro-Wilks test returns $P>0.05$ or using a quantile-quantile (q-q) plot. Categorical data was analysed using descriptive statistics and cross-tabulations. I compared variables that involved logical combinations of results, such as the presence or absence of hypertension and antihypertensive medication use. For example, if a patient were not recorded as having hypertension but were receiving antihypertensive medication, I would record them with hypertension. In cases where anomalous data was found, questionnaires would be checked in case of human error during data submission. If the questionnaire contained incorrect data, then attempts to obtain the correct information from the collection site were made. However, if this was not possible then this would be recorded as missing.

3.4.1 Missing data

As with any observational study collecting detailed medical information, the percentage of missing data for each variable differed between sites and the question asked. The percentage of missing data for each variable used, along with comparisons for sex, age of event and ethnic breakdown are summarised in Appendix 10.7. There are multiple options which could minimise the impact of missing data for my research, including deletion of cases with missing data, imputation, and exclusion of cases from specific analysis, each offering different pros and cons. First, I wanted to identify if the age of the event of stroke was different between those with missing and complete data for each ethnicity, I used an independent *t*-test and summarised the results in Table 3-4. I used age as the dependent variable for this analysis as the age of the event was a variable with a 100% response rate in the sub-population (ischaemic stroke only in 18+ year South Asian/white British population) and it would be a good population descriptor to see if age affected the percentage of missing data. TOAST subtype (28.1%) and central obesity (25.3%) saw the largest percentage of missing data within the dataset, with this largely originating from the WB population. Age, sex, and ethnicity variables contained no missing data. To assess if missing data were skewed towards a particular ethnic group or location, I used a Little's Missing Completely at Random (MCAR) test using the selection criteria of my study (ischaemic stroke only in 18+ year South Asian/white British population) and for each chapter of my study (103). MCAR test returns the probability of missing data of a variable that is unrelated to any other measured variable and is unrelated to the variable with missing values itself. For example, in my research, this test could help identify a possible failure in recording observations at a particular recruitment site. If the MCAR test returns a significant *P*-value ($P<0.005$), the data in my study would exhibit a pattern of missing data. The results from the MCAR test on my dataset reported a *P*-value of 0.53, suggesting the data was missing completely at random.

Imputation is the process of replacing the missing data with estimated values. This approach enables the inclusion of cases with missing data in analyses, instead of omitting them. The imputed data would be based on the cases that have complete data, and this can be calculated via multiple routes such as mean or median imputation or regression imputation. Mean or median imputation is the simplest type of imputation as it replaces all missing values in the variable of interest with the same imputation value. By using this method, there is an increased risk of biased results as the distribution of imputed variables can be distorted, and the variance underestimated (104). Instead of using the same imputed value for every missing value in a variable, regression imputation imputes missing values in a variable by using a regression model based on other variables with complete data. The benefit of this method is that it does not alter the shape of the distribution of the data, and the effect on the variance is minimal (105). This method also requires data to be missing completely at random, which is the case with the data in my study. While regression imputation appears to be the best option for my data, apart from increasing sample size, it does not add anything to the results as the data imputed will be estimated on the complete data. As this study contained over 5000 stroke patients, events with missing data still resulted in a large sample size. For this reason, I focused on excluding cases via listwise or pairwise. Listwise exclusion is based on the premise that if a case has missing data in the variable of interest it would be excluded from the analysis. This can distort the results. An example could be that if smoking or alcohol consumption is not as accepted in one ethnic group compared to other ethnic groups, they could be more likely to not answer the question and thus reduce the number of people included and the number of people reporting alcohol consumption or smoking. An alternative to listwise analysis is excluding cases via the pair-wise technique. The pair-wise technique includes cases in the analysis if they include missing data and will use all available data. This

technique also requires the data to be missing completely at random. For this reason, and as my data was missing completely at random, I used the pairwise exclusion criteria for my analysis. As the BRAINS database was initially designed to assess the role of genetics in South Asian stroke risk overall, the questionnaire questions were numerous and required in some cases detailed answers, the likelihood of missing data was high. To reduce missing data in future studies, ideal studies would be prospective and only focus on the aims of that particular study. This would enable clear, concise, relevant variables, which would be easier to answer and would require less time to complete.

Table 3-4: Comparison of the age of ischaemic stroke event in those with missing and complete data.

	Missing/Complete	**Missing**	**Complete**	***P*-value***
Central obesity	*n*/*n*	mean (SD), years	mean (SD), years	
WB	860/1431	71.3 (13.2)	71.9 (13.4)	0.34
BSA	279/1371	66.9 (13.8)	65.2 (14.8)	0.08
ISA	184/1095	53.4 (14.2)	52 (13.3)	0.18
Smoking history				
WB	229/2062	70.8 (13.4)	71.8 (13.3)	0.32
BSA	103/1547	66.3 (12.4)	65.5 (14.8)	0.59
ISA	9/1270	58.9 (6.8)	52.1 (13.5)	0.13
Alcohol consumption				
WB	553/1738	71.4 (13.1)	71.8 (13.4)	0.58
BSA	188/1462	65.7 (13.9)	65.5 (14.7)	0.84
ISA	6/1273	52.3 (11)	52.2 (13.5)	0.98
Hypertension				
WB	231/2060	70.9 (13.5)	71.8 (13.3)	0.36
BSA	116/1534	67.2 (11.6)	65.4 (14.8)	0.11
ISA	33/1246	50.7 (15.2)	52.2 (13.4)	0.51
Diabetes mellitus				
WB	242/2049	71.2 (13.4)	71.7 (13.3)	0.58
BSA	112/1538	67.3 (11.8)	65.4 (14.8)	0.11
ISA	38/1241	50.1 (16)	52.2 (13.4)	0.34
Hypercholesterolemia				
WB	253/2038	71.2 (13.2)	71.7 (13.3)	0.52
BSA	166/1484	68.5 (11.7)	65.2 (14.9)	0.001
ISA	179/1100	52.4 (14.5)	52.1 (13.3)	0.80
Ischaemic heart disease				
WB	239/2052	71.1 (13.3)	71.7 (13.3)	0.47
BSA	123/1527	67.5 (12.3)	65.3 (14.8)	0.11
ISA	3/1276	55.0 (8.2)	52.2 (13.4)	0.72
Atrial fibrillation				
WB	258/2033	70.9 (13.5)	71.8 (13.3)	0.032
BSA	168/1482	68.0 (12.9)	65.2 (14.8)	0.022
ISA	254/1025	52.2 (13.1)	52.2 (13.5)	0.96
TOAST stroke subtype				
WB	792/1499	69.7 (12.8)	72.7 (13.5)	<0.001
BSA	365/1285	66.4 (13.8)	65.2 (14.9)	0.18
ISA	311/968	51.2 (12.3)	52.5 (13.8)	0.15
Stroke history				
WB	218/2073	70.5 (13.3)	71.8 (13.3)	0.17
BSA	91/1559	67.4 (11.7)	65.4 (14.8)	0.12
ISA	3/1276	55.0 (8.2)	52.2 (13.4)	0.72

n denotes sample size. **P*-value is calculated using an independent *t*-test. WB, white British; BSA, UK residing South Asians; ISA, India South Asians.

3.4.2 Recruitment bias

As a cross-sectional observational study, various biases, such as selection and information bias, as well as confounding variables can affect the study's findings (106). Selection bias is when the characteristics of a study population differ systematically from those of eligible participants who were not chosen to be part of the study (such as the general population). This can impact the results of a study as they might not be generalisable to the general population. Selection bias can typically occur if you have strict recruitment criteria which can result in certain subgroups of a desired population being recruited. Nonresponse bias is another type of selection bias that arises when individuals who do not respond to a study differ systematically from those who do. This type of bias can often occur during the recruitment phase of a study. Again, if the respondent population differs from the overall population being studied, this can lead to biased results. Quay *et al* has discussed how these biases can affect South Asian recruitment in studies. The authors identified that South Asian recruitment could be hindered by language and cultural barriers, apprehensions about the potential negative outcomes of taking part, and a lack of faith in the research (15). Possible methods discussed to counter these include increased involvement of South Asian communities, offering incentives and utilising translators and translated materials to ensure language sensitivity, and establishing trust and personal connections.

As a significant proportion of recruitment was already completed before analysing BRAINS, I was unable to apply influence recruitment. For the BRAINS study, all stroke patients admitted to a secondary care site, regardless of stroke type, ethnicity, and sex, were recruited. To reduce nonresponse bias, patients were recruited by an onsite coordinator, typically a research nurse, who would be able to provide full details of the study and answer any

questions the patient might have to increase patient confidence. Though the questionnaire was completed by the onsite coordinator and the patients were not required to read these, for future studies within this demographic partnering documentation in several languages could decrease possible hesitancy in joining the study. Cash incentives could be another possible route to increase enrolment however this would add extra cost and limit sample size depending on the budget available.

Though these incentives were not in place during the patient recruitment process, I believe BRAINS is representative of the larger population of stroke patients. All those admitted to a participating hospital with a stroke event would be recruited. Though demonstrating representativeness can be difficult as there are no official demographic details of South Asian stroke in the UK, comparing the prevalence of various risk factors/comorbidities in South Asians with those previously reported, similarities are present (22,29,35). Furthermore, comparing the distribution of stroke within the BRAINS dataset, ischaemic type occurred in 88.2% of white British cases, 84.5% in UK residing South Asian cases and 90.3% of Indian South Asian cases, similar to that reported in previous studies, suggesting representativeness (22,29,35).

4 Age of Stroke Onset in South Asians

4.1 Introduction

As discussed in the literature review, there has been a paucity of data relating to the age of first-time ischaemic stroke event within the UK. Some small studies have suggested an earlier stroke onset in South Asians and increased stroke mortality compared to the white British population(35,107). Other studies have shown migration can have an adverse effect on South Asian health due to changes in living environments, differing healthcare systems (108), reduced exercise and potentially changes in diet (76,79) possibly compounded by genetic liabilities (109). Although these negative effects could be reduced by the use of technology for improving healthcare access (110), ethnic-specific analysis is likely needed to identify stroke onset differences as well as novel risk factors.

I sought to investigate differences in the age of first-time stroke onset between the white British population and South Asians residing in the UK and those in India. I used the UK and India arms of the BRAINS dataset study. The three aims of this chapter are:

1. To explore the prevalence of traditional stroke risk factors in both South Asian groups with white British patients.
2. To determine if there are ethnic differences in age of event in those with first-time ischaemic stroke.
3. If so, does the difference in age of stroke event remain after adjusting for environmental and traditional stroke risk factors.

4.2 Methods

I analysed the UK and Indian arms of the ongoing prospective international Bio-Repository of DNA in Stroke (BRAINS) study, the details of which have been discussed in chapter 3 and have previously been published (98,111). To identify the age of onset of ischaemic stroke, I excluded cases that had a previous ischaemic or haemorrhagic stroke. Cases were included if they had complete information on the age of onset, stroke history, ethnicity, and sex. All cases used in this chapter had first-time ischaemic stroke event. All analyses in this study compared BSA and ISA with WB patients.

As the sample now included those with first-time stroke event only, I wanted to assess if the effect of missing data would affect the age of event. To do this I compared the age of first-time ischaemic stroke event for each variable used, between those with missing and complete comorbidity data. This data is presented in Appendix 10.8 and is stratified for each ethnic group.

Demographic and categorical data between ISA, BSA and WB were compared using one-way Analysis of variance (*ANOVA*) and chi-square tests. The prevalence of individual risk factors between ethnicity and age were analysed by linear regression. General linear model (GLM) analysis was performed to identify the association between ethnicity and age-adjusted for potential confounders (112). Variables likely associated with age were selected with respect to biological plausibility (sex, central obesity, smoking history, alcohol history, hypertension, diabetes mellitus, hypercholesterolemia, ischaemic heart disease and atrial fibrillation). Statistical analysis used in this chapter are discussed in chapter 3.3.

4.3 Results

The combined UK and India arm of the BRAINS study consists of 5220 ischaemic stroke patients. Of these, 4038 individuals identified with first-time ischaemic stroke, 1126 (men: 757, women: 369) were ISA, 1176 (men: 761, women: 415) were BSA, and 1736 (men: 966, women: 770) were WB patients.

Demographic and clinical characteristics between ethnicity are presented in Table 4-1. BSA suffered from ischaemic stroke onset 7.2 years earlier, while ISA was 19.5 years earlier than their WB counterparts (BSA: 64.3±15.1 years, vs. ISA: 52.0±13.4 years, vs. WB: 71.5±13.5 years, $P<0.001$). BSA patients had an increased prevalence of hypertension (BSA: 76.9% vs. ISA: 68.0% vs. WB: 66.3%, $P<0.001$), diabetes mellitus (BSA: 50.3% vs. ISA: 32.9% vs. WB: 18.8%, $P<0.001$), hypercholesterolaemia (BSA: 52.6% vs. ISA: 36.4% vs. WB: 34.1%, $P<0.001$) and ischaemic heart disease (BSA: 30.3% vs. ISA: 13.6% vs. WB: 19.5%, $P<0.001$) compared to ISA and WB patients. Atrial fibrillation, smoking history and high alcohol consumption were more prevalent in WB stroke cases compared to ISA and BSA cases. Comparisons of traditional stroke risk factors between differing ethnicities are presented in Appendix 10.9.

Table 4-1: Population characteristics stratified by ethnicity.

	ISA (n=1126)	**BSA (n=1176)**	**WB (n=1736)**	***P*-value***
Average age of onset, mean (SD), years	52.0 (13.4)	64.3 (15.1)	71.5 (13.5)	<0.001
Men, *n* (%)	757 (67.4)	761 (64.7)	966 (55.6)	<0.001
Environmental Factors	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***
Central obesity	348 (35.8)	358 (35.0)	368 (31.1)	0.042
Smoking history	492 (43.9)	413 (35.5)	915 (53.3)	<0.001
Alcohol consumption	468 (41.8)	254 (23.2)	660 (45.9)	<0.001
Comorbidities	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***
Hypertension	747 (68.0)	890 (76.9)	1137 (66.3)	<0.001
Diabetes mellitus	361 (32.9)	582 (50.3)	321 (18.8)	<0.001
Hypercholesterolemia	355 (36.4)	593 (52.6)	579 (34.1)	<0.001
Ischaemic heart disease	147(13.6)	340 (30.3)	300 (19.5)	<0.001
Atrial fibrillation	56 (6.1)	131 (11.7)	372 (21.9)	<0.001

n, sample size. **P*-value is calculated using either one-way *ANOVA* for age of onset comparisons or chi-square tests for prevalence comparisons. Central obesity is classified by waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m^2). ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

Sex-specific analyses are presented in Table 4-2. ISA men suffered stroke 10.7 years and 17.0 years earlier than BSA and WB men respectively. Conversely, ISA women suffered stroke 15.5 years and 23.2 years earlier than BSA and WB women. Of the environmental factors, ISA, BSA, and WB women reported a greater prevalence of central obesity compared to men. Smoking history and alcohol consumption were greater in men compared to women for each ethnicity.

Table 4-2: Comparison of population characteristics between ethnic groups, by sex.

	Men				Women			
	ISA (n=757)	**BSA (n=761)**	**WB (n=966)**	***P*-value***	**ISA (n=369)**	**BSA (n=415)**	**WB (n=770)**	***P*-value***
Average age of onset, mean (SD), years	52.5 (12.8)	63.2 (14.7)	69.5 (13.0)	<0.001	50.9 (14.4)	66.3 (15.6)	74.0 (13.5)	<0.001
Environmental Factors	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***
Central obesity	202 (30.9)	195 (29.1)	180 (27.2)	0.34	146 (46.1)	163 (45.9)	188 (35.9)	0.002
Smoking history	422 (56.1)	380 (50.5)	580 (60.7)	<0.001	70 (19.0)	33 (8.0)	335 (44.1)	<0.001
Alcohol consumption	402 (53.5)	223 (31.6)	432 (52.8)	<0.001	66 (17.9)	31 (7.9)	228 (36.8)	<0.001
Comorbidities	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***
Hypertension	517 (70.1)	569 (76.0)	609 (63.8)	<0.001	230 (63.7)	321 (78.7)	528 (69.5)	<0.001
Diabetes mellitus	254 (34.5)	377 (50.2)	194 (20.4)	<0.001	107 (29.7)	205 (50.5)	127 (16.8)	<0.001
Hypercholesterolemia	229 (35.1)	396 (54.1)	334 (35.3)	<0.001	126 (39.0)	197 (49.9)	245 (32.5)	<0.001
Ischaemic heart disease	99 (13.6)	248 (34.3)	180 (20.8)	<0.001	48 (13.0)	92 (23.2)	120 (17.8)	0.003
Atrial fibrillation	25 (4.2)	84 (11.5)	200 (21.1)	<0.001	31 (9.6)	47 (12.0)	172 (22.8)	<0.001

n, sample size. *one-way *ANOVA* was used to compare the age of onset with all ethnic groups. Categorical variables *P*-value calculated using a chi-square test between 3 groups. Chi-square tests between BSA and ISA with WB (reference) were also calculated and displayed the same results. Central obesity is classified by waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m^2). ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

To evaluate the association of age with ethnicity, a linear regression model was performed and adjusted for the following variables: sex, central obesity, alcohol consumption, smoking history, hypertension, atrial fibrillation, and ischaemic heart disease. In a simple linear regression, both BSA and ISA were associated with an earlier age of onset (β=-9.61, SE=0.27) and accounted for 24.6% of the total variance (R^2=0.246). A forward stepwise linear regression was performed adjusting for traditional stroke risk factors (Table 4-3). In this model, South Asian ethnicity, regardless of location, continued to show a negative association with the age of onset of stroke (β=-9.31, SE=0.31). This model overall predicted 33.7% (R^2=0.337) of the variation of the age of onset of ischaemic stroke, with ethnicity accounting for 24.7% (R^2=0.247). The results of the missing value analysis indicate that missing values occur completely at random (MCAR) (P=0.69).

Table 4-3: Stepwise multivariable linear regression analysis predicting the age of onset of ischaemic stroke (years) with traditional risk factors.

Variables	Effect size (β), years	SE	*P*-value	R^2
Ethnicity: (Reference group: WB, 1 = BSA, 2 = ISA)	-9.31	0.31	<0.001	0.247
Hypertension	7.64	0.54	<0.001	0.057
Atrial fibrillation	5.41	0.74	<0.001	0.016
Ischemic heart disease	3.28	0.63	<0.001	0.006
Alcohol Consumption	-2.02	0.53	<0.001	0.005
Central obesity	-2.04	0.52	<0.001	0.003
Sex (reference group: Women)	-1.93	0.53	<0.001	0.003

* Effect size (β-coefficients), degree of change in the age of onset of ischaemic stroke (dependent variable) for every 1 unit of change in the predictor variable. SE, standard error. R^2, percent of variance in age of onset of ischaemic stroke that is explained by the set of predictor variables. Constant for the gradient (B)=67.9. Diabetes mellitus (*P*=0.06), smoking history (*P*=0.15) and Hypercholesterolemia (*P*=0.05) were excluded from the model. High significance of the *F*-test=191.9, *P*<0.001 indicates a linear relationship between the variables in the model. Total R^2 =0.337. ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

To assess the independent association of age with ethnicity among stroke patients, the analyses were repeated on the basic model (i.e., adjusted for ethnicity and sex only model) with separate adjustments for each predictor in Table 4-4. Both BSA and ISA continued to display earlier age of stroke onset regardless of the traditional risk factor being adjusted suggesting that ethnicity was independently associated with the age of onset. Adjusting for these traditional risk factors of stroke, ISA and BSA showed an even more pronounced earlier age of stroke onset of 18.9 years (ISA: 52.8 years vs. WB: 71.7 years, $P<0.001$) and 8.9 years (BSA: 62.8 years vs. WB: 71.7 years, $P<0.001$), respectively.

Table 4-4: Simple linear regression analysis predicting the age of onset of ischaemic stroke (years) adjusting for each traditional risk factor.

	ISA (WB reference group)			BSA (WB reference group)		
Risk Factor	**Effect size (*β*), years**	**SE**	***P*-value**	**Effect size (*β*), years**	**SE**	***P*-value**
Central obesity	-19.60	0.56	<0.001	-13.29	0.54	<0.001
Smoking history	-19.29	0.52	<0.001	-13.26	0.48	<0.001
Alcohol consumption	-19.36	0.54	<0.001	-13.69	0.50	<0.001
Comorbidities						
Hypertension	-19.37	0.50	<0.001	-13.50	0.45	<0.001
Diabetes mellitus	-19.63	0.52	<0.001	-13.92	0.48	<0.001
Hypercholesterolemia	-19.12	0.54	<0.001	-12.90	0.48	<0.001
Ischaemic heart disease	-18.94	0.53	<0.001	-13.25	0.48	<0.001
Atrial fibrillation	-18.27	0.55	<0.001	-11.59	0.48	<0.001
Multivariate Model	-18.77	0.65	<0.001	-13.88	0.58	<0.001

*Effect size (*β-coefficients*), degree of change in the age of onset of ischaemic stroke (dependent variable) for every 1 unit of change in the predictor variable. SE, standard error. Each model was adjusted for sex and specific stroke risk factor. Multivariate Model includes all risk factors. ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

4.4 Discussion

In this study, compared to their WB stroke counterparts, BSA and ISA suffer from an earlier ischaemic stroke onset of ~9 and ~19 years respectively following adjustment for traditional risk factors. In both men and women, ISA continued to suffer from an earlier ischaemic stroke compared to BSA and WB. Ethnicity explained approx. 25% of the variance of the age of onset, with traditional risk factors of hypertension, atrial fibrillation, ischaemic heart disease, alcohol consumption, central obesity, and sex accounting for only about 8% of the variance.

The significantly later age of onset of ischaemic stroke in BSA compared to their ISA counterpart suggests an improvement in stroke prevention associated with a UK environment (113). This study is the first migration-related study focusing on the age of first onset of ischaemic stroke of South Asians in the UK and India (23), making comparisons to previous studies limited. Earlier age of stroke onset in South Asians, regardless of location, is consistent with findings from other smaller studies both in South Asia (114–117) and the UK (118), though these do not focus on first-time stroke events. Notwithstanding the health benefits of the UK, the BSA population has not standardized with WB, although are improved compared with ISA. Gunarathne *et al* found an 8-year earlier onset compared to WB patients with data collected between 1997 and 2005 (118), suggesting that little improvement in stroke prevention has been achieved in this migrant demographic over the intervening decades. Earlier onset of stroke is not only exclusive to South Asians but also other ethnic minority groups in the UK and could highlight health inequalities for all ethnic minority groups in the UK (119,120). Previous reports have pointed out that the absence of ethnic considerations in healthcare,

coupled with systemic health inequities that escalate with age, may result in adverse health outcomes and increased mortality rates (121).

This study reports significantly higher rates of hypertension, diabetes mellitus and hypercholesterolaemia in BSA consistent with some (35,41,122–127) but not all previous studies (123). After adjusting for these factors, South Asian ethnicity explained 24.2% of the earlier onset seen in this study and was associated with an earlier age of onset of stroke. Appropriate clinical management of these comorbidities may also play a part in determining the age of stroke (128,129). Within the linear regression model, hypertension, atrial fibrillation, and ischaemic heart disease report a positive beta value, suggesting a protective effect against earlier onset of ischaemic stroke. The reason for this is likely linked to the relationship between other confounding variables in the model. When you add a confounding variable to a regression model, it can change the sign and magnitude of the coefficients of other independent variables because it accounts for some of the variation in the dependent variable that was previously attributed to them. For this reason, it is unlikely that these comorbidities offer a protective effect.

Central obesity (a known ischemic stroke risk factor) has a greater prevalence in the South Asian community (30,130,131). Though this study reports a significantly higher prevalence of central obesity in BSA, a similar prevalence among ISA when compared to the WB population, was also present. This highlights the possible changes in lifestyle/environmental factors associated with migrating to the UK such as diet and exercise. Traditional South Asian diet consisting of carbohydrate rich foods including rice and bread is more tailored to a physically demanding rural environment (89). But this carbohydrate rich diet continues in the UK (90) partnered with lower physical activity compared with the WB population (76,132,133). A

predisposition to visceral adiposity in the truncal region has resulted in the WHO recommending South Asian specific thresholds for determinators of obesity (134).

Though the increased prevalence of traditional stroke risk factors in South Asians was seen in the UK and India, the effect of migration on environmental and lifestyle factors are likely another possible cause of differing stroke risk and outcome. Accessing healthcare is an important area in stroke prevention which is often overlooked in migration studies. Though BSA have access to preventable healthcare services, knowledge about risk factors and contribution to disease is also demonstrably poor. Many BSA are not aware of the common complications of diabetes mellitus (135), with sociocultural and religious factors exaggerating this with distorted perceptions of failure at self-care and social stigma (136). Sex differences also can determine environmental and comorbidity factor prevalence. Of interest was the ~10% increase in ischaemic heart disease among BSA men compared to women. In general, ischaemic heart disease is more likely to develop at an earlier age in men (137) who usually have a greater prevalence of cardiovascular risk factors and is likely the reason for the difference.

4.5 Limitations

4.5.1 Limitations with the BRAINS dataset

Like all studies, several limitations need to be noted. BRAINS is a long running study and thresholds for risk factors and their management have changed over the intervening years. However, such transitions, if conducted locally would have resulted in a non-differential ethnic bias as any changes which could influence the results of this thesis would affect both BSA and WB. Further, many of the comorbidities (e.g., DM, hypertension, atrial fibrillation) included in this thesis are well defined, with criteria for diagnosis between the UK and India being similar. Availability of treatment offered between the UK and India will vary due to different healthcare systems, however, one of the main objectives of this study is to report the difference in comorbidity prevalence and how this impacts the age of stroke event. BRAINS did not collect information relating to treatments offered to patients, with the exception of AF, or adherence. For this reason, I only discuss the prevalence of the comorbidities in the study population and its implication on stroke risk. Comorbidity/risk factor prevalence is recorded at the time of the event. Though I am unable to comment on the length of time these comorbidities were present prior to the stroke event, much of the prevalence data collected was through treatment regimens recorded on the patient's clinical record. Although this may lead to an underestimating of the real effect size on the age of stroke event of the included stroke risk variables, the large sample size (n=4038) reflects the current impact of these risk variables on stroke in the South Asian population. Ethnicity was defined by grandparent origin. While this was self-reported, previous studies have demonstrated the accuracy of this methodology (138,139). The socioeconomic status which may influence morbidity and mortality was not collected so I am unable to assess its influence on the age of stroke onset. This is a prospective hospital-based study so conclusions cannot be extrapolated for overall or community-based age

differences. Further, older stroke patients may choose not to seek medical advice compared to younger victims which could influence this hospital-based study. However, this limitation would likely apply to either ethnic group or location. Though we did not collect detailed data on the numbers of those who chose not to participate in this prospective study, those numbers were small and broadly similar across all studied groups. To assess the representation of the ISA and BSA within our study we utilised the broader BRAINS dataset, which consists of both ischaemic and haemorrhagic events and found similar stroke subtype prevalence across the three groups in our study (35,140). This includes BSA in BRAINS reporting 84.5% of ischaemic events which is similar to previous reported prevalence (35). Further, we are unable to report specific effects of migration and how they develop as long-term follow-up was not undertaken.

Both the UK and India recruitment sites were chosen to ensure a representative sample. In the UK we identified 21 hospital sites with a high number of South Asians. India, with a geographical land mass similar to the US, is significantly more challenging to recruit a representative sample. The two hospital sites chosen, All India Institute of Medical Sciences and Sree Chitra Tirunal Institute for Medical Sciences and Technology, were identified as they are located in the north and south of the country. Furthermore, both offer free access to medical services and are thus more likely to attract a wide population from varying socioeconomic backgrounds. Finally, this is a hospital-based study and is dependent on the recruitment of patients attending hospital. Different cultures have different responses and access to seeking emergency healthcare support services. While a stroke usually presents with disabling symptoms there is a possibility that not all stroke afflicted patients attended hospital resulting in recruitment bias to this study.

4.5.2 Missing data

For this chapter, I only included those with first-time ischaemic stroke event. This resulted in the exclusion of 1182 ischaemic stroke patients who had missing stroke history data or who had suffered from a recurrent stroke event. To assess if this resulted in any type of bias, I compared the age of event between those with missing and complete data for each comorbidity (Appendix 10.8). The only significant difference of age between those with missing and complete data was seen in BSA for central obesity and hypercholesterolemia. For both, an earlier age of onset was reported in those with complete central obesity and hypercholesterolemia data. Though this was significant the difference was small, ~3-4 years, and only affected two variables reducing the impact on the linear regressions. There could be several reasons for the difference in age between cases with missing and complete data. It is possible that older patients have a higher likelihood of missing data because they may have cognitive impairment or be unable to provide accurate information during recruitment by the nurse. Additionally, younger patients may be more likely to have complete data as they might have a greater understanding of the importance of providing accurate information (141). Finally, it has been previously reported that for South Asians in the UK, there may be demographic or socioeconomic differences between the groups, with patients from certain backgrounds being more likely to have missing data due to language barriers, cultural differences, or lack of access to healthcare resources (15). Furthermore, mistrust of research, especially in the South Asian community could also be playing a role (15). To reduce the likelihood of this, a future study could run a pilot phase with the questionnaire to identify if these questions are suitable for the target population and if ethnic differences such as language could be factored in.

4.6 Summary

In this chapter, I found BSA and ISA suffered from stroke ~9 and ~19 years, respectively, earlier than their white British (WB) counterparts. Ethnicity accounted for around 25% of the variance of the earlier age of onset. These results could have considerable implications for public health policymakers in countries with sizable South Asian populations.

5 Ischaemic stroke subtype in South Asians

5.1 Introduction

In the previous chapters, I explored how the age of event varied significantly between South Asians and the white British population for ischaemic stroke. Aetiologies of ischaemic strokes varies significantly between geographical location and ethnicity though few studies have focused on South Asians, particularly those residing in the UK. Multiple criteria exist to determine the subtype of ischaemic stroke, all utilising differing observational, radiological, and biochemical tests. The most broadly utilised, and the first based on underlying stroke mechanisms is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (100). This information is crucial as it can aid in the treatment and prevention strategies for stroke.

There is a paucity of ischaemic stroke subtype data in South Asians (142), and as of yet, there has been no UK studies reporting TOAST classification in BSA. Of ischaemic subtype using alternative classification, one study using the observational based Oxfordshire Community Stroke Project criteria suggested an increase in small vessel disease prevalence compared to the white British population (35). Additionally, differing results have been reported in South Asia using the TOAST criteria (143,144).

To investigate the differences in ischaemic stroke subtype between the white British population and South Asians residing in the UK and those in India, I continued to use the BRAINS dataset. The aims of this chapter are:

1. To identify if ethnic differences in ischaemic stroke subtype exist in BSA and ISA compared with WB patients.
2. To evaluate if the differences in age of stroke onset reported in chapter 4 are linked to a specific stroke subtype.
3. Using risk factor data, determine if ethnicity is independently associated with each ischaemic stroke subtype.

5.2 Methods

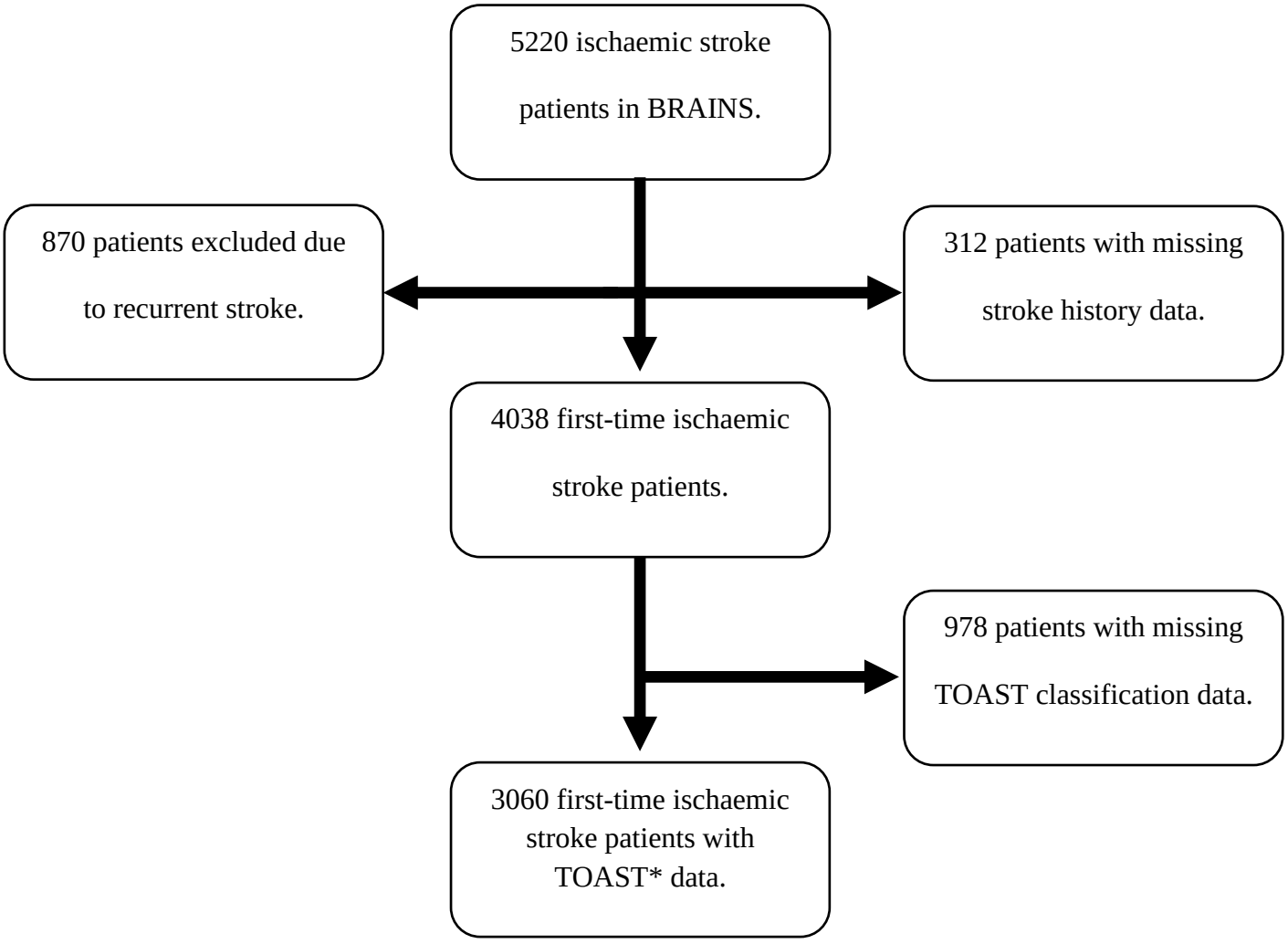
To assess the difference in ischaemic stroke subtype, I utilised the TOAST classification criteria (100). The basis for this analysis can be found in chapter 3. Cases were included if they had complete information on TOAST classification, age of onset, stroke history, ethnicity, and sex. All cases used in this chapter had first time ischaemic stroke event. All analyses in this study compared BSA and ISA with WB patients. To identify if selecting patients with complete TOAST classification data altered the demographic of the sample population, I compared the age of first-time stroke event in those with missing and complete classification data for each ethnicity and comorbidity (Appendix 10.10).

Demographic details and categorical data between ISA, BSA and WB were compared using chi-square test. The age of onset for each TOAST subtype were compared using one-way *ANOVA* tests and presented in a bar graph. Logistic regression analysis was performed to identify the association between ethnicity and ischaemic stroke subtypes, adjusted for potential confounders (112). Further, stepwise logistic regressions were performed to identify the association between each TOAST classification and ethnic groups adjusted for potential confounders. Variables were removed from the model if they crossed $P>0.05$ threshold. Variables likely associated with age were selected with respect to biological plausibility (sex, central obesity, smoking history, alcohol history, hypertension, diabetes mellitus, hypercholesterolemia, ischaemic heart disease and atrial fibrillation). Little's MCAR test was used to assess if traditional stroke risk factors with missing values were missing completely at random (103).

5.3 Results

The combined UK and Indian arm of the BRAINS study consists of 5220 patients with ischaemic stroke. Of these, 3060 individuals identified with first-time ischaemic stroke: 850 (men: 595, women: 255) were ISA: 970 (men: 630, women: 340) were BSA, and: 1240 (men: 662, women: 578) were WB patients (Figure 5-1).

Figure 5-1: Selection criteria for chapter 5.



*Stroke subtype uses the TOAST (trial of ORG 10172 in acute stroke treatment) classification (100). BRAINS (Bio-Repository of DNA in Stroke).

Demographic and clinical characteristics are presented in Table 5-1. Ischaemic stroke occurred on average 8.6 years earlier in BSA and 20.3 years in ISA compared to WB patients (P<0.001). BSA patients had an increased prevalence of established risk factors (hypertension, diabetes mellitus, hypercholesterolemia, ischaemic heart disease) more so than ISA (Table 5-1) when compared to WB patients.

Table 5-1: Population Characteristics stratified by ethnicity.

	ISA (n=850)	**BSA (n=970)**	**WB (n=1240)**	
	***n* (%)**	***n* (%)**	***n* (%)**	***P*-Value***
Age, years (SD)	52.3 (13.7)	64.0 (15.2)	72.6 (13.5)	<0.001
Men	595 (70.2)	630 (64.9)	662 (53.4)	<0.001
Central obesity	286 (39.2)	313 (35.8)	269 (32.4)	0.020
Smoking history	369 (43.6)	348 (36.0)	611 (49.7)	<0.001
Alcohol consumption	357 (42.2)	210 (22.9)	433 (44.2)	<0.001
Comorbidities	***n* (%)**	***n* (%)**	***n* (%)**	***P*-Value***
Hypertension	562 (68.0)	736 (76.5)	811 (66.2)	<0.001
Diabetes mellitus	277 (33.5)	486 (50.5)	230 (18.8)	<0.001
Hypercholesterolemia	253 (34.8)	496 (52.5)	388 (31.9)	<0.001
Ischaemic heart disease	37 (13.8)	104 (29.4)	295 (18.0)	<0.001
Atrial Fibrillation	117 (5.7)	283 (11.0)	220 (24.2)	<0.001

n, sample size; Central obesity classified by waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m^2); BSA: UK residing South Asians; ISA: South Asians residing in India; WB: White British. All comparisons made are between ethnic groups. **P*-value for the comparison between ethnicities is derived from chi-square tests for prevalences or one-way *ANOVA* for age of onset comparisons.

5.3.1 TOAST Stroke Subtype

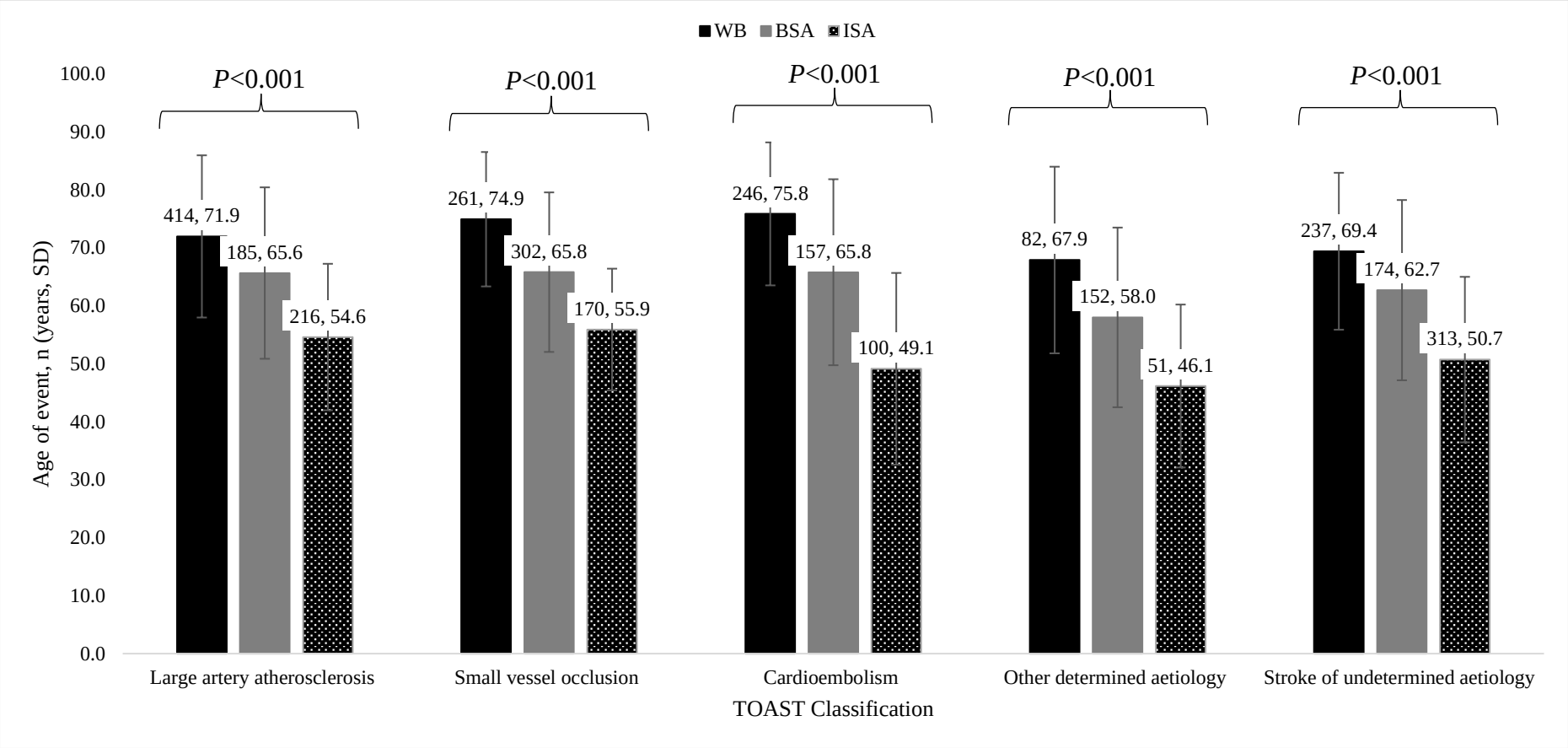
Differences in traditional stroke risk factor prevalence and population characteristics among those with different TOAST subtypes are presented in Table 5-2. The average age of stroke for each TOAST classification in BSA, ISA and WB are shown in Figure 5-2. In each of the TOAST classifications, both ISA and BSA had significantly earlier onset of ischaemic stroke compared to WB patients. Cardioembolic stroke saw the largest difference between ethnicities, with BSA and ISA suffering 10.0 years and 26.7 years earlier onset respectively than WB patients.

Table 5-2: Population characteristics stratified by ethnicity and TOAST classification.

	Large artery atherosclerosis				Small vessel occlusion				Cardioembolism			
	ISA (n=216)	**BSA (n=185)**	**WB (n=414)**		**ISA (n=170)**	**BSA (n=302)**	**WB (n=261)**		**ISA (n=100)**	**BSA (n=157)**	**WB (n=246)**	
	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**
Men	165 (76.4)	123 (66.5)	219 (52.9)	<0.001	111 (65.3)	190 (62.9)	135 (51.7)	0.006	56 (56.0)	106 (67.5)	125 (50.8)	0.004
Smoking history	119 (55.1)	72 (39.3)	199 (48.7)	0.007	74 (44.0)	90 (29.8)	102 (39.5)	0.004	27 (27.3)	57 (36.5)	126 (51.6)	<0.001
Alcohol consumption	100 (46.5)	40 (22.3)	144 (42.6)	<0.001	77 (45.6)	68 (24.3)	74 (43.5)	<0.001	33 (33.0)	37 (25.2)	95 (44.8)	0.001
Comorbidities	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**
Hypertension	147 (69.3)	144 (78.8)	272 (65.9)	0.007	144 (85.7)	240 (80.3)	181 (69.9)	<0.001	52 (54.7)	127 (81.4)	182 (74.3)	<0.001
Diabetes mellitus	81 (38.0)	96 (52.5)	76 (18.4)	<0.001	65 (38.9)	152 (50.8)	45 (17.4)	<0.001	26 (26.5)	78 (49.7)	43 (17.6)	<0.001
Hypercholesterolemia	67 (34.7)	104 (57.8)	128 (31.2)	<0.001	59 (39.3)	161 (55.3)	70 (27.2)	<0.001	39 (45.9)	78 (50.3)	92 (37.9)	0.043
Central obesity*	75 (39.1)	40 (24.5)	103 (34.6)	0.013	56 (36.6)	112 (41.5)	52 (36.6)	0.50	27 (32.1)	46 (33.1)	45 (24.7)	0.21

n, sample size; BMI, body mass index; HDL-Cholesterol, High-density lipoprotein cholesterol; * Central obesity classified by increased waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m2); ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British. All comparisons made are between ethnic groups. *P*-value is calculated using a chi-square test between 3 groups. Chi-square tests between BSA and ISA with WB (reference) were also calculated and displayed the same results. Stroke subtype uses the TOAST (trial of ORG 10172 in acute stroke treatment) classification (100).

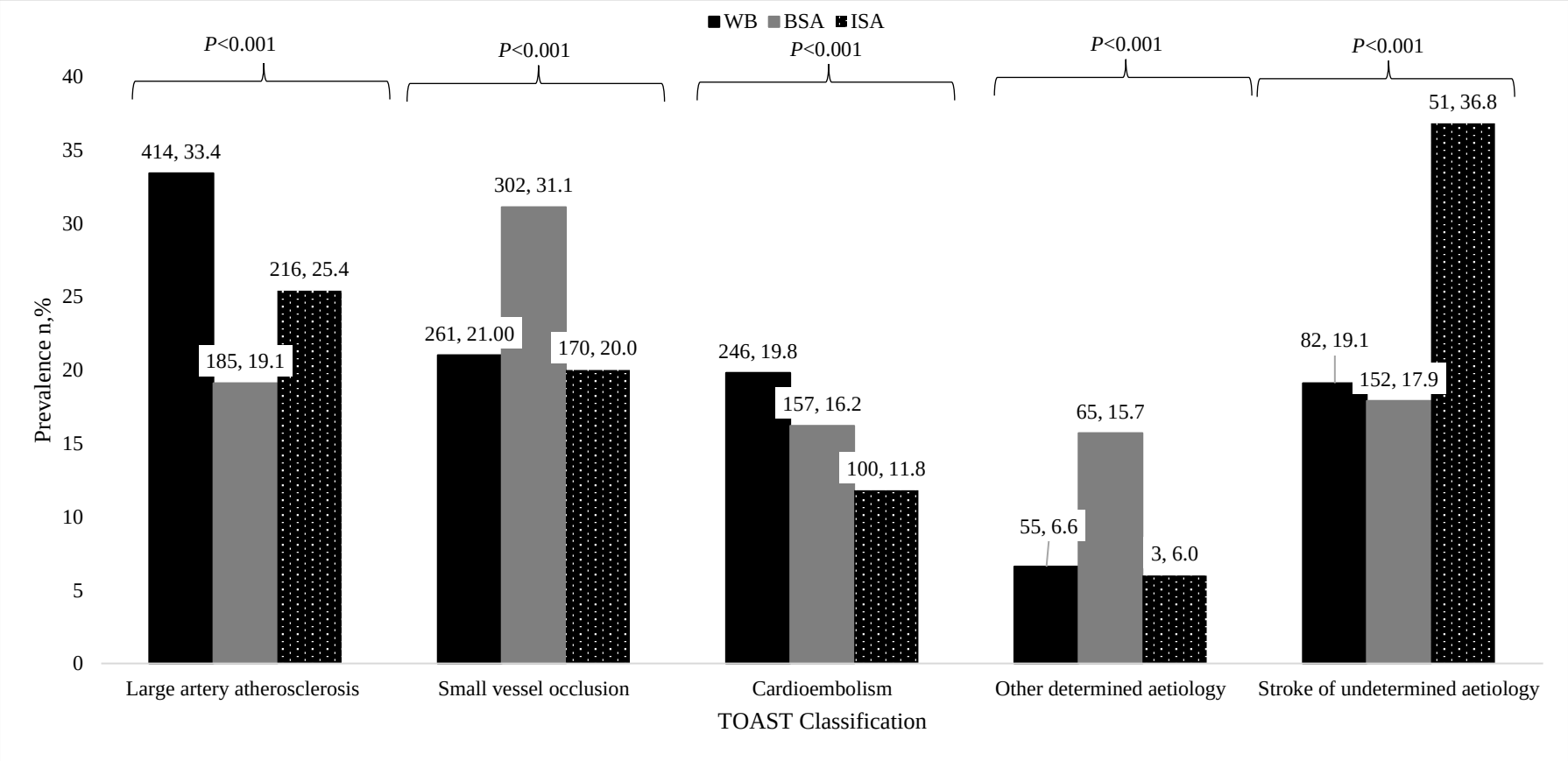
Figure 5-2: Stroke subtypes in South Asian and white British ischaemic stroke cases.



*Error bars denote standard deviation. The average age for all stroke is the combined stroke subtype. Stroke subtype uses the TOAST (trial of ORG 10172 in acute stroke treatment) classification (100). ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British. *P*-value was calculated from the comparisons between ethnic groups by an one-way *ANOVA*.

The distribution of ischaemic stroke subtype using the TOAST classification is shown in Figure 5-3. BSA patients presented with a 10.1 and 11.1% greater prevalence of small vessel occlusion compared to WB and ISA patients respectively. Moreover, WB patients presented with a significantly greater prevalence of large-artery atherosclerosis and cardioembolism compared to ISA and BSA patients. ISA patients presented with a 17.7% and 18.9% greater prevalence of stroke of undetermined aetiology compared to WB and BSA patients respectively.

Figure 5-3: Distribution of stroke subtype using the TOAST classification, stratified by ethnicity.



ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British. *P*-value calculated from chi-square test. Stroke subtype uses the TOAST (trial of ORG 10172 in acute stroke treatment) classification (100).

Adjusting for sex and age, BSA had a two-fold greater risk of small vessel occlusion compared to WB patients (Table 5-3). Similarly, ISA reported a 44% greater risk of small vessel occlusion compared to WB patients. Inversely, large artery atherosclerosis classified stroke was significantly more common in WB patients compared to BSA and ISA patients. No significant difference in cardioembolic stroke prevalence remained in BSA compared to WB.

Table 5-3: Age and sex adjusted comparison of stroke subtypes in BSA and ISA with the WB stroke populations.

	ISA vs. WB (reference group)		**BSA vs. WB (reference group)**	
TOAST Classification	**OR (95% CI)**	***P*-Value**	**OR (95% CI)**	***P*-Value**
Large artery atherosclerosis	0.71 (0.56 – 0.90)	0.005	0.47 (0.38 – 0.58)	<0.001
Small vessel occlusion	1.44 (1.09 – 1.90)	0.010	1.92 (1.57 – 2.36)	<0.001
Cardioembolism	0.67 (0.49 – 0.91)	0.011	0.90 (0.71 – 1.13)	0.35
Other determined aetiology	0.50 (0.32 – 0.78)	0.002	2.05 (1.53 – 2.76)	<0.001
Stroke of undetermined aetiology	1.86 (1.47 – 2.34)	<0.001	0.81 (0.65 – 1.02)	0.07

Reference group: white British ischaemic stroke patients; OR, Odds Ratio; 95% CI, 95% Confidence interval; ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British. Stroke subtype uses the TOAST (trial of ORG 10172 in acute stroke treatment) classification (100).

To assess if ethnicity was independently associated with differing stroke subtypes, I conducted stepwise logistic regressions comparing both BSA and ISA with WB, adjusting for stroke risk factors/comorbidities and age (Table 5-4). Small vessel occlusion remained 65% and 88% more common in both ISA and BSA respectively compared to WB patients. Cardioembolism and large artery atherosclerosis remained more prevalent in WB patients compared to both ISA and BSA. The results of the missing value analysis indicate that missing values occur completely at random (MCAR) (P=0.78).

Table 5-4: Logistic regression model to assess the risk of various ischaemic stroke subtypes (TOAST) in ISA and BSA.

ISA vs. WB (reference group)	OR (95% CI)	*P*-Value
Large artery atherosclerosis [1]	0.71 (0.53 – 0.96)	0.026
Small vessel occlusion [2]	1.65 (1.15 – 2.38)	0.007
Cardioembolism [3]	0.58 (0.39 – 0.85)	0.005
Other determined aetiology [4]	0.45 (0.26 – 0.80)	0.006
Stroke of undetermined aetiology [8]	1.26 (0.98 – 1.74)	0.16
BSA vs. WB (reference group)	**OR (95% CI)**	***P*-Value**
Large artery atherosclerosis [1]	0.37 (0.29 – 0.48)	<0.001
Small vessel occlusion [5]	1.88 (1.44 – 2.44)	<0.001
Cardioembolism [6]	0.73 (0.56 – 0.96)	0.026
Other determined aetiology [7]	2.13 (1.50 – 3.03)	<0.001
Stroke of undetermined aetiology [8]	0.74 (0.55 – 0.99)	0. 044

Reference group: white British ischaemic stroke patients; OR, Odds Ratio; 95% CI, 95% Confidence interval; ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British. Variables were removed from the model if they crossed P>0.05 threshold.

Stepwise model adjusted for:

1 = Age, sex, atrial fibrillation.
2 = Age, sex, atrial fibrillation, smoking history, central obesity.
3 = Age, sex, hypertension.
4 = Age, sex, atrial fibrillation, ischaemic heart disease.
5 = Age, sex, hypertension, atrial fibrillation.
6 = Age, sex, Smoking history, hypercholesterolemia, central obesity.
7 = Age, sex, hypertension, atrial fibrillation, central obesity.
8 = Age, sex, hypertension, diabetes mellitus, atrial fibrillation.

5.4 Discussion

In this chapter, I reported that BSA suffer from a significantly greater prevalence of small vessel occlusion compared to both WB and ISA patients. Conversely WB patients present with a greater prevalence of large artery atherosclerosis than both BSA and ISA patients. Overall and for each toast subtype ISA patients suffer from significantly earlier onset of stroke followed by BSA patients when compared to WB patients. After adjusting for traditional stroke risk factors, a ~2-fold increase in small vessel occlusion prevalence and a ~30-60% decrease in large artery atherosclerosis classified stroke was reported in both ISA and BSA patients, compared to WB patients.

Previous studies have reported that South Asians suffer from an increased prevalence of small vessel occlusion in South Asia, though this study is the first to report the prevalence of TOAST classification among BSA with first time ischaemic stroke (142,145). One study using the observational based Oxfordshire Community Stroke Project criteria suggested an increase in small vessel occlusion prevalence compared to the white British population (35). BSA reported a 10.1% greater prevalence of small vessel occlusion compared to WB patients. It has been suggested previously that the worse metabolic risk profile seen in South Asian communities could explain the increase in small vessel occlusion prevalence (146). To explore this, I adjusted the logistic regression model for metabolic and environmental risk factors for each stroke subtype and found BSA and ISA continued to report a ~2 fold increased risk of small vessel occlusion. It is likely other non-traditional risk factors, not accounted for, could be at play.

Of interest is the significant difference in cardioembolic stroke between both ISA and BSA with WB reported in this study. Though there is a lack of direct comparative studies between these groups, studies have reported ISA and WB individually. These have shown cardioembolism prevalence among ischaemic stroke varies between studies, with two studies reporting lower prevalence (6.1%–10.0%) in contrast to WB patients (144,147,148). Though both BSA and ISA report a lower prevalence of cardioembolism, BSA patients do report a higher prevalence than ISA patients. Atrial fibrillation prevalence follows a similar pattern, with ISA patients reporting the lowest atrial fibrillation prevalence, followed by BSA, and is likely the reason for the differences seen in cardioembolic stroke prevalence. As cardioembolism prevalence is lower in South Asia, new factors which are associated with migration could be resulting in increased risk, offsetting the benefits of significantly lower rates of atrial fibrillation, shown in this study. The cause of the overall lower prevalence of atrial fibrillation seen in South Asians, despite the higher prevalence of atrial fibrillation risk factors, has yet to be fully explained, however, it is likely to be related to morphologically smaller left atriums or atrial electrophysiological polymorphisms discussed in my review (149,150).

In consensus with previous literature, stroke of undetermined aetiology was the most common TOAST subtype in ISA (144,151). Although it has been theorised this is likely associated with incomplete assessments from a lack of health insurance, the TOAST criteria for small vessel occlusion and large artery atherosclerosis potentially plays an underrepresented role. To be considered for small vessel occlusion the lesion diameter is required to be <15mm. More so, to be considered for large artery atherosclerosis, patients are required to have stenosis of >50%. If either of these criteria are not met, then patients with

mild stenosis or those with small vessel occlusion but increased lesion size will be classified as undetermined (146).

In consensus with previous literature, stroke of undetermined aetiology was the most common TOAST subtype in ISA (144,151). Although it has been theorised this is likely associated with incomplete assessments from a lack of health insurance, the TOAST criteria for small vessel occlusion and large artery atherosclerosis potentially plays an underrepresented role. To be considered for small vessel occlusion the lesion diameter is required to be <15mm. More so, to be considered for large artery atherosclerosis, patients are required to have stenosis of >50%. If either of these criteria are not met, then patients with mild stenosis or those with small vessel occlusion but increased lesion size will be classified as undetermined (146).

There are similarities, but some differences, between the pattern of stroke subtypes seen in the population described in this study and those which report other UK based ethnic minority groups. Gulli *et al* recruited 1200 black and 1200 white stroke patients in South London, UK and categorised stroke using the TOAST classification system. The authors report both Black Caribbean and Black African stroke patients have a higher prevalence of small vessel occlusion (Black: 27.3% vs white British:11.8%) and a lower prevalence of large artery atherosclerosis (Black: 9.1% vs white British:13.3%) compared to the white British population. The study concludes, similarly to my study, that reason for the disparity has yet to be identified.

5.5 Limitations

Several limitations related to the BRAINS database are discussed in Chapter 4.6. Assessment for ischaemic stroke subtype using the TOAST classification criteria were made by an onsite neurologist following clinical and observational tests. The outcome of these assessments were reported to BRAINS as part of the questionnaire. Though we recorded the determined subtype, the results from specific clinical and observational diagnostic tests were not collected. As a result, I was unable to consider different classification systems and thus I cannot comment on the effect different subtype classification criteria have on the outcome of stroke subtype.

To be able to diagnose a specific TOAST subtype, a patient requires various tests. These could differ between sites and countries, thus having further implications on TOAST classification. BRAINS did not collect information on the number of tests conducted for each patient which could be used for TOAST classification. Therefore, it is not possible to comment on whether fewer tests were offered to certain populations or whether there were differences in the test utilisation rates across different groups. This could have implications for the generalisability of the findings, as well as for the identification of potential disparities or inequalities in the access and use of diagnostic tests between countries and ethnic groups. Future studies should address this gap and to better understand the factors that could influence the testing rates and outcomes of patients with differing ethnicity, characteristics, and conditions.

Using TOAST classification and stroke history as part of the selection criteria could result in a population which is not representative of the dataset. To assess if this resulted in any type of

bias, I compared the age of event between those with specific missing comorbidity data with those with complete data. I did this using the selection criteria used in this chapter (TOAST classification, age of onset, stroke history, ethnicity, and sex) (Appendix 10.10). Similar to those discussed in chapter 4.6, BSA patients reported significantly later stroke in those with missing central obesity and hypercholesterolemia data. Additionally, WB patients also reported significantly later stroke in those with missing ischaemic heart disease data. Though there could be a bias towards an earlier stroke onset, the difference will be small and could only affect the regression models which include these comorbidities.

5.6 Summary

Different stroke subtypes affect different populations, with small vessel occlusion being more prominent in all South Asians whereas the white British population have a higher prevalence of large artery atherosclerosis. Though both South Asian groups continued to suffer from a stroke earlier among all ischaemic stroke subtypes, they continued to suffer from small vessel occlusion after adjusting for traditional risk factors compared to white British patients. This suggests a potential genetic or novel risk factor is at play.

6 Metabolic risk factors

6.1 Introduction

In chapter 4, I reported the significantly higher prevalence of individual metabolic risk factors for stroke, such as diabetes mellitus. In my review of the literature, I also discussed the ethnic differences in the prevalence of individual metabolic risk factors, however, there has yet to be a large sample study which focuses on metabolic risk factors collectively in UK South Asians with first time ischaemic stroke (35). It is an important area to focus on as the presence of these risk factors all contribute to the increased risk of ischaemic stroke by 2-fold (152–154). Furthermore, the prevalence of metabolic risk factors as well as total stroke is expected to rise globally (155,156).

The prevalence of metabolic risk factors varies within different ethnic groups, though South Asians seem particularly susceptible in the general population (157). To expand our knowledge of the metabolic characteristics of South Asians with ischaemic stroke, I wanted to investigate further the cumulative differences in metabolic risk factors, and its influence on the age of event of stroke between ethnicities. The three aims of this chapter are:

1. Determine which ethnicity possessed a greater prevalence of cumulative metabolic risk factors.
2. To investigate if the prevalence of cumulative metabolic risk factors, between ethnicities, change after adjusting for environmental factors.
3. To explore if the cumulative effect of the metabolic risk factors influenced the age of event of first-time ischaemic stroke.

6.2 Methods

I continued to utilise the BRAINS dataset following the general methodology I described in chapter 3. To gauge the cumulative prevalence of the metabolic risk factors of stroke I created a new variable called metabolic risk factor. This variable is defined by the presence of one or more of these criteria: central obesity classified by increased waist circumference (Men: >102cm, Women: >88 cm) or BMI (≥30) (101), previous diagnosis of hypertension or pre-stroke treatment with antihypertensive, diabetes mellitus classified from a previous diagnosis of type I or II diabetes mellitus, hypercholesterolemia defined by previous diagnosis or serum cholesterol >5.2 mmol/L, the pre-diagnosis was reported during the interview stage if information was missing from their clinical record. This was subsequently coded to the cumulative presence of these risk factors in an individual patient, ranging from 0 in those with no risk factor present, to 3 or more.

Similarly to chapter 4, I excluded cases who had a previous ischaemic or haemorrhagic stroke so that I could assess the age of onset of first time ischaemic stroke (Appendix 10.11). Cases were included if they had complete information on the age of onset, stroke history, ethnicity, and sex. Furthermore, those with metabolic risk factor data were included (hypertension, diabetes mellitus, hypercholesterolemia, and central obesity). All analyses in this study compared BSA and ISA with WB patients.

Descriptive statistics were summarised using mean with standard deviation (SD) for continuous variables and proportion for categorical variables. One-way *ANOVA* and chi-square tests were used to compare between metabolic risk factors, sex and ethnic origins.

Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence intervals (95% CI's) describing the association between cumulative metabolic risk factors and ethnic origins among sex.

6.3 Results

A total of 4017 first time ischaemic stroke patients were included. Of these, 1124 (men: 755, women: 369) were ISA: 1170 (men: 758, women: 412) BSA, and: 1723 (men: 959, women: 764) WB patients.

Demographic and clinical characteristics including metabolic characteristics are presented in Table 6-1. To summarise, ISA and BSA men suffered stroke 16.9 years and 6.3 years earlier than WB men respectively. Conversely, ISA and BSA women suffered stroke 23.2 years and 7.8 years earlier than WB women (Table 6-1). Regardless of sex, BSA patients had an increased prevalence of hypertension, diabetes mellitus, and hypercholesterolaemia compared to ISA and WB patients (Table 6-1).

Table 6-1: Population characteristics, stratified by ethnicity and sex.

	Men				**Women**			
	ISA (n=755)	**BSA (n=758)**	**WB (n=959)**		**ISA (n=369)**	**BSA (n=412)**	**WB (n=764)**	
	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value***
Mean age, *years* (SD)	52.6 (12.8)	63.2 (14.7)	69.5 (12.9)	<0.001	50.8 (14.4)	66.2 (15.6)	74.0 (13.5)	<0.001
Smoking history	577 (60.7)	380 (50.5)	420 (56.0)	<0.001	334 (44.2)	33 (8.1)	70 (19.0)	<0.001
Alcohol consumption	431 (53.0)	223 (31.6)	401 (53.5)	<0.001	227 (36.9)	31 (7.9)	66 (17.9)	<0.001
Metabolic characteristics								
Hypertension	609 (63.8)	569 (76.0)	517 (70.1)	<0.001	528 (69.5)	321 (78.7)	230 (63.7)	<0.001
Diabetes	194 (20.4)	377 (50.2)	254 (34.5)	<0.001	127 (16.8)	205 (50.5)	107 (29.7)	<0.001
Hypercholesterolemia	334 (35.3)	396 (54.1)	229 (35.1)	<0.001	245 (32.5)	197 (49.9)	126 (39.0)	<0.001
Central obesity	180 (27.2)	195 (29.1)	202 (30.9)	0.34	188 (35.9)	163 (45.9)	146 (46.1)	0.002

n, sample size; BMI, body mass index; Central obesity classified by increased waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m2). * One-way *ANOVA* was used to compare the age of onset with all other prevalence comparisons using chi-square tests to derive *P*-value between the 3 groups. Chi-square tests between BSA and ISA with WB (reference) were also calculated and displayed the same results.

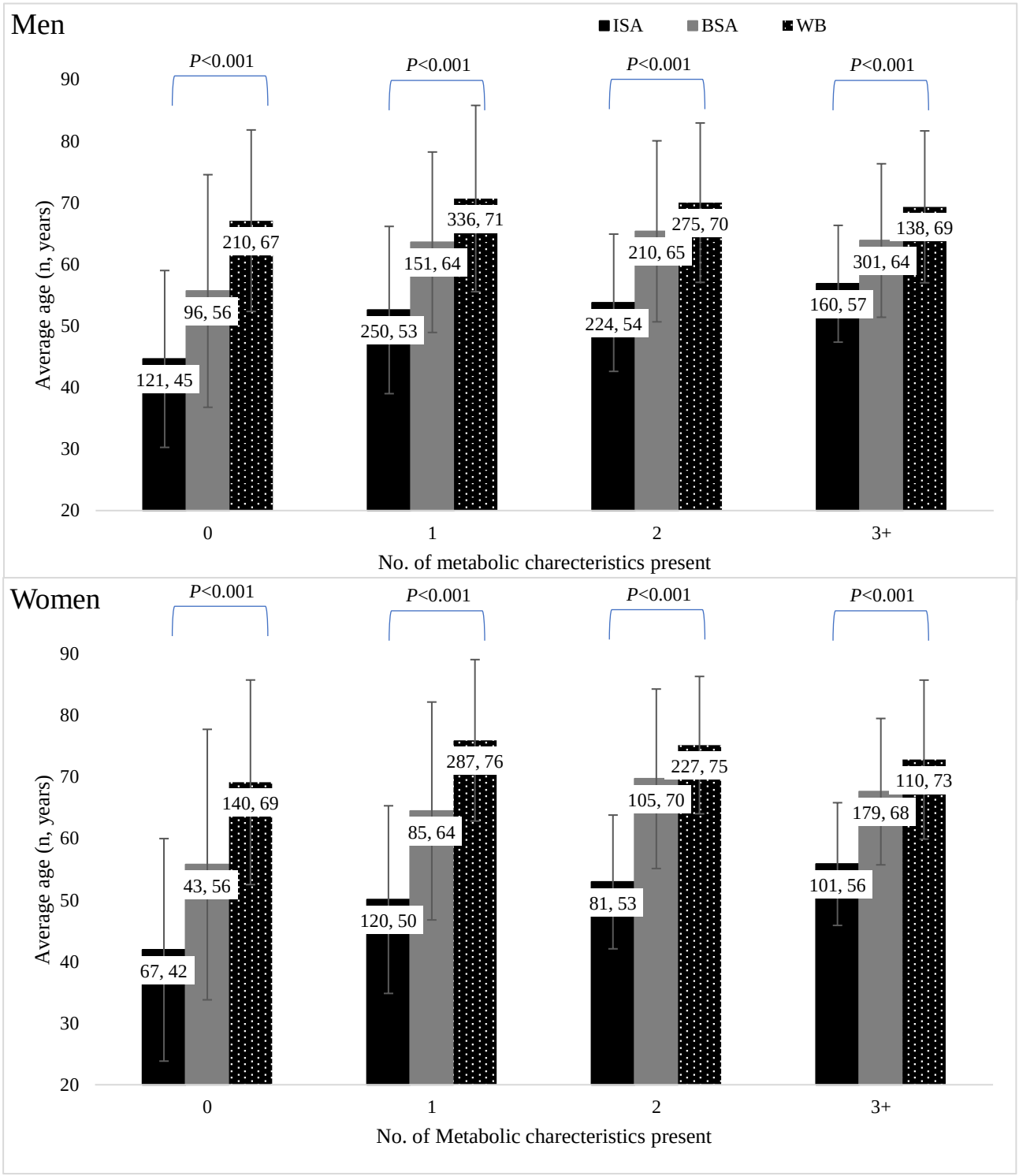
Comparisons of the cumulative prevalence of metabolic components; hypertension, diabetes mellitus, hypercholesterolemia and central obesity, are reported in Table 6-2. WB patients reported a greater percentage of those with no metabolic risk factors for both men and women. In contrast, BSA and ISA had 26.6% and 8.8% respective greater prevalence of 3+ metabolic risk factors, compared to WB patients. Sex specific differences were analysed with the only difference reported in women with 2 metabolic risk factors present (BSA: 25.5%, vs. ISA: 22.0%, vs. WB: 29.7%, P=0.017) (Table 6-2). Differences in age of first-time ischaemic stroke among those with varying cumulative prevalence of metabolic risk factors are seen in Figure 6-1.

Table 6-2: Prevalence of cumulative metabolic risk factors related components, stratified by ethnicity and sex.

	Men				Women			
No. of present metabolic risk factors *	**ISA (n=755)** ***n* (%)**	**BSA (n=758)** ***n* (%)**	**WB (n=959)** ***n* (%)**	***P*-value‡**	**ISA (n=369)** ***n* (%)**	**BSA (n=412)** ***n* (%)**	**WB (n=764)** ***n* (%)**	***P*-value‡**
0	121 (16.0%)	96 (12.7%)	210 (21.9%)	<0.001	67 (18.2%)	43 (10.4%)	140 (18.3%)	0.001
1	250 (33.1%)	151 (19.9%)	336 (35.0%)	<0.001	120 (32.5%)	85 (20.6%)	287 (37.6%)	<0.001
2	224 (29.7%)	210 (27.7%)	275 (28.7%)	0.70	81 (22.0%)	105 (25.5%)	227 (29.7%)	0.017
3+	160 (21.2%)	301 (39.7%)	138 (14.4%)	<0.001	101 (27.4%)	179 (43.4%)	110 (14.4%)	<0.001

n, sample size. *Metabolic risk factors included are hypertension, diabetes mellitus, hypercholesterolemia, and central obesity. ‡ *P*-value for the comparison between ethnicities is derived from a chi-square test. ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British.

Figure 6-1: Average age of onset (years) in the presence of varying metabolic risk factors, stratified by ethnicity and sex.



*Error bars denote standard deviation. ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British. *P*-value derived from one-way *ANOVA* tests.

The prevalence of specific clinical characteristics among those with 3 or more metabolic risk factors are presented in Table 6-3. BSA women had a significantly greater prevalence of diabetes mellitus (BSA: 87.7%, vs. ISA: 80.0%, vs. WB: 74.5%, P=0.015) whereas no significant difference was reported among men (BSA: 88.0%, vs. ISA: 90.0%, vs. WB: 82.6%, P=0.14).

Table 6-3: Population characteristics stratified by location, among those with 3+ metabolic risk factors.

	Men				**Women**			
	ISA (n=160) ***n*** **(%)**	**BSA (n=301)** ***n*** **(%)**	**WB (n=138)** ***n*** **(%)**	***P*-value***	**ISA (n=101)** ***n*** **(%)**	**BSA (n=179)** ***n*** **(%)**	**WB (n=110)** ***n*** **(%)**	***P*-value***
Smoking history	83 (52.2)	160 (53.5)	80 (58.0)	0.58	15 (15.0)	9 (5.0)	56 (50.9)	<0.001
Alcohol consumption	86 (54.1)	93 (33.3)	62 (48.8)	<0.001	16 (15.8)	7 (4.1)	29 (31.2)	<0.001
Metabolic risk factors								
Hypertension	158 (98.8)	298 (99.0)	134 (97.1)	0.30	97 (96.0)	174 (97.8)	109 (99.1)	0.34
Diabetes mellitus	144 (82.6)	265 (88.0)	144 (90.0)	0.14	80 (80.0)	157 (87.7)	82 (74.5)	0.015
Hypercholesterolemia	99 (63.1)	264 (89.2)	111 (80.4)	<0.001	74 (74.7)	152 (85.9)	90 (81.8)	0.07
Central obesity	103 (67.3)	139 (49.3)	72 (62.1)	0.001	76 (76.8)	108 (65.1)	66 (77.6)	0.043

n, sample size. Sample includes those with 3 or more metabolic risk factors. These metabolic risk factors include hypertension, diabetes mellitus, hypercholesterolemia, and central obesity. Central obesity is classified by increased waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m2). ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British. * *P*-value derived from chi-square test comparing all 3 groups. Chi-square tests between BSA and ISA with WB (reference) were also calculated and displayed the same results.

To assess if the difference in prevalence of cumulative metabolic risk factors between ethnic groups were related to age and environmental factors, ethnic specific logistic regression models of metabolic risk factors were conducted. BSA were more likely to have the presence of 2 (OR=1.58, CI 95%: 1.24 – 2.01, $P<0.001$), and 3+ (OR=4.87, CI 95%: 3.80 – 6.25, $P<0.001$) metabolic risk factors when compared to WB patients. ISA were significantly more likely to have 3+ metabolic risk factors (OR=1.96, CI 95%: 1.53 – 2.51, $P<0.001$) compared to WB patients. Stratified by sex and adjusting for age, smoking history, and alcohol consumption, this trend continues, both BSA and ISA patients continued to report a significant increase in the prevalence of cumulative metabolic risk factors (Table 6-4). The results of the missing value analysis indicate that missing values occur completely at random (MCAR) ($P=0.34$).

Table 6-4: Logistic regression model to assess the risk of cumulative metabolic risk factors in ISA and BSA ischaemic stroke patients compared with those of WB descent (reference group), stratified by sex.

	ISA (reference: WB)		BSA (reference: WB)	
No. of present metabolic risk factors*	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Men				
1 vs. 0	2.63 (1.82 – 3.80)	<0.001	1.44 (1.00 – 2.06)	0.050
2 vs. 0	2.88 (1.98 – 4.19)	<0.001	2.36 (1.66 – 3.37)	<0.001
3+ vs. 0	4.38 (2.85 – 6.74)	<0.001	5.97 (4.13 – 8.63)	<0.001
Women				
1 vs. 0	2.34 (1.34 – 4.07)	0.003	1.43 (0.84 – 2.44)	0.19
2 vs. 0	1.92 (1.08 – 3.40)	0.026	1.70 (1.01 – 2.86)	0.047
3+ vs. 0	4.17 (2.30 – 7.58)	<0.001	5.23 (3.03 – 9.03)	<0.001

Reference group: WB ischaemic stroke patients. OR, Odds Ratio; 95% CI, 95% Confidence interval. Adjusted for age, smoking and alcohol history. *Metabolic risk factors included are hypertension, diabetes mellitus, hypercholesterolemia, and central obesity. Central obesity is classified by increased waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m2). ISA: South Asians residing in India; BSA: UK residing South Asians; WB: White British.

6.4 Discussion

This present study is the largest sample to consider first time ischaemic event in South Asians with varying metabolic risk factors. In this chapter, it is reported that BSA suffer from a greater number of cumulative metabolic risk factors at the time of event, while both BSA and ISA patients continue to suffer from an earlier age of onset of stroke regardless of the number of metabolic risk factors present. Adjusting for environmental factors, BSA and ISA saw a ~4-6-fold increased risk of having 3+ metabolic risk factors.

In line with previous chapters and the review of the literature, many metabolic risk factors, including hypertension, diabetes mellitus and hypercholesterolemia had a significantly higher prevalence in both BSA and ISA patients. Furthermore, both BSA and ISA men and women saw a ~4-6-fold increased risk of having 3+ metabolic risk factors, after adjusting for environmental factors and age (158,159). Though I cannot directly compare our results with those who report Metabolic Syndrome, it is worth noting, we are unaware of any study focusing on this demographic in relation to ischaemic stroke. Looking at Metabolic Syndrome in the general population, there is an indication that the South Asian population suffer from a greater risk of Metabolic Syndrome, and thus metabolic risk factors. The SABRE study, focusing on the 40–69 years age group between 1988 and 1991, reported a higher prevalence of Metabolic Syndrome in the BSA population compared with WB, for both men (BSA: 28.8% vs. WB: 18.4%, $P<0.001$) and women (BSA: 31.8% vs. WB: 14.4%, $P<0.001$) (160). Our results followed a similar pattern of South Asians displaying a higher overall prevalence in BSA and ISA women. The SABRE study, does, also indicate an earlier onset of first-time total stroke in the presence of diabetes mellitus. The data in this chapter

and in previous chapters demonstrate that both BSA and ISA patients had ~7 and ~20 year earlier stroke compared to WB patients, respectively.

This study also reports significantly higher central obesity in both BSA and ISA patients compared to WB patients. As discussed in my review of the literature, it has been suggested this stems from a predisposition of adiposity in South Asians neonates (161). This continues to adulthood as seen in this chapter. It is worth noting environmental factors play an important role in the BSA population due to the potential acculturation of the host country's diet, away from the traditional South Asian diet, consisting of a high proportion of carbohydrate rich foods such as rice and bread (89,162). This increase in adiposity has been linked with increased insulin resistance, promoting diabetes mellitus (122,163). BSA are known to have a 3–6-time greater prevalence of diabetes mellitus while also developing it 7.8 years earlier compared to the WB population, promoting earlier hypertension (164,165). The earlier development of these metabolic risk factors is likely part of the earlier stroke onset seen in South Asians.

In this chapter, I report that, regardless of ethnicity, those who report no metabolic risk factors present at the time of stroke have an earlier first-time stroke event compared to those who report 3+. There are probably two contributing factors that exist concurrently. Metabolic risk factors included in this study are associated with increasing age (166) so it would be expected that those with a greater number of metabolic risk factors are older. This is counterintuitive in relation to stroke onset as those who are a greater number of metabolic risk factors would be expected to have an earlier onset. BRAINS did not collect information on treatment for these conditions, so I am unable to comment on if those with a greater

number of cumulative metabolic risk factors were more likely to be receiving treatment, thus reducing stroke risk and delaying onset (167). The individual metabolic risk factors are treatable but consideration of the difficulties in diagnosis and treatment compliance are needed in South Asians. Awareness of hypertension and salt intake among South Asians found only 5% are concerned about stroke and 2% about obesity. More encouragingly, 33% and 18% are concerned about diabetes mellitus and hypertension, respectively (168). Insulin resistance, which disproportionally effects South Asians seen in this study, typically requires a continuous treatment regime. Awareness is lacking, with many South Asians not being aware of the common complications associated with diabetes mellitus, the importance of screening clinics and the need for a chiropodist (135). Furthermore, sociocultural and religious factors can exasperate this decreased awareness, with the distorted perceptions of failure at self-care and social stigma (136). This reduced adherence, partnered with the consensus of metabolic risk factors stemming from insulin resistance, will increase prevalence. A small UK based trial offered a solution via digital text messages with helpful tips and suggestions, tailored to South Asians, to promote diabetes mellitus awareness among diabetics (169). Further studies could focus on this area to gauge if adherence increased.

6.5 Limitations

Limitations relating to the BRAINS database overall are discussed in chapter 4.6. This study did not report Metabolic Syndrome prevalence as I was unable to follow typically used criteria such as HDL-cholesterol. BMI is reported to be lower generally in South Asians overall, it has been suggested that a lower threshold needs to be used due to the increased risk of obesity and obesity related diseases in this demographic. The NHS has adopted the use of a BMI of 27.5 kg/m^2 as the trigger for preventive action (170). While other studies have

suggested this threshold should be lowered to 25 kg/m^2 (171). We did adjust our central obesity criteria to lower this to 25 kg/m^2 in BSA and ISA only. Though the prevalence of central obesity in BSA and ISA increased after this criteria adjustment (BSA: 49.2%, vs. ISA: 33.8%, vs. WB: 29.0%, P<0.001), no significant change occurred in the overall result. Lastly, it cannot be assumed South Asian communities in other countries will suffer from similar prevalence's of metabolic risk factors as these factors are often heavily influenced by host country environmental factors.

For this chapter, I only included those with first-time ischaemic stroke event and metabolic risk factor data. This resulted in the exclusion of 1203 ischaemic stroke patients who had missing stroke history data, who had suffered from a recurrent stroke event or who had no metabolic risk factor data. To assess if this resulted in any type of bias, I compared the age of event between those with missing and complete data for each comorbidity (Appendix 10.11). As only 21 patients with first time stroke event had no metabolic risk factors and were dropped (Appendix 10.12), differences between missing and complete data are similar to chapter 4.5. The only significant difference of age between those with missing and complete data was seen in BSA for central obesity and hypercholesterolemia. For both, an earlier age of onset was reported in those with complete central obesity and hypercholesterolemia data. Though this was significant the difference was small, ~3-4 years, and only effected two variables reducing the impact on the linear regressions.

6.6 Summary

Both ISA and BSA reported an increased risk of having 3 or more metabolic risk factors by ~4-6 fold, compared to their WB counterparts. Though the significantly greater risk remained after adjusting for environmental factors, it is likely a genetic factor is associated with the higher prevalence reported in this chapter.

7 Atrial Fibrillation in South Asian Ischaemic Stroke

7.1 Introduction

Atrial fibrillation (AF) induces a 5-fold greater risk of ischaemic stroke (172) and is estimated to affect 3.3% of the UK population (173). In my review of the literature, I discussed that despite the higher burden of most primary atrial fibrillation risk factors in South Asians (age, untreated hypertension, diabetes mellitus, and coronary heart disease), the prevalence of atrial fibrillation has been reported to be lower compared to the WB population (61), though these studies have been small and mostly local (174). In chapters 4 and 6 I briefly discussed, using data from BRAINS, that WB patients reported a significantly greater prevalence of atrial fibrillation despite the greater prevalence of cumulative metabolic risk factors in BSA and ISA.

Anticoagulant medication is the management of choice for atrial fibrillation stroke prevention and can reduce stroke risk by around 64% when compared with around 22% reduction using antiplatelet only therapy (175). Thus, current guidelines only recommend the use of anticoagulants as appropriate treatment for atrial fibrillation related stroke prevention, although their use in differing ethnic groups has not been well studied (176). Conway and Lip reported anticoagulation treatment in South Asians and white British subjects who reported a $CHADS_2$ score ≥ 2 between 2008-2011 (32). Although not all years reported were statistically significant, the results did indicate that South Asians with AF were less likely to receive anticoagulation treatment compared to their White British counterparts. This suggests a potential disparity in the provision of anticoagulation therapy among different ethnic groups with AF which needed further investigation.

In this chapter, I investigated the differences in atrial fibrillation risk and treatment given between BSA and WB ischaemic stroke patients. ISA were excluded from this chapter as there was ~10% higher proportion of missing data related to atrial fibrillation compared to WB and BSA populations (Table 3-4). In addition, ~25-75% of medication treatment data relating to ISA patients with atrial fibrillation were missing, thus full comparisons with the UK arm of BRAINS would not be reliable. Lastly, by comparing treatment data I would also be comparing treatment guidelines between India and the UK. Focusing on the UK arm only highlights the ethnic differences in treatment given without additional confounders, such as differing treatment guidelines and criteria. My aims of this chapter are:

1. Determine if atrial fibrillation remained significantly higher in WB patients after adjusting for risk factors.
2. To establish if there is a disparity in the treatment given in atrial fibrillation patients at admission between BSA and WB.
3. To investigate if WB patients are more likely to be discharged on the correct treatment for atrial fibrillation than BSA patients.

7.2 Methods

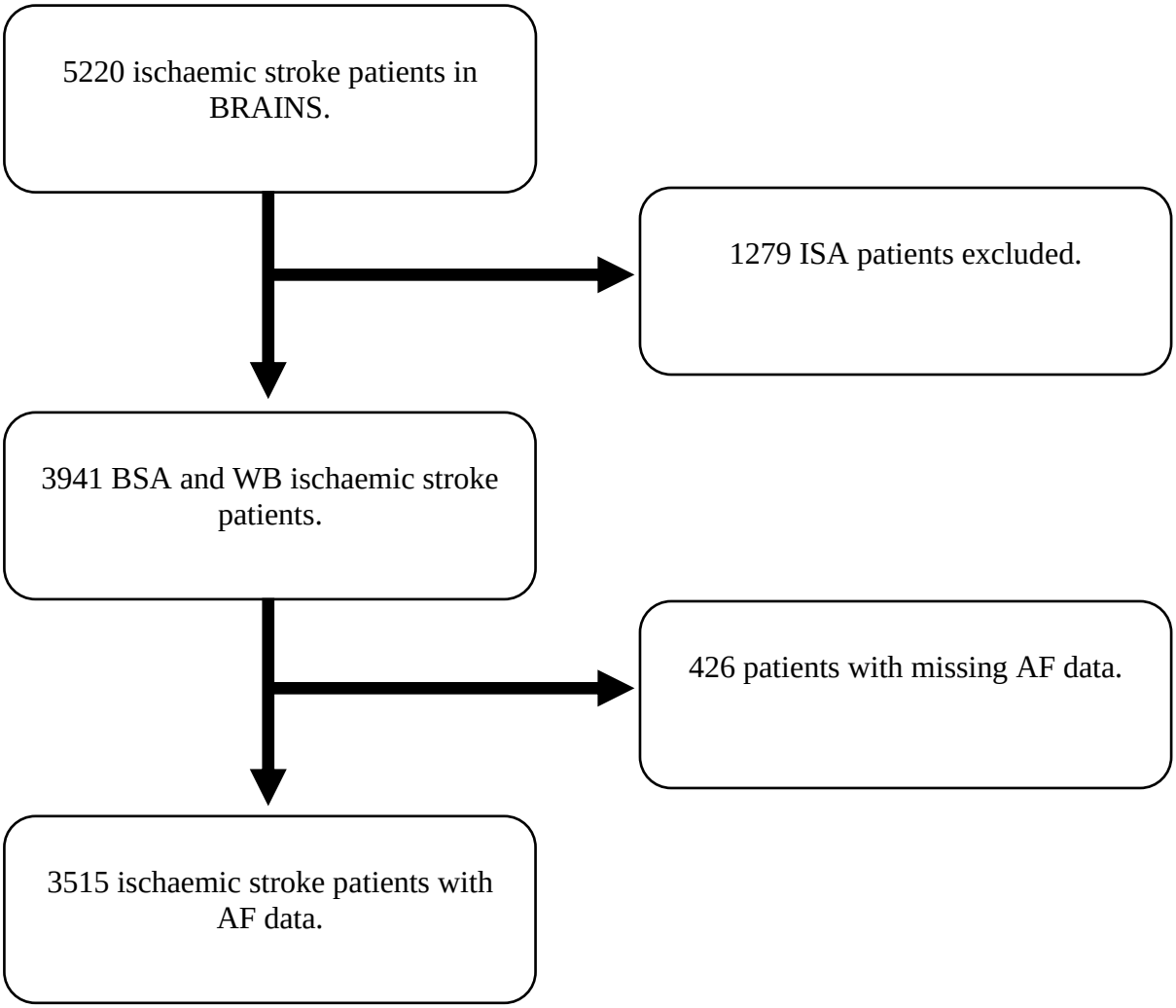
As atrial fibrillation has a relatively low prevalence in the general population, BSA and WB patients with first time and recurrent ischaemic stroke were included. I only included cases if they had complete information on the age of onset, atrial fibrillation status, ethnicity, and sex. Demographic details and categorical data between BSA and WB were compared using an independent *t*-test. The prevalence of individual risk factors between ethnic groups and atrial fibrillation status were compared by chi-square tests. A logistic regression was performed to identify an association between atrial fibrillation status and ethnic groups, adjusted for potential confounders. Variables considered to have an association with atrial fibrillation were selected with respect to literature and biological plausibility (sex, central obesity, smoking history, alcohol history, hypertension, diabetes mellitus, hypercholesterolemia, and ischaemic heart disease). Treatment details were compared using chi-square test and graphed using Microsoft Excel. Cardiovascular disease status was defined using previous/new diagnoses of ischaemic heart disease (ischaemic heart disease/angina, previous myocardial infarction), atrial fibrillation, previous ischaemic stroke, and transient ischaemic attack (TIA).

As the sample now included those with complete atrial fibrillation data only, I wanted to assess if the effect of missing data would affect the age of event. To do this I compared the age of ischaemic stroke event for each variable used, between those with missing and complete comorbidity data. This data is presented in Appendix 10.13 and is stratified for each ethnic group.

7.3 Results

Of the 3515 individuals identified with ischaemic stroke and complete atrial fibrillation data (Figure 7-1), 1482 (men:972, women:510) were BSA and 2033 (men:1141, women:892) were WB. Of these, 190 (men:123, women:70) BSA and 462 (men:252, women:210) WB stroke patients had confirmed atrial fibrillation (BSA:13.0% vs WB:22.7%, P<0.001). The results of the missing value analysis indicate that missing values occur completely at random (MCAR) (*P*=0.72).

Figure 7-1: Flow diagram of the selection process for chapter 7.



AF denotes Atrial Fibrillation. BSA: UK residing South Asians; ISA: South Asians residing in India; WB: White British. BRAINS (Bio-Repository of DNA in Stroke)

Demographic and clinical characteristics of atrial fibrillation status are presented in Table 7-1. The age of ischaemic stroke onset was significantly earlier in non-AF cases (67.4 years, SD = 14.4) compared to AF cases (75.9 years, SD = 11.4) (mean difference = 8.5 years, $P<0.001$). Comparing ethnic differences for each atrial fibrillation status, average age of stroke was significantly lower in non-AF cases compared to new-AF cases for both BSA (non-AF:64.1 years, SD = 14.8 vs new-AF: 73.9 years, SD=12.5, $P<0.001$) and WB stroke patients (non-AF:7 0.2 years, SD=13.5 vs new-AF:77.5 years, SD = 9.8, $P<0.001$). Those with pre-existing atrial fibrillation have an older average age of onset compared to those without atrial fibrillation for both BSA (non-AF: 64.1 years, SD=14.8 vs pre-existing-AF: 72.7 years, SD=12.3, $P<0.001$) and WB stroke patients (non-AF:70.2 years, SD=13.5 vs pre-existing-AF:77.1 years, SD=11.0, $P<0.001$). No significant difference in the age of event is reported between new AF and pre-existing AF (BSA: $P=0.60$, WB: $P = 0.71$). Among traditional atrial fibrillation risk factors, hypertension, and ischaemic heart disease were significantly higher in patients with atrial fibrillation.

Table 7-1: Ischaemic stroke population characteristics stratified by Atrial Fibrillation (AF) status.

	AF (n=655) Mean (SD)	**Non-AF (n=2860) Mean (SD)**	***P*-Value***
BSA, *n* (%)	193 (29.5)	1289 (45.1)	<0.001
Age, years (SD)	75.9 (11.4)	67.4 (14.4)	<0.001
Men, *n* (%)	375 (57.3)	1738 (60.8)	0.10
Environmental Factors	***n*, (%)**	***n*, (%)**	***P*-Value***
Central obesity, *n* (%)	151 (31.9)	720 (32.2)	0.89
Smoking history, *n* (%)	296 (45.5)	1338 (47.1)	0.47
Alcohol history, *n* (%)	204 (35.9)	863 (34.2)	0.47
Comorbidities	***n*, (%)**	***n*, (%)**	***P*-Value***
Hypertension	535 (82.3)	2019 (70.9)	<0.001
Diabetes mellitus	199 (30.7)	997 (34.9)	0.038
Hypercholesterolemia	278 (43.8)	1236 (43.8)	0.99
Ischaemic heart disease	220 (36.2)	622 (23.3)	<0.001

n, sample size. * Independent t-test was used to compare the age of onset with all other comparisons of prevalence using chi-square test. Central obesity is classified by waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m^2). BSA: UK residing South Asians.

To estimate the possible confounding factors of the relationship of ethnic group and atrial fibrillation status by demographic and clinical characteristics, comparisons between BSA and WB among those with atrial fibrillation are presented in Table 7-2. BSA average age of ischaemic stroke was significantly earlier (72.9 years, SD=12.3) compared to WB patients (77.2 years, SD=10.7) (mean difference =4.4 years, $P<0.001$). BSA patients were on average 3.9cm shorter and had a greater prevalence of traditional atrial fibrillation risk factors compared to WB despite having a lower incidence of atrial fibrillation (Table 7-2).

Table 7-2: Population characteristics with confirmed atrial fibrillation status stratified by ethnicity.

	BSA (n=193) Mean (SD)	**WB (n=462) Mean (SD)**	***P*-Value***
Age, years	72.9 (12.3)	77.2 (10.7)	<0.001
Men, *n* (%)	123 (63.7)	252 (54.5)	0.030
Environmental Factors	***n*, (%)**	***n*, (%)**	***P*-Value***
Height, cm	165.7 (9.9)	169.6 (9.7)	0.043
Central obesity, *n* (%)	49 (31.4)	102 (32.1)	0.88
New diagnosis, *n* (%)	32 (16.6)	99 (21.4)	0.16
Smoking history, *n* (%)	56 (29.2)	240 (52.4)	<0.001
Alcohol history, *n* (%)	41 (22.5)	163 (42.1)	<0.001
Comorbidities	***n*, (%)**	***n*, (%)**	***P*-Value***
Hypertension	174 (91.6)	361 (78.5)	<0.001
Diabetes mellitus	103 (53.9)	96 (21.0)	<0.001
Hypercholesterolemia	111 (61.0)	167 (36.9)	<0.001
Ischaemic heart disease	101 (54.0)	119 (28.3)	<0.001
Treatment at admission	***n*, (%)**	***n*, (%)**	***P*-Value***
Anticoagulation	55 (28.5)	130 (28.1)	0.93
Antiplatelet	91 (47.4)	125 (29.9)	<0.001
Combined	15 (7.8)	10 (2.4)	0.002
Treatment at discharge	***n*, (%)**	***n*, (%)**	***P*-Value***
Anticoagulation	87 (45.1)	199 (43.1)	0.64
Antiplatelet	94 (49.5)	143 (34.7)	0.001
Combined	34 (17.9)	33 (8.0)	<0.001

n, sample size. *Independent *t*-test was used to compare the age of onset, with all other comparisons using chi-square tests comparing all 3 ethnic groups. Chi-square tests between BSA and ISA with WB (reference) were also calculated and displayed the same results. Central obesity is classified by waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m^2). BSA: UK residing South Asians; WB: White British.

To evaluate the association of atrial fibrillation status with the ethnic group among ischaemic stroke cases, a logistic regression was performed. Unadjusted analyses showed BSA had a 49% lower risk of having atrial fibrillation (OR=0.51, 95%CI: 0.43:0.61, *P*<0.001). I ran a stepwise logistic regression which included age, ischemic heart disease, hypertension, and smoking history as significant variables. Adjusted for these factors, the lower risk of AF in South Asian patients was maintained (OR:0.40, 95%CI:0.33:0.49, *P*<0.001). The associations of the age of stroke event and other predictors with atrial fibrillation are reported in Table 7-3.

Table 7-3: Associations of the age of stroke event and other predictors with atrial fibrillation.

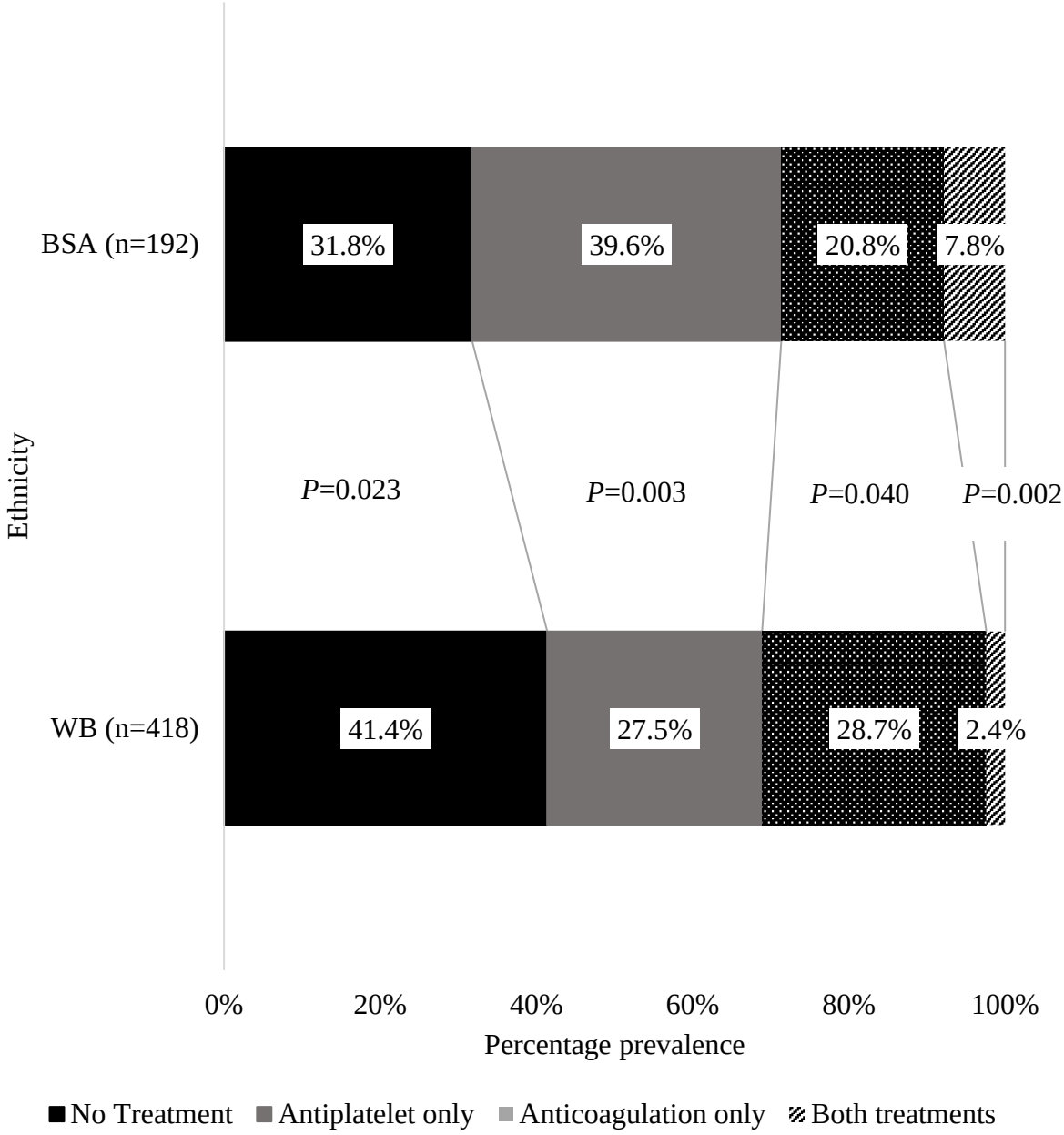
Model (Age + sex)	**Age**		**Interaction**	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Hypertension	1.05 (1.04 – 1.06)	<0.001	1.06 (1.05 – 1.07)	<0.001
Diabetes mellitus	1.05 (1.04 – 1.06)	<0.001	1.05 (1.04 – 1.06)	<0.001
Hypercholesterolemia	1.05 (1.04 – 1.06)	<0.001	1.05 (1.04 – 1.06)	<0.001
Ischaemic heart disease	1.05 (1.04 – 1.06)	<0.001	1.05 (1.04 – 1.06)	<0.001
Central Obesity	1.05 (1.04 – 1.06)	<0.001	1.06 (1.05 – 1.07)	<0.001
Smoking	1.05 (1.04 – 1.06)	<0.001	1.04 (1.03 – 1.05)	<0.001
Alcohol use	1.05 (1.04 – 1.06)	<0.001	1.06 (1.05 – 1.07)	<0.001

Every model is adjusted by age and sex. Interaction model adjusted for age, sex, specific risk factor and an interaction variable. Central obesity is classified by waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m2).

7.3.1 Treatment

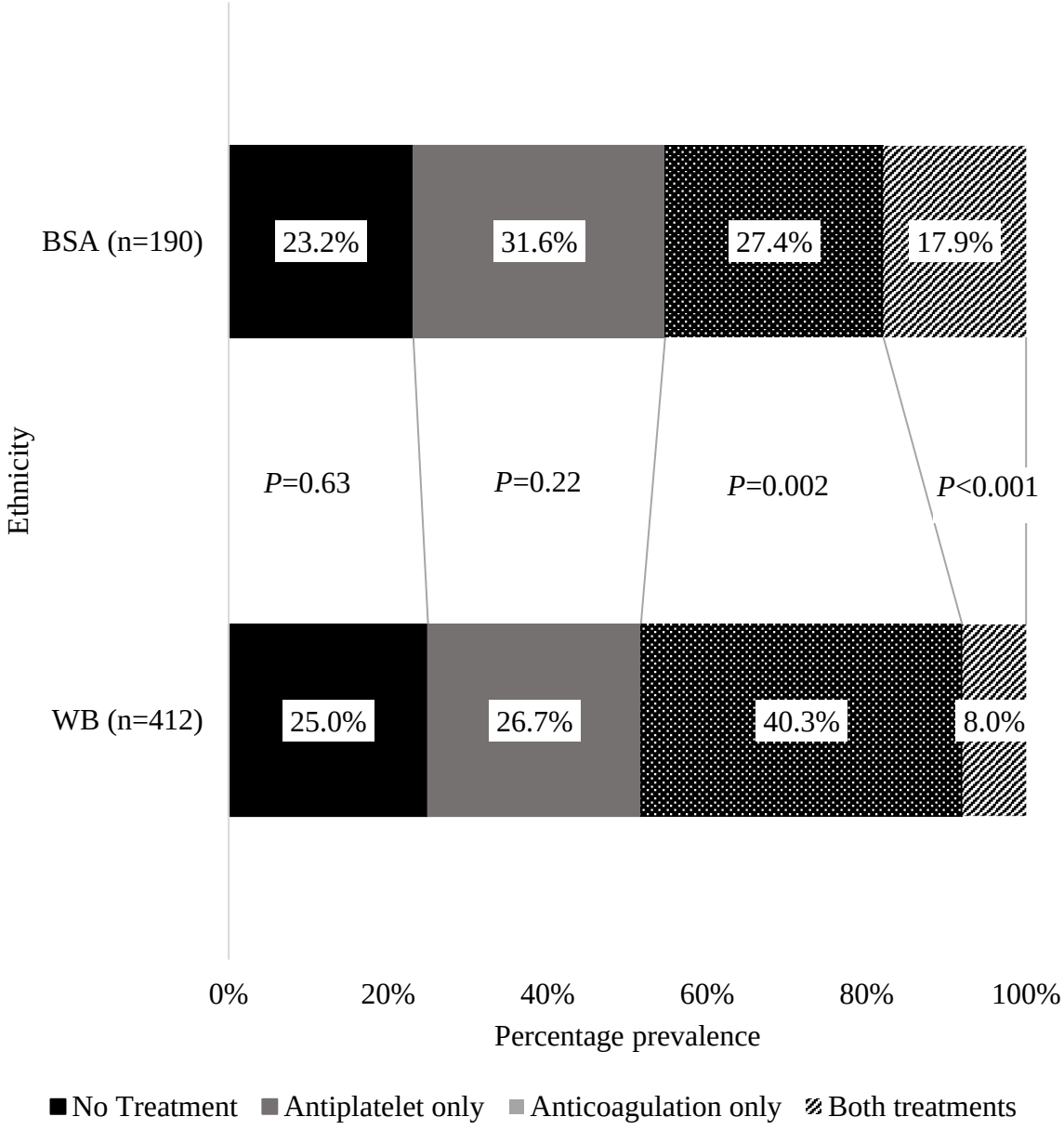
Differences in antiplatelet and anticoagulant treatment among atrial fibrillation patients are presented in Table 7-2. BSA patients with atrial fibrillation had significantly higher antiplatelet treatment on admission (BSA: 47.4% vs WB: 29.9%, $P<0.001$) and discharge (BSA: 49.5% vs. WB: 34.7%, $P=0.001$). No significant difference was seen between anticoagulation treatment at admission (BSA: 28.5% vs. WB: 28.1%, $P=0.93$) or discharge (BSA: 45.1% vs. WB: 43.1%, $P=0.64$). A combination of treatments for admission and discharge is presented in Figure 7-2 and Figure 7-3.

Figure 7-2: Distribution of anticoagulation and antiplatelet status in confirmed atrial fibrillation cases, stratified by ethnicity, at **admission.**



Antiplatelet only and anticoagulation only treatment included those that were receiving only one of those treatments. Both treatments included those receiving both antiplatelet and anticoagulant treatments. Chi-square tests were used to compare between ethnicities. BSA: UK residing South Asians; WB: White British.

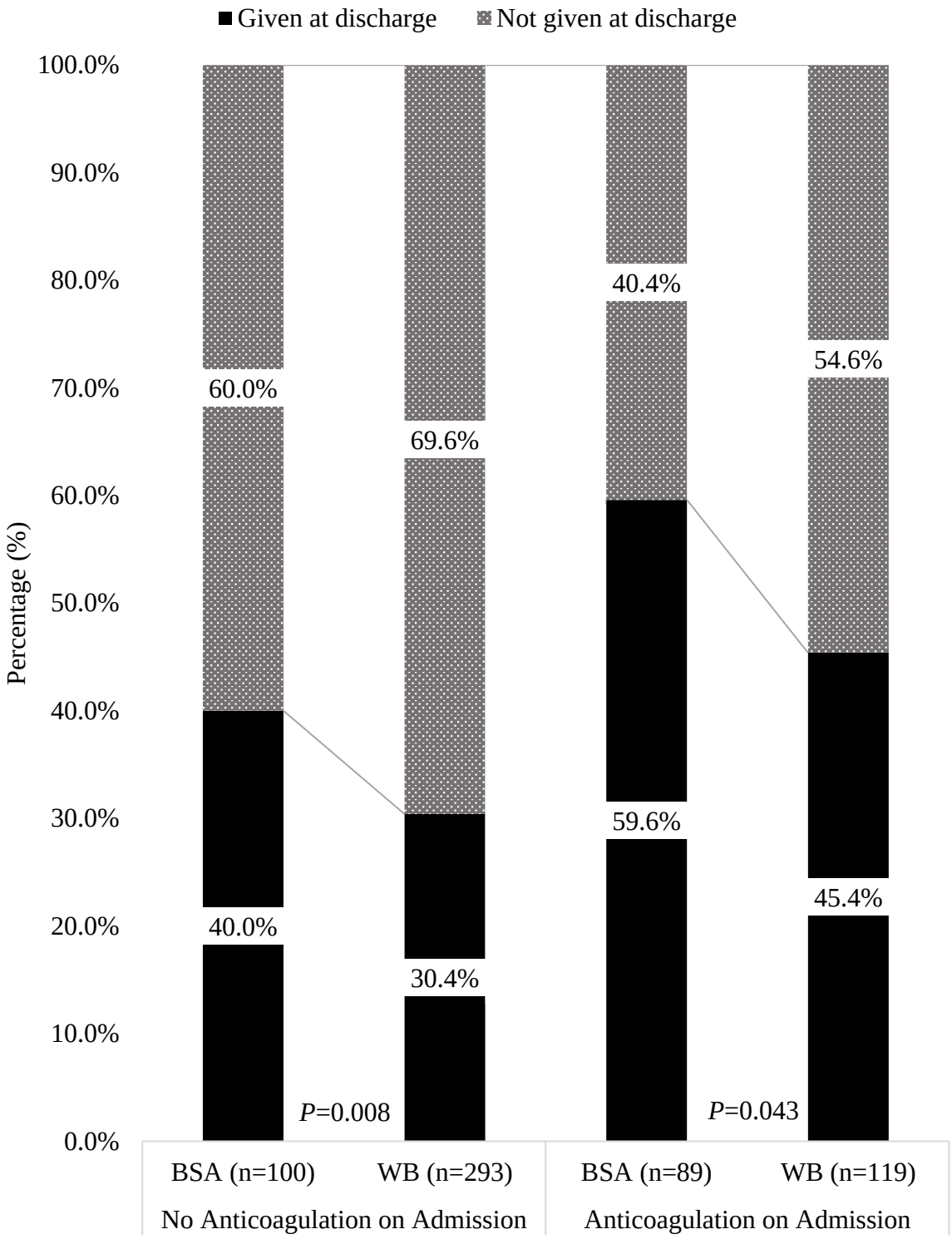
Figure 7-3: Distribution of anticoagulation and antiplatelet status in confirmed atrial fibrillation cases, stratified by ethnicity, at **discharge.**



Antiplatelet only and anticoagulation only treatment included those that were receiving only one of those treatments. Both treatments included those receiving both antiplatelet and anticoagulant treatments. Chi-square tests were used to compare between ethnicities. BSA: UK residing South Asians; WB: White British.

Changes in anticoagulation status from admission to discharge are presented in Figure 7-4. The increased prevalence of antiplatelet therapy in BSA was hypothesised to be due to an increased risk of cardiovascular disease. To test this, I compared antiplatelet prevalence between BSA and WB stroke patients (Table 7-4). Of those with cardiovascular disease, 53.8% were BSA and 49.2% were WB patients (P=0.007). In those with cardiovascular disease, BSA patients continued to show an increased prevalence of antiplatelet treatment at admission (BSA: 69.1% vs. WB: 45.5%, P<0.001) and discharge (BSA: 77.1% vs. WB: 60.7%, P<0.001). This difference was also present in those with atrial fibrillation at admission (BSA: 47.4% vs. WB: 29.9%, P<0.001) and discharge (BSA: 49.5% vs. WB: 34.7%, P=0.001). In those without cardiovascular disease, BSA patients continued to display a greater prevalence of antiplatelet therapy in the total ischaemic population only (Table 7-4).

Figure 7-4: Changes in anticoagulation treatment from admission to discharge in confirmed atrial fibrillation cases, stratified by ethnicity.



Chi-square tests were used to compare between ethnicities. Anticoagulation treatment only. BSA: UK residing South Asians; WB: White British.

Table 7-4: Antiplatelet treatment at admission and discharge stratified by ethnicity and cardiovascular disease.

	Antiplatelet Treatment	***n*, (%)**	***n*, (%)**	***P*-value***
Cardiovascular Disease	**Total ischaemic population**	**BSA (n=794)**	**WB (n=932)**	
	Admission	549 (69.1)	424 (45.5)	<0.001
	Discharge	604 (77.1)	559 (60.7)	<0.001
	AF patients only	**BSA (n=190)**	**WB (n=412)**	
	Admission	91 (47.4)	125 (29.9)	<0.001
	Discharge	94 (49.5)	143 (34.7)	0.001
Without Cardiovascular Disease	**Total ischaemic population**	**BSA (n=682)**	**WB (n=865)**	
	Admission	176 (25.8)	149 (17.2)	<0.001
	Discharge	589 (87.3)	720 (83.3)	0.032

**P*-value calculated from chi-square tests used to compare between ethnicities. Cardiovascular Disease (CVD) definition includes ischaemic heart disease (IHD, Angina, Previous MI), atrial fibrillation, previous ischaemic stroke, and TIA. n, sample size. BSA: UK residing South Asians; WB: White British.

7.4 Discussion

In this chapter, I show that BSA ischaemic stroke patients had a significantly lower prevalence of atrial fibrillation compared to their WB counterparts (13.0% vs. 22.7%, $P<0.001$). BSA with atrial fibrillation presented with an ~4 year earlier stroke event compared to their WB counterparts and were more likely to receive antiplatelet therapy at both admission and discharge despite having similar cardiovascular profiles, but no significant difference was seen overall in anticoagulation rates.

The significantly lower atrial fibrillation prevalence in BSA, despite the higher prevalence of atrial fibrillation risk factors shown here, is consistent with findings from previous smaller studies (22,35). Though these phenomena have been recorded in South Asians, there are several potential underlying mechanisms such as differing atrial electrophysiological parameters or a morphologically smaller left atrium (149,150). In this study, we did not collect data on atrial morphology though we report BSA patients being significantly smaller than WB patients with atrial fibrillation. Another possible reason for the difference existing could be related to age. As discussed in this chapter and chapter 4, South Asians have an earlier onset of ischaemic stroke. Atrial fibrillation incidence increases with age (177). With stroke onset being earlier in South Asians, it would then be expected that the prevalence of atrial fibrillation would be lower, similar to that reported in this chapter. To explore this, I conducted a logistic regression with the dependent variable being atrial fibrillation status and the dependent being ethnicity. Adjusting for age, sex, comorbidities, and environmental factors, BSA still suffered from an increased likelihood of atrial fibrillation than WB patients (OR=0.40, 95%CI:0.33-0.49, $P<0.001$). This suggests that BSA still increased the likelihood of atrial fibrillation compared to WB patients, despite the earlier age of onset. Though height

in our study was not independently associated with atrial fibrillation risk, this could be due to a strong association between ethnicity and height. Currently, no confirmed South Asian-specific genetic polymorphism has been reported which could result in the protective effect seen (62).

Treatment with anticoagulant therapy at discharge remained relatively low, 45.1% in BSA and 43.1% in WB. A previous study found 12.8% of ischaemic stroke cases who were not being treated with anticoagulation treatment at admission were ineligible for treatment at discharge (178). I also show rates of those untreated with atrial fibrillation before admission were relatively high in both ethnicities. This rate of treatment for WB cases is similar to those reported in previous studies, however, no such data has been reported for BSA cases (178). One possible reason for relatively low treatment could be a result of poor awareness of the condition and the importance of treatment. A small UK study (n=93) reported that only 49% of patients with atrial fibrillation could name the condition and 52% knew that anticoagulants prevent blood clots from forming (179). This study also looked at the combination treatments received in those with atrial fibrillation.

Antiplatelet-only treatment was the most common treatment at admission for both ethnicities, though was greater in South Asians. A similar study has also reported a higher percentage of South Asians being treated with antiplatelet therapies for ischemic stroke, though this was not exclusive to AF cases(22). The analysis in this study extended to assess the treatments prescribed for those with atrial fibrillation. Combined treatment of antiplatelet and anticoagulant treatment was significantly higher both at admission and discharge in South Asians. Over the course of the lifetime of BRAINS, there was a transition from the use of

Warfarin to NOACs. This preferred medication allowed more intervention eligibility for atrial fibrillation patients because of reduced bleeding risk associated with NOACs, and this benefit is disproportionately greater in South Asians (180,181). However, even with that individual reduced bleeding risk, combined treatment with antiplatelets can increase the risk of major bleeding, including intracranial haemorrhage (182,183). It is possible that the increased use of lone antiplatelets and/or combined with NOAC (also seen in a previous study (22)) is likely due to the increased prevalence of cardiovascular disease in South Asians. However, South Asians with cardiovascular disease were still more likely to receive antiplatelet treatment, regardless of atrial fibrillation status. Furthermore, in those without cardiovascular disease, South Asians continued to have a higher prevalence of antiplatelet therapy. We are not able to address individual management of cardiovascular disease, but a view may still exist that aspirin is beneficial for primary prevention providing a possible explanation for its use in those without cardiovascular disease.

7.5 Limitations

Limitations related to BRAINS are discussed in chapter 4.6. BRAINS is an ongoing long-term study and during its lifetime treatment for atrial fibrillation has advanced from VKA (Warfarin) to non-VKA (NOAC). With this change, cases with atrial fibrillation who might not have been eligible for vitamin-K antagonists due to increased bleed risk could now be prescribed non-vitamin-K antagonists. This transition could result in a non-differential bias but as this study compares differences between two ethnic groups, this should not affect the overall result. Additionally, the transition from $CHADS_2$ to CHA_2DS_2-VASc to calculate stroke risk could mean people who were assessed under the previous category may not have received anticoagulation (184). While this transition could have resulted in a non-differential bias, I compared ethnic differences in the percentage of those prescribed with anticoagulants before and after June 2014, the date CHA_2DS_2-VASc guidelines were introduced into the NICE protocol (185). Regardless of the date, anticoagulation treatment prior to admission was not significantly different between ethnicity ($CHADS_2$: P=0.094, CHA_2DS_2-VASc: P=0.206), and thus any effect of this transition between these protocols would be minimal. This study is not able to report adherence to anticoagulation in BSA who may have poorer anticoagulation control due to socioeconomic factors(186) which could, in part, explain their 4-year lower stroke event age seen in this study. Furthermore, NICE recommends that patients do not receive anticoagulant treatment two weeks post stroke event (187). Thus, patients may be re-prescribed anticoagulants either in the hospital (if not discharged for 2 weeks) or post discharge. As BRAINS is a hospital study, we did not collect information on patients' post discharge, we are unable to comment on whether patients received anticoagulation after the two-week period, potentially thus under reporting anticoagulant treatment prevalence.

Throughout the data collection process, new antiplatelet treatments have been offered. Of these, Ticlopidine is not commonly prescribed to UK patients. Prasugrel and Ticagrelor were recommended for preventing atherothrombotic events by NICE in July 2014 mostly in cardiac disease and are not commonly used in ischaemic stroke. Potential confounders may have varied over time, including awareness of stroke risk factors. Additionally, as BRAINS is a hospital-based study, we are unable to comment on community incidence of atrial fibrillation.

Using atrial fibrillation history and all ischaemic stroke event as part of the selection criteria could result in different population characteristics (Appendix 10.13). I compared the age of event of stroke in those with missing and complete data for each variable using the selection criteria described in chapter 7.3. Only BSA with complete hypocholesterolaemia data reported a significantly younger stroke (P=0.01). Though this difference suggests that those with complete hypercholesterolemia data included in this chapter are younger, it will not affect results such as overall atrial fibrillation risk or the treatment received as it is not included in these analyses.

7.6 Summary

BSA patients have a lower risk of atrial fibrillation compared to their WB counterparts. Though no significant difference was seen in the use of anticoagulation at admission or discharge, the use of antiplatelet medication alone in atrial fibrillation subjects was greater in BSA patients.

8 Conclusion

In this thesis, I addressed the paucity of ischaemic stroke epidemiological data in UK residing South Asians, and where feasible, South Asians in India. Though I have reported clinical data throughout, this must be the first step of future research in determining the difference in stroke overall between South Asians and Western populations such as the white British group.

A current shortfall with much of the epidemiological data regarding ischaemic stroke is the relatively low proportion of studies being conducted in ethnic minority groups in comparison to white populations in the West. This has largely resulted in our understanding of ischaemic stroke, and its risk factors, being based on Western populations and Western environmental factors. Preventative measures and post-event treatments thus rely on information that potentially does not apply to every ethnic group in any country. The findings available suggested South Asians in the UK suffered from a significantly earlier onset of ischaemic stroke, though this study's data was collected at least 17 years ago and contained a relatively small sample population (36). Furthermore, though it had been expected that traditional stroke risk factors such as diabetes mellitus and hypertension had a higher prevalence among UK residing South Asians, data either originated from studies with small sample sizes or were not current. This led to the open-ended questions, do South Asians continue to suffer from earlier onset, and if so, could traditional stroke risk factors explain the differences seen. To answer this question, I utilised the BRAINS database, where I was one of the first to conduct quality control which is outlined in chapter 3.

Given the lack of basic epidemiological data available among South Asians, especially those in the UK, in chapter 4 I tried to provide a current picture of ischaemic stroke among this group. Using the dataset to include those with first time stroke event only, I found that UK and India residing South Asians suffered from stroke ~14 and ~19 years, respectively, earlier than their white British counterparts. The prevalence of traditional risk factors such as hypertension and diabetes mellitus were significantly increased in UK residing South Asians, and these risk factors alone did not explain the earlier age of onset seen within both South Asian groups. Ethnicity explained ~25% of the variance of the age of onset, with traditional risk factors of hypertension, atrial fibrillation, ischaemic heart disease, alcohol consumption, central obesity, and sex accounting for only about 8% of the variance. This suggests a potential genetic component or environmental factor correlated with ethnicity, not assessed in this study, could be causing the earlier onset of stroke.

With this significant disparity between locations and ethnicity, I wanted to explore further to identify if the difference in the age of stroke onset affects different ischaemic stroke subtypes equally. I used the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria to identify the subtype as it relies on both observational and clinical data to attempt to identify a cause for the stroke event (100). Before my analysis, there had yet to be a study which had reported TOAST subtype in UK residing South Asians. Additionally, differing results have been reported in South Asia using the TOAST criteria (143,144). I found that small vessel occlusion was more prominent in all South Asians whereas the white British population have a higher prevalence of large artery atherosclerosis. After adjusting for traditional stroke risk factors, a ~2-fold increase in small vessel occlusion prevalence and a ~30-60% decrease in large artery atherosclerosis classified stroke was reported in both South Asian groups, compared to white British patients.

Small vessel occlusion is often linked to metabolic risk factors. Though small vessel occlusion remained more likely in South Asians regardless of location after adjusting for metabolic risk factors, little was known about the cumulative effect of these factors in South Asians with ischaemic stroke. Therefore, in chapter 6 I set out to answer this by determining if South Asians were more likely to have multiple risk factors present at the time of stroke, as well as investigating the effect of cumulative metabolic risk factors had on the age of event. I showed that both South Asian groups have an increased risk of having 3 or more metabolic risk factors by ~4-6 fold, compared to white British patients. Additionally, India residing South Asians, followed by UK residing South Asians, continued to have earlier stroke onset regardless of the number of metabolic risk factors present, which again hinted that either a novel risk factor was affecting the age of stroke event or an unknown genetic component.

In chapter 4, the prevalence of atrial fibrillation was the only traditional risk factor to be found significantly lower in both South Asian groups compared to the white British stroke patients. Atrial fibrillation is a common cause of cardioembolic stroke, though the treatment of this condition has yet to be studied. For this reason, I only focused on the UK arm of the BRAINS database as treatment regimes are likely to follow a different protocol in India. I showed that atrial fibrillation continued to be ~50% less likely in UK residing South Asians, compared to white British patients, after adjusting for traditional risk factors. I also showed there was no difference in the number of patients with atrial fibrillation being prescribed anticoagulants at admission or discharge, though the use of antiplatelet medication alone in atrial fibrillation subjects was greater in South Asians in both such settings.

In this thesis, I have discussed how South Asians with ischaemic stroke both in the UK and in India suffer from significantly earlier first-time stroke onset when compared to white British patients. It is often suggested that the reason for this earlier onset is linked to the greater prevalence of ischaemic stroke risk factors seen in South Asians as a whole. Throughout my thesis, I employed the BRAINS database to explore the traditional risk factors for stroke while also exploring ischaemic stroke subtype. I reported that though there are stark differences in ischaemic stroke risk factor prevalence and subtype, these differences alone do not fully explain the differences in age of the first-time event. My research, in parts, is novel and while I believe it updates the current understanding of ischaemic stroke in South Asians both in the UK and India, I hope it spurs further longitudinal prospective analysis of stroke in this population. This would allow the reporting of incidence rates of stroke in this under-represented population which I was unable to do in this thesis.

9 Bibliography

1. World Stroke Organization. WSO Global Stroke Fact Sheet 2022 [Internet]. 2022 [cited 2023 Apr 16]. Available from: https://www.world-stroke.org/news-and-blog/news/wso-global-stroke-fact-sheet-2022

2. World Health Organization. Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Global Health Estimates 2016. Geneva; 2018.

3. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review [Internet]. Vol. 8, The Lancet Neurology. Elsevier; 2009 [cited 2021 Jun 9]. p. 355–69. Available from: www.thelancet.com/neurology

4. Stroke Association. Stroke statistics [Internet]. 2018 [cited 2023 Apr 16]. Available from: https://www.stroke.org.uk/what-is-stroke/stroke-statistics

5. Brain Research UK. Stroke – Neurological condition [Internet]. 2023 [cited 2023 Apr 16]. Available from: https://www.brainresearchuk.org.uk/neurological-conditions/stroke

6. Lee S, Shafe ACE, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database. BMJ Open [Internet]. 2011 Jan 1 [cited 2018 Oct 25];1(2):e000269. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22021893

7. Marmot M, Bell R. Fair society, healthy lives. Public Health. 2012 Sep 1;126:S4–10.

8. Evandrou M, Falkingham J, Feng Z, Vlachantoni A. Ethnic inequalities in limiting health and self-reported health in later life revisited. J Epidemiol Community Health (1978) [Internet]. 2016 Jul 1 [cited 2019 Jan 30];70(7):653–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26787199

9. Cooke A, Butt A, Nasir R, Windsor-Shellard. Mortality from leading causes of death by ethnic group, England and Wales - Office for National Statistics [Internet]. 2021 Aug [cited 2023 Apr 16]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/mortalityfromleadingcausesofdeathbyethnicgroupenglandandwales/2012to2019

10. Chadha SL, Radhakrishnan S, Ramachandran K, Kaul U, Gopinath N. Epidemiological study of coronary heart disease in urban population of Delhi. Indian J Med Res [Internet]. 1990 Dec [cited 2019 Aug 9];92:424–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2079357

11. Enas EA, Garg A, Davidson MA, Nair VM, Huet BA, Yusuf S. Coronary heart disease and its risk factors in first-generation immigrant Asian Indians to the United States of America. Indian Heart J. 1996;48(4):343–53.

12. Lee J, Heng D, Chia KS, Chew SK, Tan BY, Hughes K. Risk factors and incident coronary heart disease in Chinese, Malay and Asian Indian males: the Singapore Cardiovascular Cohort Study. Int J Epidemiol. 2001 Oct;30(5):983–8.

13. Visram R. Ayahs, Lascars and Princes: The story of Indians in Britain 1700-1947. 2015. Chapter 9.

14. Office for National Statistics. 2011 Census: Ethnic group, local authorities in the United Kingdom. London; 2013.

15. Quay TAW, Frimer L, Janssen PA, Lamers Y. Barriers and facilitators to recruitment of South Asians to health research: a scoping review. BMJ Open [Internet]. 2017 May 1 [cited 2023 Apr 2];7(5):e014889. Available from: https://bmjopen.bmj.com/content/7/5/e014889

16. Prinjha S, Miah N, Ali E, Farmer A. Including "seldom heard" views in research: Opportunities, challenges and recommendations from focus groups with British South Asian people with type 2 diabetes. BMC Med Res Methodol [Internet]. 2020 Jun 15 [cited 2023 Apr 2];20(1):1–11. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-020-01045-4

17. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: A risk profile from the Framingham study. Stroke [Internet]. 1991 [cited 2020 Oct 24];22(3):312–8. Available from: https://pubmed.ncbi.nlm.nih.gov/2003301/

18. Cooper H. Investigating socio-economic explanations for gender and ethnic inequalities in health. Soc Sci Med [Internet]. 2002 [cited 2023 Apr 3];54(5):693–706. Available from: https://pubmed.ncbi.nlm.nih.gov/11999487/

19. Bécares L, Das-Munshi J. Ethnic density, health care seeking behaviour and expected discrimination from health services among ethnic minority people in England. Health Place [Internet]. 2013 [cited 2023 Apr 3];22:48–55. Available from: https://pubmed.ncbi.nlm.nih.gov/23603426/

20. Patel A, Berdunov V, Quayyum Z, King D, Knapp M, Wittenberg R. Estimated societal costs of stroke in the UK based on a discrete event simulation. Age

Ageing [Internet]. 2020 Feb 27 [cited 2023 Apr 2];49(2):270–6. Available from: https://pubmed.ncbi.nlm.nih.gov/31846500/

21. Stroke Working Party. National clinical guideline for stroke - Fifth edition [Internet]. 2016 [cited 2023 Mar 26]. Available from: https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx

22. Bourke J, Sylvester R, Sharma P. Ethnic variations in the management of patients with acute stroke. Postgrad Med J [Internet]. 2006 Jan [cited 2018 Nov 22];82(963):13–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16397074

23. Gunarathne A, Patel J V, Gammon B, Gill PS, Hughes EA, Lip GYH. Ischemic stroke in South Asians: a review of the epidemiology, pathophysiology, and ethnicity-related clinical features. Stroke [Internet]. 2009 Jun 1 [cited 2020 Jun 8];40(6):e415-23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19390072

24. Celentano DD, Szklo M. The Occurrence of Disease: I. Disease Surveillance and Measures of Morbidity - ClinicalKey. In: Gordis Epidemiology [Internet]. 6th ed. Elsevier Health Sciences; 2018 [cited 2023 Mar 26]. p. 41–64. Available from: https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323552295000036?scrollTo=%23top

25. Porta M. Comorbidity. In: A Dictionary of Epidemiology (DRAFT). 5th ed. Oxford: Oxford University Press; 2008.

26. Porta M. Risk Factor. In: A Dictionary of Epidemiology [Internet]. 6th ed. Oxford: Oxford University Press; 2014 [cited 2023 Apr 6]. Available from:

https://www.oxfordreference.com/display/10.1093/acref/9780199976720.001.0001/acref-9780199976720-e-1671;jsessionid=4ACCB03467A694B83A73FAA74F949906

27. Hsu RT, Ardron ME, Brooks W, Cherry D, Taub NA, Botha JL. The 1996 Leicestershire Community Stroke and Ethnicity Study: Differences and similarities between South Asian and white strokes. Int J Epidemiol [Internet]. 1999 Oct 1 [cited 2020 Sep 29];28(5):853–8. Available from: https://europepmc.org/article/med/10597982

28. Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, Forouhi NG, 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 [Internet]. 2013 Apr 30 [cited 2019 Jul 19];61(17):1777–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23500273

29. Ramadan H, Patterson C, Maguire S, Melvin I, Kain K, Teale E, et al. Incidence of first stroke and ethnic differences in stroke pattern in Bradford, UK: Bradford Stroke Study. International Journal of Stroke. 2018 Jun 1;13(4):374–8.

30. Becker E, Boreham R, Chaudhury M, Craig R, Deverill C, Doyle M, et al. Health Survey for England - 2004: Health of ethnic minorities [Internet]. Sproston K, Mindell J, editors. Vol. 1. London: The Information Centre; 2004 [cited 2019 Mar 8]. p. 1–435. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2004-health-of-ethnic-minorities-main-report#resources

31. Balarajan R, Raleigh VS. Patterns of mortality among Bangladeshis in England and Wales. Ethn Health. 1997 Mar;2(1–2):5–12.

32. Conway DSG, Lip GYH. Ethnicity in relation to atrial fibrillation and stroke (the West Birmingham Stroke Project). American Journal of Cardiology. 2003 Dec 15;92(12):1476–9.

33. Harding S, Rosato M, Teyhan A. Trends for coronary heart disease and stroke mortality among migrants in England and Wales, 1979–2003: slow declines notable for some groups. Heart [Internet]. 2008 Apr [cited 2022 Sep 6];94(4):463. Available from: /pmc/articles/PMC2565582/

34. Gunarathne A, Patel J V., Potluri R, Gammon B, Jessani S, Hughes EA, et al. Increased 5-year mortality in the migrant South Asian stroke patients with diabetes mellitus in the United Kingdom: The West Birmingham Stroke Project. Int J Clin Pract [Internet]. 2007 Nov 23 [cited 2018 Dec 21];62(2):197–201. Available from: http://doi.wiley.com/10.1111/j.1742-1241.2007.01580.x

35. Banerjee S, Biram R, Chataway J, Ames D. South Asian strokes: lessons from the St Mary's stroke database. QJM: An International Journal of Medicine [Internet]. 2010 Jan 1;103(1):17–21. Available from: http://dx.doi.org/10.1093/qjmed/hcp148

36. Gunarathne A, Patel J V., Potluri R, Gill PS, Hughes EA, Lip GYHH. Secular trends in the cardiovascular risk profile and mortality of stroke admissions in an inner city, multiethnic population in the United Kingdom (1997–2005). J Hum Hypertens [Internet]. 2008 Jan 2 [cited 2018 Dec 27];22(1):18–23. Available from: http://www.nature.com/articles/1002265

37. Lawlor DA, West J, Fairley L, Nelson SM, Bhopal RS, Tuffnell D, et al. Pregnancy glycaemia and cord-blood levels of insulin and leptin in Pakistani and white British mother–offspring pairs: findings from a prospective pregnancy cohort. Diabetologia. 2014 Dec 3;57(12):2492–500.

38. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. The Lancet [Internet]. 2016 Aug 20;388(10046):761–75. Available from: https://doi.org/10.1016/S0140-6736(16)30506-2

39. Cruickshank JK, Jackson SH, Bannan LT, Beevers DG, Beevers M, Osbourne VL. Blood pressure in black, white and Asian factory workers in Birmingham. Postgrad Med J. 1983 Oct;59(696):622–6.

40. McKeigue PM, Marmot MG, Syndercombe Court YD, Cottier DE, Rahman S, Riemersma RA. Diabetes, hyperinsulinaemia, and coronary risk factors in Bangladeshis in east London. Br Heart J. 1988 Nov;60(5):390–6.

41. Whitty CJM, Brunner EJ, Shipley MJ, Hemingway H, Marmot MG. Differences in biological risk factors for cardiovascular disease between three ethnic groups in the Whitehall II study. Atherosclerosis. 1999 Feb 1;142(2):279–86.

42. Knight T, Smith Z, Lockton JA, Sahota P, Bedford A, Toop M, et al. Ethnic differences in risk markers for heart disease in Bradford and implications for preventive strategies. J Epidemiol Community Health (1978). 1993 Apr 1;47(2):89–95.

43. Cappuccio F, Cook DG, Atkinson RW, Wicks PD. The Wandsworth Heart and Stroke Study. A population-based survey of cardiovascular risk factors in

different ethnic groups. Methods and baseline findings. Nutrition, Metabolism & Cardiovascular Diseases. 1998;8:371–85.

44. Agyemang C, Bhopal RS. Is the blood pressure of South Asian adults in the UK higher or lower than that in European white adults? A review of cross-sectional data. J Hum Hypertens [Internet]. 2002 [cited 2022 Feb 15];16(11):739–51. Available from: https://pubmed.ncbi.nlm.nih.gov/12444535/

45. Battu HS, Bhopal R, Agyemang C. Heterogeneity in blood pressure in UK Bangladeshi, Indian and Pakistani, compared to White, populations: divergence of adults and children. Journal of Human Hypertension 2018 32:11 [Internet]. 2018 Sep 4 [cited 2022 Feb 15];32(11):725–44. Available from: https://www.nature.com/articles/s41371-018-0095-5

46. Potluri R, Natalwala A. Increasing prevalence of haemorrhagic stroke among South Asian patients in the United Kingdom from 1997 to 2005. Journal of Clinical Neuroscience. 2009 Apr 1;16(4):605.

47. Eastwood S V, Tillin T, Chaturvedi N, Hughes AD. Ethnic Differences in Associations Between Blood Pressure and Stroke in South Asian and European Men. Hypertension [Internet]. 2015 Sep [cited 2019 Feb 13];66(3):481–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26169047

48. Gunarathne A, Patel J V, Gammon B, Hughes EA, Lip GY. Impact of mean arterial blood pressure on higher arterial stiffness indices in South Asians compared to white Europeans. J Hypertens. 2008 Jul;26(7):1420–6.

49. Park CM, Tillin T, March K, Jones S, Whincup PH, Mayet J, et al. Adverse effect of diabetes and hyperglycaemia on arterial stiffness in Europeans, South Asians, and African Caribbeans in the SABRE study. J Hypertens [Internet].

2016 Feb 1 [cited 2020 Oct 13];34(2):282–9. Available from: /pmc/articles/PMC4841389/?report=abstract

50. Dhawan S. Birth weights of infants of first generation Asian women in Britain compared with second generation Asian women. BMJ. 1995 Jul 8;311(6997):86.

51. Harding S, Rosato MG, Cruickshank JK. Lack of change in birthweights of infants by generational status among Indian, Pakistani, Bangladeshi, Black Caribbean, and Black African mothers in a British cohort study. Int J Epidemiol. 2004 Dec;33(6):1279–85.

52. Forouhi NG. Ethnicity and the Metabolic Syndrome. In: Byrne CD, Wild SH, editors. The Metabolic Syndrome. Chichester, UK: John Wiley & Sons, Ltd; 2006. p. 43–84.

53. Nightingale CM, Rudnicka AR, Owen CG, Cook DG, Whincup PH. Patterns of adiposity and obesity among South Asian and white European children: Child Heart and Health Study in England. J Epidemiol Community Health (1978). 2009 Oct 1;63(Suppl 2):60–60.

54. Lakshmi S, Metcalf B, Joglekar C, Yajnik CS, Fall CH, Wilkin TJ. Differences in body composition and metabolic status between white UK and Asian Indian children (EarlyBird 24 and the Pune Maternal Nutrition Study). Pediatr Obes. 2012 Oct 1;7(5):347–54.

55. Wardle J, Wrightson K, Gibson L. Body fat distribution in South Asian women and children. Int J Obes [Internet]. 1996 Mar 1 [cited 2020 Oct 21];20(3):267–71. Available from: https://europepmc.org/article/med/8653149

56. Forouhi N, Sattar N, McKeigue P. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. Int J Obes. 2001 Sep 12;25(9):1327–31.

57. Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti KGMMMM, et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. 1999 Jul 24;319(7204):215–20.

58. France MW, Kwok S, McElduff P, Seneviratne CJ. Ethnic trends in lipid tests in general practice. QJM: An International Journal of Medicine. 2003 Dec 1;96(12):919–23.

59. Donin AS, Nightingale CM, Owen CG, Rudnicka AR, McNamara MC, Prynne CJ, et al. Ethnic differences in blood lipids and dietary intake between UK children of black African, black Caribbean, South Asian, and white European origin: the Child Heart and Health Study in England (CHASE). Am J Clin Nutr. 2010 Oct 1;92(4):776–83.

60. Sniderman AD, Bhopal R, Prabhakaran D, Sarrafzadegan N, Tchernof A. Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. Int J Epidemiol. 2007 Feb 1;36(1):220–5.

61. Gillott RG, Willan K, Kain K, Sivananthan UM, Tayebjee MH. South Asian ethnicity is associated with a lower prevalence of atrial fibrillation despite greater prevalence of established risk factors: a population-based study in Bradford Metropolitan District. Europace [Internet]. 2016 Mar 3 [cited 2019 Mar 25];19(3):euw010. Available from:

https://academic.oup.com/europace/article-lookup/doi/10.1093/europace/euw010

62. O'Neill J, Tayebjee MH. Why are South Asians seemingly protected against the development of atrial fibrillation? A review of current evidence. Trends Cardiovasc Med. 2017 May 1;27(4):249–57.

63. O'Neill J, Jegodzinski L, Tayebjee MH. Incidence of subclinical atrial fibrillation in a South Asian population. Pacing and Clinical Electrophysiology. 2018 Dec;41(12):1600–5.

64. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994 Feb;89(2):724–30.

65. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and Risk Factors for Atrial Fibrillation in Older Adults. Circulation. 1997 Oct 7;96(7):2455–61.

66. Zhuang J, Wang Y, Tang K, Li X, Peng W, Liang C, et al. Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. Europace. 2012 May 1;14(5):638–45.

67. Chahal NS, Lim TK, Jain P, Chambers JC, Kooner JS, Senior R. Ethnicity-related differences in left ventricular function, structure and geometry: a population study of UK Indian Asian and European white subjects. Heart. 2010 Mar 1;96(6):466–71.

68. Lean M, Han T, Bush H, Anderson A, Bradby H, Williams R. Ethnic differences in anthropometric and lifestyle measures related to coronary heart disease risk between South Asian, Italian and general-population British women living in the west of Scotland. Int J Obes. 2001 Dec 11;25(12):1800–5.

69. O'Neill J, Swoboda PP, Plein S, Tayebjee MH. Left atrial size and function in a South Asian population and their potential influence on the risk of atrial fibrillation. Clin Cardiol. 2018 Oct 1;41(10):1379–85.

70. Wakimoto H, Maguire CT, Kovoor P, Hammer PE, Gehrmann J, Triedman JK, et al. Induction of atrial tachycardia and fibrillation in the mouse heart. Cardiovasc Res. 2001 Jun;50(3):463–73.

71. O'Neill J, Tayebjee MH. Electrophysiological properties of the South Asian heart. Heart Asia. 2018 Nov 1;10(2):11079.

72. Tada H, Shiffman D, Smith JG, Sjögren M, Lubitz SA, Ellinor PT, et al. Twelve–Single Nucleotide Polymorphism Genetic Risk Score Identifies Individuals at Increased Risk for Future Atrial Fibrillation and Stroke. Stroke. 2014 Oct;45(10):2856–62.

73. The Social Science Research Council. Acculturation: An Exploratory Formulation. Am Anthropol. 1954 Dec 1;56(6):1000–2.

74. Singh GK, Siahpush M. Ethnic-immigrant differentials in health behaviours, morbidity, and cause-specific mortality in the United States: an analysis of two national data bases. Hum Biol [Internet]. 2002 Feb [cited 2019 Feb 7];74(1):83–109. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11931581

75. Murray KE, Klonoff EA, Garcini LM, Ullman JB, Wall TL, Myers MG. Assessing Acculturation Over Time: A Four-year Prospective Study of Asian American Young Adults. Asian Am J Psychol. 2014 Sep;5(3):252–61.

76. Fischbacher CM, Hunt S, Alexander L. How physically active are South Asians in the United Kingdom? A literature review. J Public Health (Bangkok). 2004;26(3):250–8.

77. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ. 1999 May 29;318(7196):1460–7.

78. Jood K, Redfors P, Rosengren A, Blomstrand C, Jern C. Self-perceived psychological stress and ischemic stroke: A case-control study. BMC Med. 2009 Oct 1;7(1):53.

79. Williams ED, Steptoe A, Chambers JC, Kooner JS. Psychosocial risk factors for coronary heart disease in UK South Asian men and women. J Epidemiol Community Health (1978). 2009 Dec 20;63(12):986–91.

80. National Statistics. Health Survey for England 2017 Cardiovascular diseases. London; 2018. 25 p.

81. Williams R, Bhopal R, Hunt K. Coronary Risk in a British Punjabi Population: Comparative Profile of Non-Biochemical Factors. Int J Epidemiol. 1994 Feb;23(1):28–37.

82. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. Br Med J. 1989;298(6676):789–94.

83. Fischer F, Kraemer A. Meta-analysis of the association between second-hand smoke exposure and ischaemic heart diseases, COPD and stroke Environmental health. BMC Public Health. 2015 Dec 1;15(1).

84. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovi D. Low cigarette consumption and risk of coronary heart disease and stroke: Meta-analysis of 141 cohort studies in 55 study reports. Vol. 360, BMJ (Online). BMJ Publishing Group; 2018. p. 5855.

85. Pan B, Jin X, Jun L, Qiu S, Zheng Q, Pan M. The relationship between smoking and stroke. Medicine. 2019 Mar 1;98(12):e14872.

86. Constance J, Lusher J, Murray E. The use of smokeless tobacco among UK South Asian communities. Vol. 6. 2019. 49–53 p.

87. Rahman M, Fukui T. Bidi smoking and health. Public Health. 2000 Mar 1;114(2):123–7.

88. Roth MA, Aitsi-Selmi A, Wardle H, Mindell J. Under-reporting of tobacco use among Bangladeshi women in England. J Public Health (Bangkok) [Internet]. 2009 Sep 1 [cited 2019 Mar 10];31(3):326–34. Available from: https://academic.oup.com/jpubhealth/article-lookup/doi/10.1093/pubmed/fdp060

89. Leung G, Stanner S. Diets of minority ethnic groups in the UK: influence on chronic disease risk and implications for prevention. Nutr Bull. 2011 Jun 1;36(2):161–98.

90. Smith Z, Knight T, Sahota P, Kernohan E, Baker M. Dietary patterns in Asian and Caucasian men in Bradford: differences and implications for nutrition education. Journal of Human Nutrition and Dietetics. 1993 Aug 1;6(4):323–33.

91. Simmons D, Williams R. Dietary practices among Europeans and different South Asian groups in Coventry. British Journal of Nutrition. 1997 Jul 9;78(1):5–14.

92. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. The Lancet. 2006 Jan 28;367(9507):320–6.

93. National Statistics UK. Health Survey for England 2004: The Health of Minority Ethnic Groups. London; 2005.

94. He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. J Hum Hypertens. 2002 Nov 25;16(11):761–70.

95. Perry IJ, Beevers DG. Salt intake and stroke: a possible direct effect. J Hum Hypertens. 1992 Feb;6(1):23–5.

96. Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. BMJ. 1991 Mar 9;302(6776):560–4.

97. Office for National Statistics. Population of England and Wales [Internet]. Ethnicity facts and figures. 2018 [cited 2019 Feb 13]. Available from: https://www.ethnicity-facts-figures.service.gov.uk/british-population/national-and-regional-populations/population-of-england-and-wales/latest

98. Yadav S, Schanz R, Maheshwari A, Khan MS, Slark J, de Silva R, et al. Bio-Repository of DNA in stroke (BRAINS): A study protocol. BMC Med Genet [Internet]. 2011 Dec 2 [cited 2019 Apr 29];12(1):34. Available from: http://bmcmedgenet.biomedcentral.com/articles/10.1186/1471-2350-12-34

99. O'Brien R, Potter-Collins A. 2011 Census analysis: Ethnicity and religion of the non-UK born population in England and Wales [Internet]. London; 2015 [cited 2018 Nov 22]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/2011censusanalysisethnicityandreligionofthenonukbornpopulationinenglandandwales/2015-06-18#toc

100. Adams HPJ, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35–41.

101. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovasc Dis. 2016 Mar 21;5:204800401663337.

102. UK Ministry of Housing C& LG. English indices of deprivation 2019 [Internet]. 2019 [cited 2023 Mar 6]. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019

103. Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values. J Am Stat Assoc. 1988 Dec;83(404):1198.

104. Lodder P. To Impute or not Impute: That's the Question. Advising on research methods: Selected topics 2013. 2013;

105. Kang H. The prevention and handling of the missing data. Korean J Anesthesiol [Internet]. 2013 May [cited 2023 Feb 19];64(5):402. Available from: /pmc/articles/PMC3668100/

106. Pandis N. Cross-sectional studies. American Journal of Orthodontics and Dentofacial Orthopedics [Internet]. 2014 Jul 1 [cited 2023 Apr 6];146(1):127–9. Available from: http://www.ajodo.org/article/S0889540614004430/fulltext

107. Wild S, McKeigue P. Cross sectional analysis of mortality by country of birth in England and Wales, 1970-92. BMJ. 1997 Mar 8;314(7082):705–10.

108. Nirula SR, Naik M, Gupta SR. NHS vs Modicare: The Indian Healthcare v2.0. Are we ready to build the healthier India that we envisage? J Family Med Prim Care [Internet]. 2019 [cited 2021 Sep 10];8(6):1835. Available from: /pmc/articles/PMC6618227/

109. Yadav S, Hasan N, Marjot T, Khan MS, Prasad K, Bentley P, et al. Detailed Analysis of Gene Polymorphisms Associated with Ischemic Stroke in South Asians. Baron JC, editor. PLoS One. 2013 Mar 7;8(3):e57305.

110. Yadav JK, Nepal G, Shing YK, Banerji RR, Gajurel BP. An opportunity to improve Acute Ischemic Stroke care in the South Asian region through telestroke services. Annals of Medicine and Surgery [Internet]. 2021 Dec 1 [cited 2022 Aug 1];72:103115. Available from: /pmc/articles/PMC8636765/

111. Cotlarciuc I, Khan MS, Maheshwari A, Yadav S, Khan FY, Al-Hail H, et al. Bio-repository of DNA in stroke: a study protocol of three ancestral populations. JRSM Cardiovasc Dis [Internet]. 2012 Jul [cited 2022 Feb 11];1(4):1–8. Available from: /pmc/articles/PMC3738328/

112. Nelder JA, Wedderburn RWM. Generalized Linear Models. J R Stat Soc Ser A [Internet]. 1972 [cited 2021 Nov 3];135(3):370. Available from: https://www.jstor.org/stable/10.2307/2344614?origin=crossref

113. Pandian JD, Sudhan P. Stroke Epidemiology and Stroke Care Services in India. J Stroke. 2013;15(3):128.

114. Dalal PM, Malik S, Bhattacharjee M, Trivedi ND, Vairale J, Bhat P, et al. Population-Based Stroke Survey in Mumbai, India: Incidence and 28-Day Case Fatality. Neuroepidemiology [Internet]. 2008 Nov [cited 2021 Aug 1];31(4):254–61. Available from: https://www.karger.com/Article/FullText/165364

115. Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS, et al. Incidence, Types, Risk Factors, and Outcome of Stroke in a Developing Country. Stroke [Internet]. 2009 Apr 1 [cited 2021 Aug 1];40(4):1212–8. Available from: https://www.ahajournals.org/doi/abs/10.1161/STROKEAHA.108.531293

116. Nagaraja D, Gururaj G, Girish N, Panda S, Roy AK, Sarma GRK, et al. Feasibility study of stroke surveillance: Data from Bangalore, India. Indian J Med Res. 2009;130(4):396–403.

117. Wasay M, Khatri IA, Kaul S. Stroke in South Asian countries [Internet]. Vol. 10, Nature Reviews Neurology. Nature Publishing Group; 2014 [cited 2020 Oct 7]. p. 135–43. Available from: https://pubmed.ncbi.nlm.nih.gov/24514866/

118. Gunarathne A, Patel J v, Potluri R, Gill PS, Hughes EA, Lip GYH. Secular trends in the cardiovascular risk profile and mortality of stroke admissions in an inner city, multiethnic population in the United Kingdom (1997–2005). J Hum

Hypertens [Internet]. 2008 Jan 2 [cited 2018 Dec 27];22(1):18–23. Available from: http://www.nature.com/articles/1002265

119. Gulli G, Rutten-Jacobs LCA, Kalra L, Rudd AG, Wolfe CDA, Markus HS. Differences in the distribution of stroke subtypes in a UK black stroke population - final results from the South London Ethnicity and Stroke Study. BMC Med [Internet]. 2016 May 20 [cited 2023 Apr 3];14(1). Available from: https://pubmed.ncbi.nlm.nih.gov/27197724/

120. Fluck D, Fry CH, Gulli G, Affley B, Robin J, Kakar P, et al. Adverse stroke outcomes amongst UK ethnic minorities: a multi-centre registry-based cohort study of acute stroke. Neurological Sciences [Internet]. 2023 [cited 2023 Apr 3];1:1. Available from: /pmc/articles/PMC9891657/

121. Nazroo JY. The structuring of ethnic inequalities in health: economic position, racial discrimination, and racism. Am J Public Health [Internet]. 2003 Feb [cited 2019 Feb 6];93(2):277–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12554585

122. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. The Lancet. 1991 Feb 16;337(8738):382–6.

123. Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti KGMMMM, et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. BMJ. 1999 Jul 24;319(7204):215–20.

124. Khattar RS, Swales JD, Senior R, Lahiri A. Racial variation in cardiovascular morbidity and mortality in essential hypertension. Heart. 2000 Mar 1;83(3):267–71.

125. Venugopalan VY, Bhatia R, Pandian J, Khurana D, Kaul S, Sylaja PN, et al. Regional differences in ischemic stroke in India (north vs. south): https://doi.org/101177/1747493019828538 [Internet]. 2019 Jan 31 [cited 2021 Oct 14];14(7):706–14. Available from: https://journals.sagepub.com/doi/full/10.1177/1747493019828538

126. PN S, JD P, S K, MVP S, D K, LH S, et al. Ischemic Stroke Profile, Risk Factors, and Outcomes in India: The Indo-US Collaborative Stroke Project. Stroke [Internet]. 2018 [cited 2021 Sep 14];49(1):219–22. Available from: https://pubmed.ncbi.nlm.nih.gov/29167386/

127. Pathak A, Kumar P, Pandit AK, Chakravarty K, Misra S, Yadav AK, et al. Is Prevalence of Hypertension Increasing in First-Ever Stroke Patients?: A Hospital-Based Cross-Sectional Study. Ann Neurosci [Internet]. 2018 Apr 1 [cited 2021 Sep 14];25(4):219–22. Available from: https://www.karger.com/Article/FullText/487066

128. The National Institute for Health and Care Excellence. Type 2 diabetes in adults: management [Internet]. NICE guideline. 2015 [cited 2020 Oct 23]. Available from: https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations

129. The National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management [Internet]. NICE guideline. 2019 [cited 2020 Oct 23]. Available from:

https://www.nice.org.uk/guidance/ng136/chapter/Recommendations#treating-and-monitoring-hypertension

130. Forouhi NG, Sattar N, McKeigue PM. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. Int J Obes. 2001;25(9):1327–31.

131. Wasim H, Al-Daghri NM, Chetty R, McTernan PG, Barnett AH, Kumar S. Relationship of serum adiponectin and resistin to glucose intolerance and fat topography in South-Asians. Cardiovasc Diabetol [Internet]. 2006 May 2 [cited 2019 Apr 13];5(1):10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16669997

132. Hayes L, White M, Unwin N, Bhopal R, Fischbacher C, Harland J, et al. Patterns of physical activity and relationship with risk markers for cardiovascular disease and diabetes in Indian, Pakistani, Bangladeshi and European adults in a UK population. J Public Health Med. 2002 Sep 1;24(3):170–8.

133. Khunti K, Stone MA, Bankart J, Sinfield PK, Talbot D, Farooqi A, et al. Physical activity and sedentary behaviours of South Asian and white European children in inner city secondary schools in the UK. Fam Pract. 2007 Jun;24(3):237–44.

134. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004 Jan;363(9403):157–63.

135. Hawthorne K. South Asian diabetic patients need more education about their illness. Vol. 314, British Medical Journal. BMJ Publishing Group; 1997. p. 1486.

136. Patel V, Morrissey J, Goenka N, James D, Shaikh S. Diabetes care in the Hindu patient: cultural and clinical aspects. Br J Diabetes Vasc Dis. 2001 Nov 20;1(2):132–5.

137. Leening MJG, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. BMJ [Internet]. 2014 Nov 17 [cited 2022 Aug 1];349. Available from: https://www.bmj.com/content/349/bmj.g5992

138. Department of Health. A practical guide to ethnic monitoring in the NHS and social care. London; 2005 Jul.

139. Regenstein M, Sickler D. Race, Ethnicity, and Language of Patients: Hospital Practices Regarding Collection of Information to Address Disparities in Health Care. Health Policy and Management Faculty Publications [Internet]. 2006 Jan 1 [cited 2020 Dec 3]; Available from: https://hsrc.himmelfarb.gwu.edu/sphhs_policy_facpubs/206

140. Pandian JD, Sudhan P. Stroke Epidemiology and Stroke Care Services in India. J Stroke [Internet]. 2013 [cited 2022 Mar 23];15(3):128. Available from: /pmc/articles/PMC3859004/

141. Hardy SE, Allore H, Studenski SA. Missing Data: A Special Challenge in Aging Research. J Am Geriatr Soc [Internet]. 2009 Apr [cited 2023 Apr 14];57(4):722. Available from: /pmc/articles/PMC2695652/

142. Syed NA, Khealani BA, Ali S, Hasan A, Akhtar N, Brohi H, et al. Ischemic stroke subtypes in Pakistan: the Aga Khan University Stroke Data Bank. J Pak Med Assoc. 2003 Dec;53(12):584–8.

143. Lipska K, Sylaja PN, Sarma PS, Thankappan KR, Kutty VR, Vasan RS, et al. Risk factors for acute ischaemic stroke in young adults in South India. J Neurol Neurosurg Psychiatry [Internet]. 2007 Sep [cited 2022 Apr 5];78(9):959. Available from: /pmc/articles/PMC2117871/

144. Dash D, Bhashin A, Pandit A kumar, Tripathi M, Bhatia R, Prasad K, et al. Risk Factors and Etiologies of Ischemic Strokes in Young Patients: A Tertiary Hospital Study in North India. J Stroke [Internet]. 2014 [cited 2022 Apr 4];16(3):173. Available from: /pmc/articles/PMC4200587/

145. Deleu D, Hamad AA, Kamram S, El Siddig A, Al Hail H, Hamdy SMK. Ethnic Variations in Risk Factor Profile, Pattern and Recurrence of Non-Cardioembolic Ischemic Stroke. Arch Med Res. 2006 Jul 1;37(5):655–62.

146. Kim BJ, Kim JS. Ischemic Stroke Subtype Classification: An Asian Viewpoint. J Stroke [Internet]. 2014 [cited 2022 Apr 5];16(1):8. Available from: /pmc/articles/PMC3961817/

147. Kaul S, Sunitha P, Suvarna A, Meena AK, Uma M, Reddy JM. Subtypes of ischemic stroke in a metropolitan city of South India (one year data from a hospital based stroke registry). Neurol India. 2002 Dec 31;50(1):8–14.

148. Wafa HA, Wolfe CDA, Rudd A, Wang Y. Long-term trends in incidence and risk factors for ischaemic stroke subtypes: Prospective population study of the South London Stroke Register. Willey JZ, editor. PLoS Med [Internet]. 2018

Oct 5 [cited 2020 Jun 14];15(10):e1002669. Available from: https://dx.plos.org/10.1371/journal.pmed.1002669

149. Gillott RG, Willan K, Kain K, Sivananthan UM, Tayebjee MH. South Asian ethnicity is associated with a lower prevalence of atrial fibrillation despite greater prevalence of established risk factors: A population-based study in Bradford Metropolitan District. Europace. 2017 Mar 1;19(3):356–63.

150. O'Neill J, Swoboda PP, Plein S, Tayebjee MH. Left atrial size and function in a South Asian population and their potential influence on the risk of atrial fibrillation. Clin Cardiol. 2018 Oct 1;41(10):1379–85.

151. Patel AR, Patel AR, Desai S. The Underlying Stroke Etiology: A Comparison of Two Classifications in a Rural Setup. Cureus. 2019 Jul 17;

152. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation. 2004 Jan 6;109(1):42–6.

153. Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS. Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. Stroke. 2005 Jul;36(7):1372–6.

154. Najarian RM, Sullivan LM, Kannel WB, Wilson PWF, D'Agostino RB, Wolf PA. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke the framingham offspring study. Arch Intern Med. 2006 Jan 9;166(1):106–11.

155. Avan A, Digaleh H, Di Napoli M, Stranges S, Behrouz R, Shojaeianbabaei G, et al. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: An ecological analysis from the Global Burden of Disease Study 2017. BMC Med. 2019 Oct 24;17(1).

156. World Health Organization. Global Health Estimates 2016: Disease burden and mortality estimates. Geneva: World Health Organization; 2018.

157. Pandit K, Goswami S, Ghosh S, Mukhopadhyay P, Chowdhury S. Metabolic syndrome in South Asians. Indian J Endocrinol Metab [Internet]. 2012 [cited 2022 Feb 13];16(1):44. Available from: /pmc/articles/PMC3263197/

158. Pitsavos C, Panagiotakos D, Weinem M, Stefanadis C. Diet, Exercise and the Metabolic Syndrome. The Review of Diabetic Studies. 2006;3(3):118–118.

159. Sun K, Liu J, Ning G. Active Smoking and Risk of Metabolic Syndrome: A Meta-Analysis of Prospective Studies. PLoS One. 2012 Oct 17;7(10).

160. Tillin T, Forouhi N, Johnston DG, McKeigue PM, Chaturvedi N, Godsland IF. Metabolic syndrome and coronary heart disease in South Asians, African-Caribbeans and white Europeans: a UK population-based cross-sectional study. Diabetologia. 2005 Apr 10;48(4):649–56.

161. Krishnaveni G v, Hill JC, Veena SR, Leary SD, Saperia J, Chachyamma KJ, et al. Truncal adiposity is present at birth and in early childhood in South Indian children. Indian Pediatr. 2005 Jun;42(6):527–38.

162. Lean MEJ, Han TS, Bush H, Anderson AS, Bradby H, Williams R. Ethnic differences in anthropometric and lifestyle measures related to coronary heart

disease risk between South Asian, Italian and general-population British women living in the west of Scotland. Int J Obes. 2001 Dec 11;25(12):1800–5.

163. Ramachandran A, Snehalatha C, Dharmaraj D, Viswanathan M. Prevalence of glucose intolerance in Asian Indians: Urban-rural difference and significance of upper body adiposity. Diabetes Care. 1992;15(10):1348–55.

164. Primatesta P, Bost L, Poulter NR. Blood pressure levels and hypertension status among ethnic groups in England. J Hum Hypertens. 2000 Feb 21;14(2):143–8.

165. Hanif W, Susarla R. Diabetes and cardiovascular risk in UK South Asians - an overview. British Journal of Cardiology. 2018 Sep;25(2):8–13.

166. Kuk JL, Ardern CI. Age and Sex Differences in the Clustering of Metabolic Syndrome Factors: Association with mortality risk. Diabetes Care [Internet]. 2010 Nov [cited 2023 Feb 9];33(11):2457. Available from: /pmc/articles/PMC2963512/

167. Rundek T, Sacco RL. Risk Factor Management to Prevent First Stroke [Internet]. Vol. 26, Neurologic Clinics. NIH Public Access; 2008 [cited 2020 Sep 16]. p. 1007–45. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2666965/

168. Ipsos MORI. South Asian Community “Unconcerned” By Salt’s High Stroke Risk [Internet]. 2006 [cited 2020 Feb 2]. Available from: https://www.ipsos.com/ipsos-mori/en-uk/south-asian-community-unconcerned-salts-high-stroke-risk

169. Prinjha S, Ricci-Cabello I, Newhouse N, Farmer A. British South Asian Patients’ Perspectives on the Relevance and Acceptability of Mobile Health

Text Messaging to Support Medication Adherence for Type 2 Diabetes: Qualitative Study. JMIR Mhealth Uhealth. 2020;8(4):e15789.

170. NICE. Overview | Obesity prevention | Guidance | NICE. London; 2006.

171. Vikram NK, Pandey RM, Misra A, Sharma R, Devi JR, Khanna N. Non-obese (body mass index < 25 kg/m2) Asian Indians with normal waist circumference have high cardiovascular risk. Nutrition. 2003 Jun 1;19(6):503–9.

172. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The framingham study. Neurology. 1978 Oct 1;28(10):973–7.

173. Adderley NJ, Ryan R, Nirantharakumar K, Marshall T. Prevalence and treatment of atrial fibrillation in UK general practice from 2000 to 2016. Heart. 2019 Jan 1;105(1):27–33.

174. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010 Oct 1;31(19):2369–429.

175. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Vol. 146, Annals of Internal Medicine. American College of Physicians; 2007. p. 857–67.

176. NICE. Management of AF [Internet]. 2020 [cited 2020 Sep 9]. Available from: https://cks.nice.org.uk/topics/atrial-fibrillation/management/management-of-af/

177. Morseth B, Geelhoed B, Linneberg A, Johansson L, Kuulasmaa K, Salomaa V, et al. Age-specific atrial fibrillation incidence, attributable risk factors and risk

of stroke and mortality: results from the MORGAM Consortium. Open Heart [Internet]. 2021 Jul 1 [cited 2023 Feb 24];8(2):e001624. Available from: https://openheart.bmj.com/content/8/2/e001624

178. Han TS, Fry CH, Fluck D, Affley B, Gulli G, Barrett C, et al. Anticoagulation therapy in patients with stroke and atrial fibrillation: A registry-based study of acute stroke care in Surrey, UK. BMJ Open. 2018 Jul 1;8(7):22558.

179. Lane DA, Ponsford J, Shelley A, Sirpal A, Lip GYH. Patient knowledge and perceptions of atrial fibrillation and anticoagulant therapy: Effects of an educational intervention programme. The West Birmingham Atrial Fibrillation Project. Int J Cardiol. 2006 Jun 28;110(3):354–8.

180. Li YG, Lee SR, Choi EK, Lip GYH. Stroke Prevention in Atrial Fibrillation: Focus on Asian Patients. Korean Circ J [Internet]. 2018 Aug 1 [cited 2022 Oct 28];48(8):665. Available from: /pmc/articles/PMC6072666/

181. Kim SM, Jeon ET, Jung JM, Lee JS. Real-world oral anticoagulants for Asian patients with non-valvular atrial fibrillation: A PRISMA-compliant article. Medicine [Internet]. 2021 Aug 8 [cited 2022 Oct 28];100(32):e26883. Available from: /pmc/articles/PMC8360482/

182. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med [Internet]. 2017 Oct 5 [cited 2022 Oct 28];377(14):1319–30. Available from: https://pubmed.ncbi.nlm.nih.gov/28844192/

183. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J

Med [Internet]. 2020 May 21 [cited 2022 Oct 28];382(21):1994–2004. Available from: https://pubmed.ncbi.nlm.nih.gov/32222135/

184. Zhu WG, Xiong QM, Hong K. Meta-analysis of CHADS2 versus CHA2DS2-VASc for predicting stroke and thromboembolism in atrial fibrillation patients independent of anticoagulation. Vol. 42, Texas Heart Institute Journal. Texas Heart Institute; 2015. p. 6–15.

185. National Institute for Health and Care Excellence (UK). Atrial fibrillation: management [Internet]. Guidance. NICE; 2014 [cited 2020 Oct 18]. Available from: https://www.nice.org.uk/guidance/cg180

186. Zulkifly H, Cheli P, Lutchman I, Bai Y, Lip GYH, Lane DA. Anticoagulation control in different ethnic groups receiving vitamin K antagonist therapy for stroke prevention in atrial fibrillation. Thromb Res. 2020 Aug 1;192:12–20.

187. NICE. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. NICE; 2019.

10 Appendix

10.1– Ethical Approval confirmation.

Riverside Research Ethics Committee
Room 3E03A
3rd Floor
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Tel: 020 8846 7282
Fax: 020 8846 7283
Email: katherine.bolton@chelwest.nhs.uk

02 August 2004

Dr P Sharma
Department of Neurology
Hammersmith Hospital Acute Stroke Unit
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Dear Dr Sharma

Full title of study: The British Repository of DNA in Stroke (BRAINS)
REC reference number: 04/Q0401/40
Protocol number: n/a

Thank you for your letter of 12 July 2004, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman and Mr P Thomas (lay member).

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Site: Charing Cross Hospital
Principal Investigator: Dr P Sharma

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Correspondence from Dr Sharma (12/07/04)

Patient Consent Form (Version 2, 12/07/04)
Unaffected Sibling Consent Form (Version 2, 12/07/04)
Spouse Consent Form (Version 2, 12/07/04)
Relative Consent Form (Version 2, 12/07/04)
Parent Consent Form (Version 2, 12/07/04)
GP Information Sheet (Version 2, 12/07/04)
Follow-up Letter (Version 2, 12/07/04)
Application Form (Version 1, 12/05/04)

Management approval

The study may not commence until final management approval has been confirmed by the organisation hosting the research.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Notification of other bodies

We shall notify the host organisation that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

REC reference number: 04/Q0401/40	**Please quote this number on all correspondence**

Yours sincerely

Dr C Mackworth-Young
Chairman

Enclosures Standard approval conditions

10.2- Percentage of the UK South Asian population per region.

Location	Percentage of South Asians in the region (%)
London	12.1
Northeast England	8.9
West Midlands	8.9
Yorkshire and The Humber	6.0
Northwest England	4.9
Southeast England	3.2
East England	3.2
East Midlands	2.9
Wales	1.3
Southwest England	1.0

Data derived from England and Wales Census 2011 (14).

10.3– Example patient consent form.

ICR2UL

Imperial College Healthcare NHS
NHS Trust

PATIENT CONSENT FORM

Study title: To establish DNA repository of all haemorrhagic and ischaemic stroke patients of any age.

Acronym: Brains- British Repository of DNA in Stroke.

REC Ref: 04/Q0401/40

Please review the study information sheet carefully. You are free to withdraw from the study at any point without giving a reason. Your present or future care will not be affected should you decide not to participate or to withdraw from the study at any point.

	Initial boxes to agree
1. I have read and understood the **Participant Information Sheet; version 3 dated 21st January 2016** for the above study. I have had the opportunity to consider the information, ask questions about the project and have had these answered satisfactorily.	
2. I understand why the research is being done and any foreseeable risks involved.	
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
4. I understand that relevant sections of my medical notes and data collected during the study may be looked at confidentially by members of the medical research team or Imperial College London as sponsor or regulatory authorities who would not normally be involved with my clinical care. I give permission for these individuals to have access to my records.	
5. I agree to my GP being informed of my participation in this study.	
6. I agree to participate in the above study.	
7. I agree that the DNA and blood samples that I have given can be looked after and stored for use in current and future projects, as described in the information sheet. These samples can be used if I lose the capacity to understand or communicate about the project.	
8. I am happy to be contacted by telephone or letter by the study team to provide more information about this study, receive an update on study progress or about future research projects.	

Thank you for your participation in this study.

Name of Participant (PRINT)	Date	Signature (Participant)
	_ _ / _ _ / _ _ _ _	

This form was completed by the patient; I can confirm that the patient fully agrees to the study. YES | NO

Name of Researcher (PRINT)	Date	Signature
	_ _ / _ _ / _ _ _ _	

Assigned study reference *(completed by local study team):*	_ _ _ _ _ _

10.4 – Example relative consent form.

ICR2UL

Imperial College Healthcare NHS
NHS Trust

RELATIVE CONSENT FORM

Study title: To establish DNA repository of all haemorrhagic and ischaemic stroke patients of any age.

Acronym: Brains- British Repository of DNA in Stroke.

REC Ref: 04/Q0401/40

Please review the study information sheet carefully. You are free to withdraw from the study at any point without giving a reason. Your present or future care will not be affected should you decide not to participate or to withdraw from the study at any point.

	Initial boxes to agree
1. I hereby consent on behalf of _____ [Patient name] _____to take part in the above study, the nature and purpose of which have been explained. Any questions patient wished to ask have been answered to his/her satisfaction. I have also read and understood the **Participant Information Sheet; version 3 dated 21st January 2016** for the above study.	☐
2. I understand why the research is being done and any foreseeable risks involved.	☐
3. I understands that his/ her participation is voluntary and that he/ she is free to withdraw at any time without necessarily giving a reason, and that this will in no way affect the care s/he receives as a patient.	☐
4. I understand that relevant sections of his/ her medical notes and data collected during the study may be looked at confidentially by members of the medical research team or Imperial College London as sponsor or regulatory authorities who would not normally be involved with his/ her clinical care. I give permission for these individuals to have access to his/ her records.	☐
5. I agree to inform his/ her GP of his/ her participation in this study.	☐
6. I agree that the DNA and blood samples that he/ she has given can be looked after and stored for use in current and future projects, as described in the information sheet. These samples can be used if he/ she lose the capacity to understand or communicate about the project.	☐
7. I am happy to be contacted by telephone or letter by the study team to provide more information about this study, receive an update on study progress or about future research projects.	☐

Thank you for your participation in this study.

Name of Relative (PRINT)	Date	Signature (Relative)
_____	_ _ / _ _ / _ _ _ _	_____

If this form was completed by a proxy (or scribe), representing the patients' verbal wishes, I can confirm that the person fully agrees to the study. YES | NO

Name of Researcher (PRINT)	Date	Signature
_____	_ _ / _ _ / _ _ _ _	_____

Assigned study reference *(completed by local study team)*:	_ _ _ _ _ _

1 copy for participant; original for researcher; 1 copy to be kept with hospital notes

10.5 – Example BRAINS questionnaire for the UK data collection.

ICCRU

Imperial College Healthcare NHS Trust

BRAINS- British Repository of DNA in Stroke

Patient's ID number							

Details of Recruitment

Trial SITE: **NHS #**_____ **Hospital #**_____		**Date recruited** __ __/__ __/__ __ __ __ (d d m m y y y y)
Name of Patient:		**DOB:** __ __/__ __/__ __ __ __ (d d m m y y y y)
Address: (patient's label)		
Contact details for follow-up call:	Landline Cell phone Friend/ relative	__ __
Place of birth (town/ country):		/
Blood sample	Blood taken Yes ☐/ No ☐ When: __ __/__ __/__ __ __ __ (d d m m y y y y)	**Blood sample number=patient identification number (local centre)** __ __ __ __ __ __
Date of Stroke /event	:_____/_____/_____ (d d / m m / y y y y)	
Diagnosis: (one of those must apply)	Ischaemic Stroke Yes ☐/ No ☐ TACI☐, PACI☐, LACI☐, POCI☐ Haemorrhagic Stroke Yes ☐/ No ☐ Venous Sinus Thrombosis Yes ☐/ No ☐ **if yes, see additional questions (q6-q10)*** TIA Yes ☐/ No ☐ AVM Yes ☐/ No ☐ Aneurysm Yes ☐/ No ☐ Subarachnoid Yes ☐/ No ☐	

QNO	Question	Response
1.	Was stroke associated with	1. ☐ Dissection 2. ☐ PFO 3. ☐ MI 4. ☐ None
2.	Gender	0. ☐ female 1. ☐ male
3.	Ethnicity	
4.	Native Language	
5.	Religion	

After completing the sections above please detached this first page from the form and fax it on the day of enrolment to the BRAINS coordinator to 020 8846 7284 to confirm the recruitment

Interviewer name:_____ **date of form filled**_____

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BRAINS- British Repository of DNA in Stroke

Patient's ID number							

QNo	Question					Response		
*** Venous Sinus Thrombosis – additional questions**								
6.	Past history of malignancy?					1. ☐ Yes go to q 7 2. ☐ No go to q 8		
7.	Please specify the malignancy							
8.	Intake of oral contraceptive at the time of stroke?					1. ☐ Yes 2. ☐ No 3. ☐ Don't know		
9.	Is patient pregnant?					1. ☐ Yes 2. ☐ No		
10.	Or did give birth recently (last 3 months)?					1. ☐ Yes 2. ☐ No ☐ Don't know		
Patient's medical history								
11.	Does patient has any co-morbids? (Tick, if new diagnosis at this admission)	1.Hypertension	Yes ☐	No ☐	Don't Know ☐	1. New ☐		
		2.Diabetes Mellitus	Yes ☐	No ☐	Don't know ☐	2. New ☐		
		3.IHD/Angina	Yes ☐	No ☐	Don't know ☐	3. New ☐		
		4.Hypercholesterolemia	Yes ☐	No ☐	Don't know ☐	4. New ☐		
		5.Atrial Fibrillation	Yes ☐	No ☐	Don't know ☐	5. New ☐		
		6.PVD	Yes ☐	No ☐	Don't know ☐	6. New ☐		
		7.MI	Yes ☐	No ☐	Don't know ☐	7. New ☐		
		8.Migraine with aura	Yes ☐	No ☐	Don't know ☐	8. New ☐		
		9.Migraine without aura	Yes ☐	No ☐	Don't know ☐	9. New ☐		
12.	Does patient has previous history of stroke?					1. ☐ Isc. stroke 2. ☐ Haem. Stroke 3. ☐ TIA 4. ☐ None go to q 14		
13.	In which year did you had this stroke?					_____ year (YYYY)		
14.	Cigarettes history					0. ☐ Never smoke go to q 16 1. ☐ Ex-smoker 2. ☐ Current smoker		
15.	On average how many cig/day?					Cig _____ /day		
16.	Alcohol drinking history (unit/week)					Drinks _____ unit(s)/Wk		
17.	Patient's family history					1. ☐ Stroke Don't know ☐ 2. ☐ IHD/Angina Don't know ☐ 3. ☐ DM Don't know ☐ 4. ☐ MI Don't know ☐ 5. ☐ PVD Don't know ☐ 6. ☐ Hypertension Don't know ☐ 7. ☐ None of above		

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BRAINS- British Repository of DNA in Stroke

Patient's ID number							

QNo	Question		Response
18.	medicine on admission	1. Aspirin ☐ 2. Clopidogrel ☐ 3. Aspirin + Clopidogrel ☐ 4. Dipyridamole ☐ 5. Aspirin + Dipyridamole ☐ 6. Warfarin ☐ 7. Statin ☐ 8. Antihypertensive ☐ 9. None of above ☐	a) Dose _____mg/day b) Dose _____mg/day c) Dose _____+_____mg/day d) Dose _____mg/day e) Dose _____+_____mg/day f) INR _____ g) Dose _____mg/day Please specify the name of statin_____
19.	Blood pressure on admission		_____/_____ mmhg
20.	Temperature on admission		_____ °C
21.	Hip: _____ cm		
22.	Waist (While patient is in laying/sitting position) :_____ cm		
23.	Height : _____ cm		
24.	Weight: _____ kg		
25.	Carotid endartectomy		0. ☐ Not done 1. ☐ Done
26.	Thrombolysed		0. ☐ Not done 1. ☐ Done
27.	Medicine given at the time of discharge	1. Aspirin ☐ 2. Clopidogrel ☐ 3. Aspirin + Clopidogrel ☐ 4. Dipyridamole ☐ 5. Aspirin + Dipyridamole ☐ 6. Statin ☐ 7. Antihypertensive ☐ 8. Warfarin ☐ 9. None ..... ☐	1. Dose _____mg/day 2. Dose _____mg/day 3. Dose ____+____mg/day 4. Dose _____mg/day 5. Dose ____+____mg/day 6. Dose _____mg/day Please specify the name of statin_____
28.	NIHSS on admission :_____ on discharge :_____ (please attach copy of NIHSS)		
29.	Barthel on admission :_____ on discharge :_____ (please attach copy of Barthel)		
30.	Discharge		1. ☐ Home 2. ☐ Nursing Home 3. ☐ Rehabilitation 4. ☐ Local DGH 0. ☐ RIP
	Question		**Response**

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BRAINS- British Repository of DNA in Stroke

Patient's ID number							

QNo		
ECG and ECHO section		
31.	ECG done	0. ☐ No go to q 33 1. ☐ Yes
32.	Findings of ECG	0. ☐ Normal 1. ☐ LVH 2. ☐ AF 3. ☐ Ventricular ectopics 4. ☐ Atrial Ectopics 5. ☐ Don't know 6. ☐ None of above
33.	ECHO done	1. ☐ No go to q 35 2. ☐ Yes
34.	Findings of Echo	0. ☐ Normal 1. ☐ LVH 2. ☐ PFO 3. ☐ Thrombus 4. ☐ None of above 5. ☐ Don't know
Brain Imaging		
35.	Brain Imaging	1. ☐ CT 2. ☐ MRI 3. ☐ Not done
35a	Lesion location	1. ☐ Anterior a. Right ☐ b. Left ☐ c. Bilateral ☐ 2. ☐ Posterior 3. ☐ Anterioposterior
36.	Intracranial vessel imaging	1. ☐ CTA 2. ☐ Angiogram 3. ☐ MRA 4. ☐ None go to q 39
37.	Intracranial stenosis	0. ☐ No 1. ☐ Yes
38.	Intracranial stenosis (%)	_____% (1) LVD (large artery atherosclerosis) ☐ (2) SVD (small vessel occlusion) ☐ (3) Cardioembolism ☐ (4) Combined (2 or more causes identified) ☐ (5) Stroke of other determined etiology ☐ (6) Negative evaluation (no cause found) ☐
39.	**TO A S T CLASSIFICATION**	

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BRAINS- British Repository of DNA in Stroke

Patient's ID number							

QNo	Question	Response
Extra cranial Vessel Imaging		
40.	Extra cranial Vessel Imaging	1. ☐ Doppler 2. ☐ MRA 3. ☐ CTA 4. ☐ Not done
41.	Doppler findings (please attach copy of Doppler scan)	R CCA Velocity_____ (cm/s) R ICA Velocity _____(cm/s) L CCA Velocity _____(cm/s) L ICA Velocity _____(cm/s) R vertebral stenosis_____(cm/s or txt) L vertebral stenosis_____(cm/s or txt) R CCA stenosis_____% R ICA stenosis_____% L CCA stenosis_____% L ICA stenosis_____% R CCA plaque_____ (Plaque/IT/Normal) R ICA plaque_____(Plaque/IT/Normal)L CCA plaque_____ (Plaque/IT/Normal) L ICA plaque_____(Plaque/IT/Normal) Basilar stenosis_____
Blood section		
42.	Glucose: _____ Y ☐/Result_____	Not done ☐
43.	Total Cholesterol: Y ☐/Result_____	Not done ☐
44.	HDL-Cholesterol: Y ☐/Result_____	Not done ☐
45.	LDL-Cholesterol: Y ☐/Result_____	Not done ☐
46.	Triglyceride: Y ☐/Result_____	Not done ☐
47.	ESR: _____Y ☐/Result_____	Not done ☐
48.	CRP: _____Y ☐/Result_____	Not done ☐
49.	Troponin: _____Y ☐/Result_____	Not done ☐
50.	Protein C: _____Y ☐/Result_____	Not done ☐
51.	Protein S: _____Y ☐/Result_____	Not done ☐
52.	Fibrinogen: _____Y ☐/Result_____	Not done ☐
53.	Antithrombin 11: Y ☐/Result_____	Not done ☐
54.	Factor V: _____Y ☐/Result_____	Not done ☐
55.	Homocysteine: Y ☐/Result_____	Not done ☐
56.	Prothrombin: Y ☐/Result_____	Not done ☐
57.	Antiphospholipid: Y ☐/Result_____	Not done ☐

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BRAINS- British Repository of DNA in Stroke

Patient's ID number							

PATIENT'S SPOUSE/ PARTNER DETAILS (CONTROL GROUP)

Name of Patient:		**DOB:** __ __/__ __/__ __ __ __ (d d m m y y y y)	
Place of birth (town/ country):		/	
QNO	**Question**		**Response**
1.	Gender		0. ☐ female 1. ☐ male
2.	Ethnicity		
3.	Is this person (control) related to the patient?		1. ☐ Yes 2. ☐ No go to q 5
4.	If yes please specify relationship		1. ☐ First cousin 2. ☐ Second cousin 3. Other Please specify_____
5.	Religion		
6.	Native Language		
7.	BP today		_____/_____**mmHg**
8.	Medical Past history?	1. Hypertension 2. Diabetes Mellitus 3. IHD/Angina 4. Hypercholesterolemia 5. Atrial Fibrillation 6. PVD 7. MI 8. Migraine with aura 9. Migraine without aura 10. Ischaemic stroke 11. Haemorrhagic stroke 12.TIA	Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐
Blood sample	Blood taken Yes ☐/ No ☐ When: __ __/__ __/__ __ __ __ (d d m m y y y y)		**Blood sample number=patient identification number** (local centre) __ __ __ __ __ __

10.6 – Example BRAINS questionnaire for the India data collection.

Genetics of stroke in South Asians (www.brainsgenetics.com)

Data Collection Form (DCF) **Patient's ID number** __ __ __ __ __ __

(1) DETAILS OF RECRUITMENT

Trial SITE:	**Date recruited**
1=Inpatient _____ 2=outpatient _____	__ __/__ __/__ __ __ __ (d d m m y y y y)

(2) PATIENT'S PERSONAL DETAILS

Name of Patient:	**DOB:** __ __/__ __/__ __ __ __ (d d m m y y y y)	
Address: (patient's label)	**Gender:** Male ☐ Female ☐	
Contact details for follow-up call:	Landline …… Cell phone …… Friend/ relative ……	
Place of birth (town/ country):	/	
Ethnicity:	**Native Language:**	
Religion:		
Economic Status	☐ (1) Bed ☐ (2) Electricity ☐ (3) Table ☐ (4) Toilet ☐ (5) Roofed house ☐ (6) Water Filter ☐ (7) Fan ☐ (8) Cooler ☐ (9) Cooking Gas ☐ (10) T.V ☐ (11) Phone/ Mobile ☐ (12) Scooter/ Bike ☐ (13) Sofa set ☐ (14) Curtain in windows ☐ (15). Refrigerator ☐ (16) Mixer Grinder ☐ (17) Dining Table ☐ (18) Toaster ☐ (19) Aqua guard ☐ (20) Microwave oven ☐ (21) Computer ☐ (22). Geyser ☐ (23) R.O Water Purifier System ☐ (24) Car ☐ (25). A.C.	
Blood sample	Blood taken Yes ☐/ No ☐ When: __ __/__ __/__ __ __ __ (d d m m y y y y)	**Blood sample number=patient identification number (local centre)** __ __ __ __ __ __
Date of stroke / event	__ __/__ __/__ __ __ __ (d d m m y y y y)	

Genetics of stroke in South Asians (www.brainsgenetics.com)

Data Collection Form (DCF) **Patient's ID number** __ __ __ __ __ __

(3) PATIENT'S DIAGNOSIS AND MEDICAL HISTORY

Diagnosis: (one of those must apply)	Ischaemic Stroke Yes ☐/ No ☐ TACI☐, PACI☐, LACI☐, POCI☐ Haemorrhagic Stroke* Yes ☐/ No ☐ Venous Sinus Thrombosis Yes ☐/ No ☐ TIA Yes ☐/ No ☐ AVM Yes ☐/ No ☐ Aneurysm Yes ☐/ No ☐ Subarachnoid Yes ☐/ No ☐	
***For Haemorrhagic Stroke only** Site of Bleed	1. Basal Ganglia ☐ 2. Cortical ☐ 3. Cerebella ☐ 4. Brain steam ☐	
Patient's PAST history		**Tick, if new diagnosis at this admission**
Hypertension Yes ☐ No☐ Don't know ☐		New ☐
Diabetes Mellitus Yes ☐ No☐ Don't know ☐		New ☐
IHD/Angina Yes ☐ No☐ Don't know ☐		New ☐
Hypercholesterolemia Yes ☐ No☐ Don't know ☐		New ☐
Atrial Fibrillation Yes ☐ No☐ Don't know ☐		New ☐
PVD Yes ☐ No☐ Don't know ☐		New ☐
MI Yes ☐ No☐ Don't know ☐		New ☐
Migraine with aura Yes ☐ No☐ Don't know ☐		New ☐
Migraine without aura Yes ☐ No☐ Don't know ☐		New ☐
Patient's previous Strokes	Ischaemic Stroke Yes ☐ No☐ Haemorrhagic Stroke Yes ☐ No☐ TIA Yes ☐ No☐ Rheumatic heart fever Yes ☐ No☐	When_____(year)
Stroke associated with	**Dissection** Yes ☐/ No☐ **PFO** Yes ☐/ No☐ **MI** Yes ☐/ No☐	
Patient's Family History:	Stroke Yes ☐ No ☐ Don't know ☐ IHD/Angina Yes ☐ No ☐ Don't know ☐ Diabetes Mellitus Yes ☐ No ☐ Don't know ☐ MI Yes ☐ No ☐ Don't know ☐ PVD Yes ☐ No ☐ Don't know ☐ Hypertension Yes ☐ No ☐ Don't know ☐ None of above Yes ☐ No ☐ Don't know ☐	
Smoking etc	Cigarettes none ☐ Ex ☐ current ☐ per day_____	

Genetics of stroke in South Asians (www.brainsgenetics.com)

Data Collection Form (DCF) **Patient's ID number** __ __ __ __ __ __

	Tobacco chewing none ☐ Ex ☐ current ☐ per day_____ Hookas none ☐ Ex ☐ current ☐ per day_____ Beedi none ☐ Ex ☐ current ☐ per day_____
Alcohol (see attached for unit details)	Drinks _____unit(s) per week
Anthropometric measurements	Hip: _____cm Waist:_____ cm Height: _____cm Weight:_____ kg **BMI**: _____
Medicine on admission:	Aspirin ☐ Dose _____mg/day Clopidogrel ☐ Dose _____mg/day Aspirin + Clopidogrel ☐ Dose _____+_____mg/day Dipyridamole ☐ Dose _____mg/day Aspirin + Dipyridamole ☐ Dose _____+_____mg/day Warfarin ☐ INR _____ Statin ☐ Name_____Dose_____mg/day Antihypertensive ☐ None of above ☐

PATIENT'S MEDICAL STATUS ON ADMISSION

BLOODS	**Glucose:**	Y ☐/Result_____ Not done ☐
	Total Cholesterol:	Y ☐/Result_____ Not done ☐
	HDL-Cholesterol:	Y ☐/Result_____ Not done ☐
	LDL-Cholesterol:	Y ☐/Result_____ Not done ☐
	Triglyceride:	Y ☐/Result_____ Not done ☐
	ESR:	Y ☐/Result_____ Not done ☐
	CRP:	Y ☐/Result_____ Not done ☐
	Troponin:	Y ☐/Result_____ Not done ☐
	Protein C:	Y ☐/Result_____ Not done ☐
	Protein S:	Y ☐/Result_____ Not done ☐
	Fibrinogen:	Y ☐/Result_____ Not done ☐
	Antithrombin 11:	Y ☐/Result_____ Not done ☐
	Factor V:	Y ☐/Result_____ Not done ☐
	Homocysteine:	Y ☐/Result_____ Not done ☐
	Prothrombin:	Y ☐/Result_____ Not done ☐

Genetics of stroke in South Asians (www.brainsgenetics.com)

Data Collection Form (DCF) **Patient's ID number** __ __ __ __ __ __

	Antiphospholipid: Y ☐/Result_____ Not done ☐
BP on admission _____/_____mmHg	**Temperature on admission** _____° C
Carotid endarterectomy Done ☐/ Not done ☐	**Thrombolysed** Done ☐/ Not done ☐
Intracranial vessel imaging (please attached copy of report)	**CTA** Done ☐/ Not done ☐ **MRA** Done ☐/ Not done ☐ **Angiogram** Done ☐/ Not done ☐
Intracranial stenosis: Yes ☐ _____% No ☐	
Extracranial Vessel Imaging: Dopplers Done ☐/ Not done ☐ MRA Done ☐/ Not done ☐ CTA Done ☐/ Not done ☐ **(please attached copy of report)**	**Brain Imaging:** (please attached report) CT Done ☐/ Not done ☐ MRI Done ☐/ Not done ☐ **Lesion location** ☐ Anterior ☐ Right ☐ Left ☐ Bilateral ☐ Posterior ☐ Anterioposterior
R ICA stenosis _____% **L ICA stenosis** _____% **R CCA stenosis** _____% **L CCA stenosis** _____% **R vertebral stenosis** _____% **L vertebral stenosis** _____% **Basilar stenosis** _____%	**TO A S T CLASSIFICATION** (1) LVD (large artery atherosclerosis) ☐ (2) SVD (small vessel occlusion) ☐ (3) Cardioembolism ☐ (4) Combined (2 or more causes identified) ☐ (5) Stroke of other determined etiology ☐ (6) Negative evaluation (no cause found) ☐
ECG Done☐ Not done ☐ **(please attached copy)**	**ECHO** Done☐ Not done ☐ **(please attached copy)**
Result: Normal ☐ LVH ☐ AF ☐ Ventricular ectopics ☐ Atrial ectopics: ☐ None of above ☐ Don't know ☐	Result: Normal ☐ LVH ☐ PFO ☐ Thrombus ☐ None of above ☐ Don't know ☐

Genetics of stroke in South Asians (www.brainsgenetics.com)

Data Collection Form (DCF) **Patient's ID number** __ __ __ __ __ __

NIHSS:	On admission _____	On discharge _____
Barthel:	On admission _____	On discharge _____
MRS	On admission _____	On discharge _____
Discharge:	Home ☐ Rehabilitation ☐ Local DGH ☐	Nursing Home ☐ RIP ☐
Medicine on discharge	Aspirin ☐ Clopidogrel ☐ Aspirin + Clopidogrel ☐ Dipyridamole ☐ Aspirin + Dipyridamole ☐ Statin ☐ Antihypertensive ☐ Warfarin ☐	Dose _____mg/day Dose _____mg/day Dose _____+_____mg/day Dose _____mg/day Dose _____+_____mg/day Dose_____mg/day_Name_____

Follow up After one year of first event	
Did patient have	1. Stroke /TIA ☐ 2. MI ☐ 3. Died ☐ 4. No event ☐

Genetics of stroke in South Asians (www.brainsgenetics.com)

Data Collection Form (DCF) **Patient's ID number** __ __ __ __ __ __

(4) PATIENT'S SPOUSE/ PARTNER DETAILS (CONTROL GROUP)

Name and address of Spouse/ Partner		**DOB:** __ __/__ __/__ __ __ __ (d d m m y y y y) **Gender:** Male ☐ Female ☐	
Contact details for follow-up call	Landline ..... Cell phone ..... Friend/ relative		
Place of birth (town/ country):	/		
Ethnicity:		**Religion:**	
Native Language:		**BP today** _____/_____mmHg	
Medical Past History:	Hypertension	Yes ☐	No ☐ Don't know ☐
	Diabetes Mellitus	Yes ☐	No ☐ Don't know ☐
	IHD/Angina	Yes ☐	No ☐ Don't know ☐
	Hypercholesteremia	Yes ☐	No ☐ Don't know ☐
	Atrial Fibrillation	Yes ☐	No ☐ Don't know ☐
	PVD	Yes ☐	No ☐ Don't know ☐
	MI	Yes ☐	No ☐ Don't know ☐
	Migraine with aura	Yes ☐	No ☐ Don't know ☐
	Migraine without aura	Yes ☐	No ☐ Don't know ☐
	Ischaemic Stroke	Yes ☐	No ☐ Don't know ☐
	Haemorrhagic Stroke	Yes ☐	No ☐ Don't know ☐
	TIA	Yes ☐	No ☐ Don't know ☐
Economic Status	☐ (1) Bed ☐ (2) Electricity ☐ (3) Table ☐ (4) Toilet ☐ (5) Roofed house ☐ (6) Water Filter ☐ (7) Fan ☐ (8) Cooler ☐ (9) Cooking Gas ☐ (10) T.V ☐ (11) Phone/ Mobile ☐ (12) Scooter/ Bike ☐ (13) Sofa set ☐ (14) Curtain in windows ☐ (15). Refrigerator ☐ (16) Mixer Grinder ☐ (17) Dining Table ☐ (18) Toaster ☐ (19) Aqua guard ☐ (20) Microwave oven ☐ (21) Computer ☐ (22). Geyser ☐ (23) R.O Water Purifier System ☐ (24) Car ☐ (25). A.C.		

Genetics of stroke in South Asians (www.brainsgenetics.com)

Data Collection Form (DCF) **Patient's ID number** __ __ __ __ __ __

Hip_____cm	Height_____cm	
Waist_____cm	Weight_____kg	**BMI**_____
Blood sample	Blood taken Yes ☐/ No ☐ When: __ __/__ __/__ __ __ __ (d d m m y y y y)	**Blood sample number=control identification number (local centre):** __ __ __ __ __ __

10.7- Population characteristics stratified by missing values status.

	***n* (%)**	**Missing**	***n* (%)**	**Complete**	***P*-value***
Central obesity					
Age of onset, mean (SD), years	1323 (25.3)	67.9 (14.8)	3897 (74.7)	64.0 (16.0)	<0.001
Men / Women, n (%)	1323 (25.3)	778 (24.1)/545 (27.4)	3897 (74.7)	2456 (75.9)/1441 (72.6)	0.006
WB / BSA / ISA, n (%)	1323 (25.3)	860 (37.5)/279 (16.9)/184 (14.4)	3897 (74.7)	1431 (62.5)/1371 (83.1)/1095 (85.6)	<0.001
Smoking history					
Age of onset, mean (SD), years	341 (6.5)	69.1 (13.2)	4879 (93.5)	64.7 (15.9)	<0.001
Men / Women, n (%)	341 (6.5)	204 (6.3)/137 (6.9)	4879 (93.5)	3030 (93.7)/ 1849 (93.1)	0.40
WB / BSA / ISA, n (%)	341 (6.5)	229 (10.0)/ 103 (6.2)/ 9 (0.7)	4879 (93.5)	2062 (90.0)/1547 (93.8)/1270 (99.3)	<0.001
Alcohol consumption					
Age of onset, mean (SD), years	747 (14.3)	69.8 (13.6)	4473 (85.7)	64.1 (16.0)	<0.001
Men / Women, n (%)	747 (14.3)	421 (13.0)/ 326 (16.4)	4473 (85.7)	2813 (87.0)/1660 (83.6)	0.001
WB / BSA / ISA, n (%)	747 (14.3)	553 (24.1)/188 (11.4)/6 (0.5)	4473 (85.7)	1738 (75.9)/1462 (88.6)/1273 (99.5)	<0.001
Hypertension					
Age of onset, mean (SD), years	380 (7.3)	68.0 (14.2)	4840 (92.7)	64.7 (15.9)	<0.001
Men / Women, n (%)	380 (7.3)	231 (7.1)/149 (7.5)	4840 (92.7)	3003 (92.9)/1837 (92.5)	0.56
WB / BSA / ISA, n (%)	380 (7.3)	231 (10.1)/116 (7.0)/33 (2.6)	4840 (92.7)	2060 (89.9)/1534 (93.0)/1246 (97.4)	<0.001
Diabetes mellitus					
Age of onset, mean (SD), years	392 (7.5)	68.1 (14.6)	4828 (92.5)	64.7 (15.9)	<0.001
Men / Women, n (%)	392 (7.5)	233 (7.2)/159 (8.0)	4828 (92.5)	3001 (92.8)/1827 (92.0)	0.29
WB / BSA / ISA, n (%)	392 (7.5)	242 (10.6)/112 (6.8)/38 (3.0)	4828 (92.5)	2049 (89.4)/1538 (93.2)/1241 (97.0)	<0.001
Hypercholesterolemia					
Age of onset, mean (SD), years	598 (11.5)	64.8 (15.5)	4622 (88.5)	65.0 (15.8)	0.83
Men / Women, n (%)	598 (11.5)	377 (11.7)/221 (11.1)	4622 (88.5)	2857 (88.3)/1765 (88.9)	0.56

WB / BSA / ISA, n (%)	598 (11.5)	253 (11.0)/166 (10.1)/179 (14.0)	4622 (88.5)	2038 (89.0)/1484 (89.9)/1100 (86.0)	0.003
Ischaemic heart disease					
Age of onset, mean (SD), years	365 (7.0)	69.8 (13.1)	4855 (93.0)	64.6 (15.9)	<0.001
Men / Women, n (%)	365 (7.0)	218 (6.7)/147 (7.4)	4855 (93.0)	3016 (93.3)/1839 (92.6)	0.36
WB / BSA / ISA, n (%)	365 (7.0)	239 (10.4)/123 (7.5)/3 (0.2)	4855 (93.0)	2052 (89.6)/1527 (92.5)/1276 (99.8)	<0.001
Atrial fibrillation					
Age of onset, mean (SD), years	680 (13.0)	63.2 (15.7)	4540 (87.0)	65.2 (15.8)	0.002
Men / Women, n (%)	680 (13.0)	456 (14.1)/224 (11.3)	4540 (87.0)	2778 (85.9)/1762 (88.7)	0.003
WB / BSA / ISA, n (%)	680 (13.0)	258 (11.3)/168 (10.2)/254 (19.9)	4540 (87.0)	2033 (88.7)/1482 (89.8)/1025 (80.1)	<0.001
TOAST stroke subtype					
Age of onset, mean (SD), years	1468 (28.1)	65.0 (14.8)	3752 (71.9)	65.0 (16.2)	0.92
Men / Women, n (%)	1468 (28.1)	899 (27.8)/569 (28.7)	3752 (71.9)	2335 (72.2)/1417 (71.3)	0.51
WB / BSA / ISA, n (%)	1468 (28.1)	792 (34.6)/365 (22.1)/311 (24.3)	3752 (71.9)	1499 (65.4)/1285 (77.9)/968 (75.7)	<0.001
Stroke history					
Age of onset, mean (SD), years	312 (6.0)	69.5 (13.0)	4908 (94.0)	64.7 (15.9)	<0.001
Men / Women, n (%)	312 (6.0)	188 (5.8)/124 (6.2)	4908 (94.0)	3046 (94.2)/1862 (93.8)	0.52
WB / BSA / ISA, n (%)	312 (6.0)	218 (9.5)/91 (5.5)/3 (0.2)	4908 (94.0)	2073 (90.5)/1559 (94.5)/1276 (99.8)	<0.001

n denotes sample size. **P*-value is calculated using either independent *t*-test for age of onset comparisons or a chi-square test for prevalence comparisons. WB, white British; BSA, UK residing South Asians; ISA, Indian South Asians.

10.8 - Comparison of the age of ischaemic stroke event in those with missing and complete data for each included variable, using chapter 4's selection criteria.

	Missing/Complete *n*/*n*	Missing value Years (SD)	Complete Years (SD)	*P*-value*
Central obesity				
WB	552/1184	71.2 (13.4)	71.7 (13.4)	0.48
BSA	152/1024	66.6 (15.0)	63.9 (15.1)	0.040
ISA	155/971	53.3 (14.2)	51.7 (13.3)	0.17
Smoking history				
WB	20/1716	70.8 (14.5)	71.5 (13.4)	0.80
BSA	12/1164	59.2 (16.0)	64.3 (15.1)	0.24
ISA	5/1121	61.0 (6.4)	51.9 (13.4)	0.13
Alcohol consumption				
WB	299/1437	71.4 (13.5)	71.5 (13.4)	0.94
BSA	80/1096	62.8 (16.2)	64.4 (15.0)	0.38
ISA	6/1120	52.3 (11.0)	52.0 (13.4)	0.95
Hypertension				
WB	22/1714	73.2 (14.1)	71.5 (13.4)	0.54
BSA	19/1157	67.3 (12.1)	64.2 (15.1)	0.37
ISA	28/1098	51.4 (15.3)	52.0 (13.3)	0.83
Diabetes mellitus				
WB	29/1707	74.6 (13.8)	71.4 (13.4)	0.21
BSA	19/1157	67.8 (13.6)	64.2 (15.1)	0.30
ISA	30/1096	50.8 (16.6)	52.0 (13.3)	0.63
Hypercholesterolemia				
WB	37/1699	73.6 (13.1)	71.5 (13.4)	0.34
BSA	49/1127	68.7 (11.9)	64.1 (15.2)	0.034
ISA	150/976	51.3 (14.4)	52.1 (13.2)	0.51
Ischaemic heart disease				
WB	26/1710	74.2 (13.5)	71.5 (13.4)	0.31
BSA	25/1151	66.5 (14.4)	64.2 (15.1)	0.46
ISA	0/1126	---	52.0 (13.4)	---
Atrial fibrillation				
WB	36/1700	73.8 (13.8)	71.4 (13.4)	0.29
BSA	54/1122	67.5 (14.7)	64.1 (15.1)	0.11
ISA	212/914	51.7 (13.2)	52.0 (13.4)	0.80

Selection criteria for chapter 4: complete information of age of onset, ethnicity, and sex. **P*-value was determined using an independent *t*-test to compare the age of onset. *n* demotes the sample population. ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

10.9 - Comparison of population characteristics of ISA and BSA with WB.

	ISA vs WB		BSA vs WB	
	Difference	***P*-Value***	**Difference**	***P*-Value***
Average age of onset, mean years	19.5	<0.001	7.2	<0.001
Men (%)	11.8	<0.001	9.1	<0.001
TOAST Stroke Subtype	%		%	
Large artery atherosclerosis	8.0	<0.001	14.3	<0.001
Small vessel occlusion	1.0	0.56	10.1	<0.001
Cardio-embolism	8.0	<0.001	3.6	<0.001
Environmental Factors	%		%	
Central obesity	4.7	0.02	3.9	0.042
Smoking history	9.4	<0.001	17.8	<0.001
Alcohol consumption	4.1	0.036	22.7	<0.001
Comorbidities	%		%	
Hypertension	1.7	0.35	10.6	<0.001
Diabetes mellitus	14.1	<0.001	31.5	<0.001
Hypercholesterolemia	-2.3	0.231	18.5	<0.001
Ischaemic heart disease	5.9	<0.001	10.8	<0.001
Atrial fibrillation	15.8	<0.001	10.2	<0.001

*Independent *t*-test was used to compare the age of onset with all others using Chi-square tests. Central obesity is classified by waist circumference (men: >102cm, women: >88 cm) or BMI (≥30 kg/m^2). ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

10.10 - Age of first-time stroke event between those with missing and complete for each included variable, using chapter 5's selection criteria.

	Missing/Complete	Missing	Complete	*P*-value*
Central obesity	*n*/*n*	Years (SD)	Years (SD)	
WB	409/831	72.2 (13.4)	72.8 (13.5)	0.50
BSA	95/875	67.1 (15.4)	63.6 (15.1)	0.036
ISA	120/730	53.3 (14.9)	52.1 (13.6)	0.38
Smoking history				
WB	11/1229	74.8 (11.3)	72.6 (13.5)	0.58
BSA	3/967	71.0 (6.6)	63.9 (15.2)	0.42
ISA	4/846	60.3 (7.1)	52.2 (13.8)	0.24
Alcohol consumption				
WB	261/979	71.7 (13.5)	72.8 (13.5)	0.21
BSA	51/919	62.3 (16.1)	64.1 (15.1)	0.42
ISA	4/846	58.0 (4.5)	52.2 (13.8)	0.40
Hypertension				
WB	14/1226	77.4 (12.5)	72.5 (13.5)	0.18
BSA	8/962	68.1 (12.8)	63.9 (15.2)	0.44
ISA	23/827	52.8 (14.9)	52.2 (13.7)	0.85
Diabetes mellitus				
WB	16/1224	80.7 (12.1)	72.5 (13.5)	0.015
BSA	7/963	71.7 (11.0)	63.9 (15.2)	0.18
ISA	22/828	51.3 (17.2)	52.3 (13.7)	0.75
Hypercholesterolemia				
WB	22/1218	78.1 (11.9)	72.5 (13.5)	0.051
BSA	26/944	70.5 (10.8)	63.8 (15.2)	0.005
ISA	123/727	51.2 (15.1)	52.4 (13.5)	0.34
Ischaemic heart disease				
WB	16/1224	78.6 (11.7)	72.5 (13.5)	0.07
BSA	7/963	66.7 (15.3)	63.9 (15.2)	0.63
ISA	0/850	--	52.3 (13.7)	--
Atrial fibrillation				
WB	23/1217	77.7 (12.9)	72.5 (13.5)	0.064
BSA	27/943	67.5 (13.2)	63.9 (15.2)	0.22
ISA	200/650	51.7 (13.4)	52.4 (13.9)	0.53

Selection criteria for chapter 5: complete information of age of onset, TOAST classification, ethnicity, and sex. **P*-value was determined using an independent *t*-test to compare the age of onset. *n* demotes the sample population. ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

10.11 - Age of first-time stroke event between those with missing and complete for each included variable, using chapter 6's selection criteria.

	Missing/Complete	Missing	Complete	*P*-value*
Central obesity	*n*/*n*	Years (SD)	Years (SD)	
WB	552/1184	71.2 (13.4)	71.7 (13.4)	0.48
BSA	152/1024	66.6 (15.0)	63.9 (15.1)	0.040
ISA	155/971	53.3 (14.2)	51.7 (13.3)	0.17
Smoking history				
WB	20/1716	70.8 (14.5)	71.5 (13.4)	0.80
BSA	12/1164	59.2 (16.0)	64.3 (15.1)	0.24
ISA	5/1121	61.0 (6.4)	51.9 (13.4)	0.13
Alcohol consumption				
WB	299/1437	71.4 (13.5)	71.5 (13.4)	0.94
BSA	80/1096	62.8 (16.2)	64.4 (15.0)	0.38
ISA	6/1120	52.3 (11.0)	52.0 (13.4)	0.95
Hypertension				
WB	22/1714	73.2 (14.1)	71.5 (13.4)	0.54
BSA	19/1157	67.3 (12.1)	64.2 (15.1)	0.37
ISA	28/1098	51.4 (15.3)	52 .0(13.3)	0.83
Diabetes mellitus				
WB	29/1707	74.6 (13.8)	71.4 (13.4)	0.21
BSA	19/1157	67.8 (13.6)	64.2 (15.1)	0.30
ISA	30/1096	50.8 (16.6)	52.0 (13.3)	0.63
Hypercholesterolemia				
WB	37/1699	73.6 (13.1)	71.5 (13.4)	0.34
BSA	49/1127	68.7 (11.9)	64.1 (15.2)	0.034
ISA	150/976	51.3 (14.4)	52.1 (13.2)	0.51
Ischaemic heart disease				
WB	26/1710	74.2 (13.5)	71.5 (13.4)	0.31
BSA	25/1151	66.5 (14.4)	64.2 (15.1)	0.46
ISA	0/1126	---	52.0 (13.4)	---
Atrial fibrillation				
WB	36/1700	73.8 (13.8)	71.4 (13.4)	0.29
BSA	54/1122	67.5 (14.7)	64.1 (15.1)	0.11
ISA	212/914	51.7 (13.2)	52.0 (13.4)	0.80

Selection criteria for chapter 6: complete information of age of onset, ethnicity, metabolic risk factor data and sex. **P*-value was determined using an independent *t*-test to compare the age of onset. *n* demotes the sample population. ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

10.12 – Number of metabolic risk factors with complete data, stratified by ethnicity.

No. of metabolic risk factors* with complete data.	ISA (*n*=1126) *n* (%)	BSA (*n*=1176) *n* (%)	WB (*n*=1736) *n* (%)	Total (*n*=4038) *n* (%)
0	2 (0.2)	6 (0.5)	13 (0.7)	21 (0.5)
1	9 (0.8)	6 (0.5)	11 (0.6)	26 (0.6)
2	54 (4.8)	14 (1.2)	9 (0.9)	77 (1.9)
3	220 (19.5)	169 (14.4)	537 (30.9)	926 (22.9)
4	841 (74.7)	981 (83.4)	1166 (67.2)	2988 (74.0)

n demotes the sample population. *Metabolic risk factors included are hypertension, diabetes mellitus, hypercholesterolemia, and central obesity. ISA: South Asians residing in India. BSA: UK residing South Asians. WB: White British.

10.13 - Age of stroke event between those with missing and complete data for each included variable, using chapter 7's selection criteria.

	Missing/Complete	Missing	Complete	*P*-value*
Central obesity	*n*/*n*	Years (SD)	Years (SD)	
WB	624/1409	71.4 (13.1)	72.0 (13.4)	0.37
BSA	179/1303	67.2 (14.6)	65.0 (14.8)	0.051
Smoking history				
WB	17/2016	73.6 (11.9)	71.8 (13.3)	0.56
BSA	8/1474	58.3 (18.0)	65.3 (14.8)	0.18
Alcohol consumption				
WB	339/1694	71.9 (12.9)	71.8 (13.3)	0.86
BSA	87/1395	64.3 (15.7)	65.3 (14.7)	0.55
Hypertension				
WB	7/2026	70.7 (15.3)	71.8 (13.3)	0.83
BSA	10/1472	69.7 (10.8)	65.2 (14.8)	0.34
Diabetes mellitus				
WB	8/2025	79.9 (11.3)	71.7 (13.3)	0.08
BSA	4/1478	71.0 (5.1)	65.2 (14.8)	0.11
Hypercholesterolemia				
WB	19/2014	73.8 (10.6)	71.8 (13.3)	0.50
BSA	39/1443	69.4 (9.8)	65.1 (14.9)	0.01
Ischaemic heart disease				
WB	4/2029	74.8 (12.4)	71.8 (13.3)	0.65
BSA	4/1478	61.3 (15.2)	65.2 (14.8)	0.59
Antiplatelets admission				
WB	236/1797	71.0 (13.9)	71.9 (13.2)	0.35
BSA	6/1476	71.0 (15.7)	65.2 (14.8)	0.34
Antiplatelets discharge				
WB	248/1785	71.2 (13.8)	71.9 (13.2)	0.44
BSA	24/1458	65.1 (15.1)	65.2 (14.8)	0.97

Selection criteria for chapter 7: complete information of age of onset, atrial fibrillation status, ethnicity, and sex. **P*-value was determined using an independent *t*-test to compare the age of onset. *n* demotes the sample population. BSA: UK residing South Asians. WB: White British.

10.14 – Metabolic Syndrome poster presentation given to the European and World stroke conference, using preliminary data from the BRAINS database in 2018.

Differences In UK South Asians And European Ischaemic Stroke Patients: Results From The Bio-repository Of DNA In Stroke (BRAINS) Study

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Background

South Asians in the UK have an increased risk of stroke. Metabolic syndrome appears prevalent in this group. Environmental and genetic factors play major roles but there has been little research on stroke in patients of South Asian ancestry despite the UK hosting the largest congregation of this group outside the Indian subcontinent. To gain insights into this discrepancy we established BRAINS, the world's largest South Asian stroke DNA repository.

Aims

Prior to a GWAS for ancestral stroke risk loci, we sought to compare the prevalence and risk factors of Metabolic Syndrome between South Asian, and white European with ischaemic stroke

Method

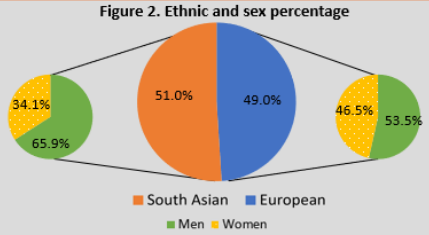
- BRAINS is an ongoing global (UK, Middle East, India, Sri Lanka) repository of stroke patients.
- Data collected includes risk factors and other compounding factors for all haemorrhagic and ischaemic stroke patients of adult age >18 years old. DNA is stored.
- Data for the UK cohort was collected at multiple sites nationwide.
- Data was filtered so only South Asian and white European stroke cases remained
- Metabolic Syndrome was defined per the NCEP ATP III guidelines [Table 1]
- Cases were included if we could define Metabolic Syndrome status
- Comparisons of outcomes between ethnic groups and risk factors were made using chi-squared test and logistic regression.

Table 1. NCEP ATP III Metabolic Syndrome Definition

	Men	Women
Hypertension	≥130/≥85 mmHg or previous diagnosis	≥130/≥85 mmHg or previous diagnosis
Hyperglycaemia	≥6.1 mmol/L or previous diagnosis	≥6.1 mmol/L or previous diagnosis
Triglycerides	≥1.7 mmol/L	≥1.7 mmol/L
Low HDL-Cholesterol	<1.03 mmol/L	<1.29 mmol/L
High waist circumference	≥102 cm or BMI≥30	≥88 cm or BMI≥30

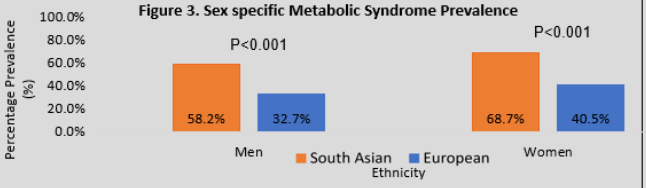
Results

Figure 2. Ethnic and sex percentage



- The mean (SD) age of stroke onset was 6 years earlier in South Asian men (South Asian: 62.8±14.1 years, vs white European : 68.8±13.3 years, 95%CI = 4.5 – 7.6, P<0.001) and 7.1 years earlier in women (South Asian: 66.6±15.1 years, vs white European: 73.7±13.6 years, 95%CI = 5.1 – 9.2, P<0.001) compared with white European.
- 1009 (661 men, 348 women) South Asian and 966 (559 males, 407 women) white European with Ischemic stroke were included.

Figure 3. Sex specific Metabolic Syndrome Prevalence



- Prevalence of Metabolic Syndrome, defined by the ATP III guidelines, was significantly higher in South Asians regardless of sex [Figure 3]

Table 2. Sex stratified prevalence of Metabolic Syndrome components

	Men			Women		
	South Asian (n=661)	White European (n=559)	P-value	South Asian (n=348)	White European (n=407)	P-value
Hypertension	83.1%	63.7%	<0.001	85.3%	70.5%	<0.001
Hyperglycaemia	72.0%	46.2%	<0.001	76.1%	45.0%	<0.001
Hypertriglyceridemia	39.7%	32.7%	0.045	39.9%	28.1%	0.007
Low HDL-Cholesterol	50.7%	37.7%	<0.001	49.2%	34.3%	<0.001
Waist circumference	50.5%	46.3%	0.262	77.4%	71.0%	0.127

- This increase of metabolic syndrome prevalence [Table 2] is driven by increased prevalence of each component.
- South Asians have significantly higher prevalence of all Metabolic Syndrome components excluding waist Circumference

Table 3. Sex stratified step-wise logistic regression analysis comparing Metabolic Syndrome risk between South Asians and white Europeans (reference group)

	Men		Women	
Model	OR (95% CI)	P-Value	OR (95% CI)	P-Value
1	2.87 (2.27 – 3.62)	<0.001	3.22 (2.38 – 4.34)	<0.001
2	2.81 (2.21 – 3.57)	<0.001	3.25 (2.38 – 4.43)	<0.001
3			2.65 (1.89 – 3.72)	<0.001

- Model 1: Unadjusted
- Model 2: Adjusted for age
- Model 3: Adjusted for age and alcohol use (Women only)

- South Asian men and women saw a 2.8 and 2.7 fold increased risk of Metabolic Syndrome, respectively, after adjusting for confounding factors, compared to the European population.

Conclusion

South Asians experienced a ~3 fold increased risk of having Metabolic Syndrome, as defined by the ATP III definition, compared to white Europeans. South Asians suffered from a 6-7 year earlier ischaemic stroke while also suffering from an adverse risk profile. These risk factors explain the increased prevalence of Metabolic Syndrome in South Asians, however the pathology is still not fully understood. Genetics may play a role in these findings and BRAINS is now undergoing a genome wide analysis.

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