

Primary prevention of stroke in high stroke risk populations:
examining impact of modifiable risk factors and
risk stratification in Older Adults and
South Asians using two longitudinal cohorts

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Thesis submitted for the degree of Doctor of Philosophy
Field of Study: Epidemiology

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Declaration

I, Ayesha Ahmed confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Ayesha Ahmed

24.11.2023

Abstract

Background

Older adults and South Asians (SAs) carry high stroke burden. Primary prevention of stroke involves population-level and high-risk approaches for risk factor modification. However, impact of risk factors and validity of risk assessment tools can vary across age and ethnicity. Additionally, whether N-terminal-pro-B-type-natriuretic-peptide (NT-proBNP), reflecting subclinical cardiac dysfunction, improves stroke risk prediction in these groups is unclear.

Aims

To inform primary prevention of stroke in cardiovascular disease (CVD) free older adults and SAs by examining impact of smoking, body mass index, physical activity, diet, cholesterol, blood pressure (BP) and glucose levels using American Heart Association's cardiovascular health (CVH) model; risk assessment; and contribution of NT-proBNP to risk stratification.

Methods

The thesis used data from British Regional Heart Study (BRHS) following men (40-59y) for forty years, and Southall and Brent Revisited Study following SAs (40-69y) for two decades; to estimate population attributable fraction (PAF) of stroke resulting from sub-optimal CVH. Stroke-specific and composite-CVD risk prediction tools were validated for stroke risk in older BRHS men. Incremental value of NT-proBNP in classifying stroke risk was examined in both cohorts.

Results

In BRHS men, PAF of stroke decreased from 39% (95%CI 10-58) in midlife to 6% (-17-25) in older age, with BP the main metric retaining a (reduced) contribution. Among SAs, PAF was 36% (11-53) with main contributions from BP, glucose, and body mass index. In older BRHS men, all risk tools discriminated stroke risk weakly, with comparable risk prediction overall. Using recommended CVD prevention thresholds, composite-CVD tools had poor specificity for stroke. NT-proBNP modestly improved reclassification of older BRHS men and SAs without incident stroke.

Conclusions

Impact of CVH on stroke decreases with age. Among SAs, optimal midlife CVH can avert $>1/3^{\text{rd}}$ of incident stroke. Stroke risk discrimination in older adults requires improvement. NT-proBNP augments stroke risk prediction among both groups.

Impact Statement

Stroke is a major cause of cardiovascular mortality, morbidity and complex disability among older adults, and South Asians who experience events early compared to European populations. Primary prevention employs population-level modification of traditional cardiovascular risk factors and targeted intervention in individuals with increased risk following risk assessment.

The 'cardiovascular health' or CVH model has been promoted as central for primary prevention of CVD including stroke, but distributions of its 7 component health factors and their associations with stroke vary with age and ethnicity. This implies population-level benefit may not be uniform across sub-groups. Likewise, ability of cardiovascular risk tools to correctly predict stroke risk among older adults and South Asians remains unclear. This thesis produces related evidence with potential to inform public health strategy, clinical practice, and further research for strengthening stroke prevention in both high-risk groups.

For public health decision makers, understanding that the fraction of stroke averted by optimizing CVH reduces with ageing, while BP persists as the main albeit weaker contributor to impact, suggests limited utility of the CVH construct as a stroke prevention strategy for older adults. The finding additionally highlights to local administrators a need to deliver effective, tailored services for the older population for detection and management not only of high BP but importantly of other age-linked causes of stroke such as atrial fibrillation.

In comparison, knowledge that around 40% of strokes among middle-aged South Asians could be avoided by achieving optimal CVH reconfirms its value as the basis for prevention, and the need for culturally appropriate interventions for modifying BP, glucose levels and obesity as priority ethnicity-specific risk factors. Moreover, that South Asians receive at least as much incremental protection from better CVH as Europeans can be especially relevant for clinical interactions and public health campaigns in contexts where South Asians form a minority, to offer reassurance and encourage engagement and behaviour change.

The thesis documents that although prediction of stroke in old age by composite-CVD risk tools was comparable to if not better than by stroke-specific tools, this was less

than ideal. For clinicians, this provides increased awareness of the potential for incorrectly assigning high risk to some who may be at low risk, and hence careful risk communication, shared decision making and additional work up. More widely this adds to scientific debate on considering age-appropriate risk thresholds.

Performance of risk tools in predicting stroke among South Asians could not be assessed and remains a priority for future research. Additionally, the thesis notes the ability of NT-proBNP to correctly downgrade stroke risk, and hence potential use in preventing unnecessary intervention, in CVD free older adults and South Asians. It is envisaged researchers will formally examine the clinical utility of NT-proBNP in augmenting stroke risk prediction, and its role in guiding intensity of preventive management in both populations.

Thesis findings have been presented to health care professionals and researchers at departmental meetings and international conferences. Results have also been disseminated as peer reviewed articles in academic journals, with further manuscripts under preparation.

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Abbreviations

AF	atrial fibrillation
AHA	American Heart Association
AUROC	area under the receiver operating curve
BMI	body mass index
BP	blood pressure
BNP	B-type natriuretic peptide
BRHS	British Regional Heart Study
CAC	coronary artery calcium
CE	cardio-aortic embolism
CHD	coronary heart disease
CHS	cardiovascular health study
CI	confidence interval
CIF	cumulative incidence function
CKD	chronic kidney disease
CRP	C-reactive protein
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability adjusted life year
DBP	diastolic blood pressure
EDI	elderly diet index
eGFR	estimated glomerular filtration rate
FEV1	forced expiratory volume in 1 second
FFV	fresh fruit and vegetables
FPG	fasting plasma glucose
FSRP	Framingham stroke risk profile
GBD	Global Burden of Disease
GP	general practitioner
HDL	high-density lipoprotein

HES	hospital episode statistics
HF	heart failure
HR	hazard ratio
hs-cTnT	high sensitivity cardiac Troponin-T
HS	haemorrhagic stroke(s)
IC	intermittent claudication
ICH	intracerebral haemorrhage
IL-6	interleukin 6
IMD	index of multiple deprivation
IS	ischaemic stroke(s)
KM	Kaplan-Meier
LAA	large artery atherosclerosis
LDL	low-density lipoprotein
LS7	Life's Simple 7
LVH	left ventricular hypertrophy
MASALA	Mediators of Atherosclerosis in South Asians Living in America
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
NHS	National Health Service
NICE	National Institute For Health And Care Excellence
NP	natriuretic peptide
NT-proBNP	N-terminal pro B-type natriuretic peptide
PA	physical activity
PAF	population attributable fraction
PCE	Pooled Cohort Equations
PY	person years
REGARDS	REasons for Geographic and Racial Differences in Stroke
R-FSRP	revised Framingham stroke risk profile
SA	South Asian
SAH	subarachnoid haemorrhage

SAO	small artery occlusion
SBP	systolic blood pressure
SCORE	systematic coronary risk evaluation
SLE	systemic lupus erythematosus
Sn/Sp	percent sensitivity/percent specificity
SVD	small vessel disease
TIA	transient ischaemic attack
TC	total cholesterol
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
UK	United Kingdom
US	United States
WHO	World Health Organization

Chapter 1. Introduction

1.1 Background and Thesis Rationale

1.1.1 Stroke and its Continuing Burden

Stroke is clinically defined as the sudden onset of neurological symptoms of vascular origin lasting more than 24h or leading to death (1). It is a major cause of morbidity and mortality worldwide (2). Stroke was responsible for a quarter of the disability adjusted life years (DALYs) due to cardiovascular disease in Europe in 2019 (3). In the United Kingdom (UK), there has been a steady decrease in deaths due to stroke over the last 20 years. Yet stroke events still cause 6% of all deaths, and in 2018 were ranked as the 4th leading cause of death overall (4). Further, the number of hospital admissions due to stroke has remained more or less constant over the last decade, with more than 135,000 strokes occurring in 2019 (5); and stroke continues to be the leading cause of complex disability (6). Certain population subgroups bear a disproportionately larger burden of stroke. These include older adults (7-9) and people of South Asian (SA) ancestry (10, 11).

Stroke and Ageing

Incidence of stroke rises sharply with age (8, 9). In the UK, the greatest burden of stroke lies among people above age 70y (6, 12); and health care costs of stroke exceed those of coronary heart disease (CHD) (13). The UK spends nearly £26 billion annually in stroke related health and social care costs (14). By 2038, 1 in 4 persons is projected to be ≥65y (15). It is estimated that unless improved measures to prevent strokes and related disability are implemented, with population ageing over the next two decades, the societal costs of stroke will treble (16).

Stroke among South Asians

People of SA origin comprising natives of 8 densely populated countries of the region (Afghanistan, India, Pakistan, Bangladesh, Maldives, Sri Lanka, Bhutan and Nepal), as well as the rapidly expanding diaspora, make up nearly a quarter of the world's population (17) and experience a high burden of cardiovascular disease (CVD) and stroke globally (10, 11, 18). SAs are the largest non-White minority group in the UK (19), and compared to the White European majority are noted to have higher risk of

stroke (20, 21) and higher stroke mortality (22). SAs are also mostly younger at first presentation of CVD including stroke (12, 23), and potentially more likely to develop certain post-event complications such as dementia (24), both of which compound their stroke related disability.

1.1.2 Primary Prevention of Stroke

Primary prevention i.e., preventing the development of disease in susceptible but disease-free individuals, is considered the best approach for reducing the global stroke burden (25), and rests on risk factor modification. The latest European Stroke Action Plan aims to reduce the absolute number of strokes in Europe by 10% over 2018-2030 (26), and emphasizes risk factor modification through both population-wide strategies and individualized interventions based on improved personalised stroke risk assessment. Risk factors of stroke include high blood pressure (BP), smoking, diabetes, dyslipidaemias, lack of physical activity (PA), poor diet and nutrition, obesity, alcohol consumption, cardiovascular conditions such as heart disease and arrhythmias, and psychosocial stress (27). Many of these factors also contribute to CHD (28). In most countries, including the UK, stroke prevention thus forms part of wider CVD prevention strategies, based on a combination of national and local approaches to reduce population prevalence of risk factors, and identification and preventive treatment of those at high risk (29-32).

Stroke is also closely linked to presence of disease in the peripheral vascular territory. Peripheral arterial disease is itself associated with both increased risk and severity of stroke, sharing smoking and diabetes as key risk factors (33). Even more broadly, stroke survivors are likely to experience multimorbidity, i.e., the presence of two or more chronic conditions within the same individual (34); due to stroke, having risk factors leading to stroke, and/or developing conditions resulting from stroke such as dementia and mental or physical ill health (35). Such individuals are noted to have poorer functional and mortality outcomes (36). Examining primary prevention of stroke by risk factor modification among older adults and SAs therefore also has implications for reducing their wider burden of multimorbidity (34, 37-39).

Impact of Risk Factors

The population level impact of risk factors i.e., the burden of a disease attributable to risk factors, is dependent on both their population prevalence as well as the strength of their associations with disease outcomes (40). Risk factor distributions are known to differ between younger and older individuals (13, 41, 42). Relatedly, attenuation (43) and even reversal (44) of associations between traditional risk factors and CVD (45), including stroke (46, 47) has been observed with ageing. Differences in cardiovascular risk factor profiles between SAs and other ethnic groups are also well known (28, 48, 49). The limited stroke-specific research in SAs similarly indicates that they may be more susceptible to the effect of some risk factors such as BP and diabetes (50, 51). The influence of risk factors, and by extension the impact of risk factor modification, across population subgroups is therefore nuanced and variable.

In 2010, the American Heart Association (AHA), selected smoking, body mass index (BMI), PA, diet patterns, total cholesterol, BP and fasting plasma glucose (FPG) - Life's Simple 7 (LS7), as a collective concept of 'cardiovascular health' (CVH), that could be measured, scored, and modified to reduce the burden of CVD (52). The model has been widely explored to compare the health of populations, and as a prognostic tool for CVD outcomes (53, 54). Achieving high CVH has been estimated to have a substantial impact in avoiding the burden of total CVD (55). However, there is limited prospective research on how CVH specifically impacts stroke in an elderly population (56), and hardly any among SAs. While the CVH model is not formally used in the UK, public health approaches focus on improving the same LS7 metrics, and evidence regarding their collective impact can guide stroke prevention efforts in these high-risk groups.

Stroke Risk Assessment

Currently stroke risk is clinically assessed as part of the composite risk of CVD (57-59). While stroke and CHD have a common basis in atherosclerosis, aspects of their pathophysiology are distinct, and literature suggests that the role and predictive power of conventional risk factors likely differs between the two (60-64). This becomes more concerning in old age when risk factor associations attenuate; underlying mechanisms of stroke change (65); and the proportion of CVD constituted by strokes increases (66, 67) necessitating preventive intervention to be more stroke focused. Older adults are more apprehensive about the risk of a life-changing illness like stroke than of death

(68). So far it is unclear how well composite-CVD prediction tools such as QRISK3 (58) and Pooled Cohort Equations (PCE) (57), derived from predominantly middle-aged adults, capture the true risk of stroke events in older adults; compared to stroke-specific tools like the Framingham Stroke Risk Profile (FSRP) (69), and QStroke (20).

Improving Risk Stratification – Role of Natriuretic Peptides

Clinical decisions on lifestyle or drug-based interventions following risk assessment are often a challenge for those at intermediate or borderline risk, and especially in older adults with frailty, multimorbidity and increased risk of adverse events (70). Incremental information provided by newer markers added to current risk tools can help refine risk stratification (71) and potentially guide preventive management.

With ageing, functional, and architectural abnormalities of the heart such as arrhythmias and heart failure (HF) become progressively important precursors in stroke aetiology (72, 73). Natriuretic peptides (NPs) are important blood markers of cardiac dysfunction (74), released by cardiac muscle in response to atrial/ventricular wall stress, with broad neuroendocrine effects. Clinical thresholds of B-type Natriuretic Peptide (BNP) and its inactive form Amino-Terminal Pro B-type Natriuretic Peptide or NT-proBNP are widely used for diagnosis and prognosis of symptomatic HF (74), and even low grade elevations, reflecting early cardiac structural and functional changes (75) have been linked to cardiovascular outcomes, including stroke (76-78). Strokes vary in severity from fatal events to transient ischaemic attacks (TIAs), the incidence of which also rises with age (79). TIAs are themselves critical forerunners of stroke (80) contributing to overall stroke risk. Integrating biomarkers that relate subclinical cardiac malfunction to all relevant endpoints in risk tools may improve stroke risk prediction in older adults. However, limited evidence is available on the long-term associations of NPs with the range of stroke presentations in older populations (81).

Furthermore, most research exploring NPs has been conducted in populations of European (76) and African ancestry (77, 82). SAs carry a higher burden of heart disease, including HF, from a comparatively younger age (83). Yet there is hardly any comparison of the distribution of NPs in apparently healthy SAs and Europeans; their use as markers of future stroke risk; and their added value in refining stroke risk among SAs.

1.2 Thesis Aim & Objectives

Older adults and SAs are two vulnerable populations that need dedicated stroke prevention strategies (84, 85). The overall aim of this doctoral research was to inform primary prevention of stroke in these groups by examining the impact of CVH on stroke, risk assessment, and the potential contribution of NPs to risk stratification. The specific objectives of the work were to:

1. Examine the prevalence of CVH (and its component modifiable LS7 metrics), its associations with and its impact on, stroke risk in older age; and among SAs.
2. Externally validate, and compare the performance of, stroke-specific (FSRP and QSTROKE) and composite-CVD risk tools (QRISK3 and PCE) for predicting stroke risk in older age.
3. Examine associations of NT-proBNP with stroke events (TIAs, non-fatal and fatal strokes) in older age; and with total stroke among SAs.
4. Examine if addition of NT-proBNP to current risk prediction models improves stroke risk stratification in older age; and among SAs.

1.3 Overview of Methods

This thesis analyses epidemiological data from two prospective cohorts – the British Regional Heart Study (BRHS) for objectives relating to older age; and the Southall and Brent Re-visited study (SABRE) for objectives relating to SAs. Due to differences in age ranges and ethnicities examined, data have not been pooled and results are cohort specific. All statistical analyses have been conducted in STATA (versions 14-17). Below is an overview of the cohorts, with methodologies described in detail in Chapter 3.

1.3.1 The British Regional Heart Study

Briefly, the BRHS began in 1978-1980 by recruiting a socially representative sample of 7735 men aged 40-59y, drawn at random from age-sex registers of 24 primary care practices across Britain (86). Men provide questionnaire-based socio-demographic, health, and lifestyle history; underwent physical examination and blood work.

Participants have since been followed periodically up to present day, by regular postal questionnaires; and for mortality and cardiovascular morbidity through linkage to National Health Service (NHS) Central Register and by reports from general practitioners (GPs). In 1998-2000, 4252 surviving men (60-79y) participated in the 20y re-examination; when they completed a mailed questionnaire; underwent clinical measurements; and provided fasting blood samples (86). The thesis makes use of measures from this 20y re-examination linked with data on stroke events and deaths to June 2018 to study all 4 objectives; and uses measures from the recruitment phase in analyses exploring change in CVH between midlife and old age.

BRHS is well suited for the study of stroke in older adults by virtue of its extended follow-up of a large representative sample of British men, from middle to older age. Loss to follow-up is minimal. Stroke capture is objective and reliable: the incidence rates of stroke observed using the study protocol, during both middle and older age, have been comparable with national data (87, 88). In addition, BRHS records TIA as a specific outcome, although this is based only on GP reports. CVH metrics are available at two key time points in the lifespan, and multiple biomarkers at older age have been measured using validated clinical assays. However, nearly all men participating in the BRHS are of European ethnicity (99%) so generalizability of findings to women and the wider British population is limited. See further details in Chapter 3.

1.3.2 The Southall And Brent RE-visited Study

The SABRE study is a multi-ethnic cohort of European, and first-generation SA and African-Caribbean participants (n=4857, 40-69y), that were randomly recruited from primary care physician lists and industrial workplaces in London boroughs of Southall and Brent in 1988-1991. At this baseline, participants completed a socio-demographic, health, and lifestyle questionnaire; underwent clinical examination and provided fasting blood samples (89). Ethnicity was agreed based on name, country of birth, appearance, and further enquiry in case of doubt, with SA defined as having ancestral origins in India, Pakistan or Bangladesh. Since baseline, participants have been flagged for cause-specific mortality (via the UK Office of National Statistics). Follow-up visits have taken place at 20y (V2, 2008-2011) and at 25-30y (V3, 2014-2018) (90). Hospital Episode Statistics have been provided by NHS Digital for traced participants.

This thesis uses ethnicity specific baseline data on CVH and blood biomarkers from a reasonably large cohort of SA and European participants linked longitudinally to cardiovascular events and death up to V2 (20y). Follow-up at V2 is available for 90% of participants and stroke events have been identified using multiple sources: participant report of physician diagnosed stroke, primary care record review, hospital admissions and causes of death. However, the number of stroke events is modest, and this limits analysis by fatal and non-fatal events, as well as formal validation of risk prediction tools that have a 10y horizon (therefore objective 2 is only explored in BRHS). SABRE participants are also predominantly male. Importantly, ethnicity is a complex socio-cultural construct, based on (self-)identification across a variety of characteristics including language, beliefs, religion, values, history, nationality, dietary practices, and behaviours (91, 92). As an ethnic group, SA is a high-level categorization that masks the diverse subpopulations that have resulted from complex interactions between migration, language, environment and culture of the region (93) and thus experience a range of social determinants which could influence health. Even in SABRE, the majority of SA participants (or their parents) hail from India, and more than half belong to the Punjabi Sikh faith (94), limiting the applicability of findings to the many other SA sub-groups in their native and non-native lands, and indeed to second generation diaspora. However, researching ethnicity necessitates its operationalization in some form, which while being imperfect (95) does allow insight (even if limited) into the health of a people with some shared characteristics. SABRE is one of few studies, internationally, with long-term follow-up of first-generation SAs, allowing an ethnic comparison of associations of mid-life health markers with later life outcomes. See further details in Chapter 3.

1.4 Thesis Structure

After this introductory chapter, the structure of the thesis is as follows: **Chapter 2** is a literature review relating to epidemiology and aetiology of stroke, generally and in older adults and SAs, as well as how this differs from CHD. It also describes evidence on the relationship between CVH and stroke; CVD and stroke risk assessment tools, and their performance relevant to these population subgroups; as well as current evidence on the association between NT-proBNP and CVD and stroke outcomes and its

incremental value when added to conventional risk predictor models. **Chapter 3** describes the design and methodology of BRHS and SABRE; measures and outcomes from both cohorts used in this thesis; and the statistical techniques used in the thesis to analyse data. **Chapter 4 – 7** correspond to each of the 4 objectives of this thesis (listed above) and include an introduction summarizing the chapter-specific literature review and rationale, aims and specific objectives; chapter-specific methods; followed by results (including tables and figures), a discussion of the key findings and how they relate to existing evidence, strengths and limitations of the analysis and brief implications. **Chapter 8** is the concluding section which highlights the key findings and contributions to stroke research resulting from the four objectives, their public health relevance for primary prevention of stroke and their implications for further research. The appendices hold details of supplementary methods and results, and sensitivity analyses.

1.5 Thesis Outputs

This doctoral research has resulted in 2 peer-reviewed publications, and 3 oral and 1 poster presentations at national and international conferences. A further 2 journal articles are in preparation.

Publications

- **Ahmed, A.**, Ambler, G., Pinto Pereira, S. M., Lennon, L., Papacosta, O., Whincup, P., & Wannamethee, G. (2023). Stroke risk in older British men: Comparing performance of stroke-specific and composite-CVD risk prediction tools. *Preventive Medicine Reports*, 31, 102098. <https://doi.org/10.1016/j.pmedr.2022.102098> (96).
- **Ahmed, A.**, Pinto Pereira, S. M., Lennon, L., Papacosta, O., Whincup, P., & Wannamethee, G. (2020). Cardiovascular Health and Stroke in Older British Men: Prospective Findings From the British Regional Heart Study. *Stroke*, STROKEAHA120030546. <https://doi.org/10.1161/STROKEAHA.120.030546> (97).

Oral Presentations

- Society of Social Medicine and Population Health, Annual Scientific Meeting, Sept 2022. *Prospective Associations of Cardiovascular Health with Stroke and Coronary Heart Disease in Europeans and South Asians* https://jech.bmj.com/content/76/Suppl_1/A24.2 (98).
- European Stroke Organization Conference, Sept 2021. *Prospective associations of NT-proBNP and Troponin-T with stroke events in older British men free of cardiovascular disease* <https://journals.sagepub.com/doi/10.1177/23969873211034932> (99).
- Society of Social Medicine and Population Health, Annual Scientific Meeting, Sept 2020. *Cardiovascular Health and Stroke in older British men: prospective findings from the British Regional Heart Study* https://jech.bmj.com/content/74/Suppl_1/A24.2 (100).

Poster Presentation

- American Heart Association's Epidemiology and Prevention/Lifestyle and Cardiometabolic Health 2023 Scientific Sessions *N-terminal Pro B-type Natriuretic Peptide Improves Stratification of Cardiovascular Disease and Specifically Stroke Risk in South Asians* https://www.ahajournals.org/doi/10.1161/circ.147.suppl_1.P334 (101).

Chapter 2. Literature Review

2.1 Introduction

This chapter presents a review of literature with the following aims:

1. To elaborate on the aetiology, risk factors and epidemiology of stroke in general and specifically in older adults and SAs (sections 2.2.1-2.2.4).
2. To describe available evidence relating to the burden of stroke attributable to different risk factors in both high-risk groups, and discuss similarities and differences between stroke, CHD and peripheral arterial disease and what this may mean for primary prevention of stroke (section 2.2.5).
3. To define CVH and discuss available evidence on its distribution, associations with and impact on cardiovascular outcomes especially stroke in older adults and SAs (sections 2.3.1-2.3.4).
4. To describe CVD and stroke risk assessment tools; and highlight challenges in/alternatives to using these for capturing stroke risk in older adults and SAs (sections 2.4.1-2.4.7).
5. To summarise studies describing the association between NT-proBNP and stroke outcomes and the limited evidence on its incremental value in refining the prediction of stroke risk in both older adults and SAs (sections 2.5.1-2.5.6).
6. To summarises key points of the review and highlight the gaps in evidence which this thesis aims to address (section 2.6).

2.1.1 Review Methods

Literature reviewed included systematic and narrative reviews of previous evidence, individual prospective studies and where these were not available cross-sectional evidence. Searches focusing on the research questions were conducted separately: through Web of Science, PubMed, Ovid Medline and Embase interfaces, without restrictions for date or language of publication. Strategies included a combination of MeSH terms and key words applied to title/abstract fields and are elaborated on in Appendix 2.1. Searches were conducted initially over 2019-2020, updated regularly

using automated search alerts until February 2023 and supplemented with key cross-referenced articles from reference lists and using forward citation.

2.2 Overview of Stroke

2.2.1 Defining Stroke

The traditional definition of stroke is clinical, and time-based. According to the World Health Organization (WHO) stroke has been defined as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (102). If neurological signs and symptoms disappear in less than 24 hrs, the event is classically termed a TIA (1). Strokes result from an interruption in blood supply; more commonly because of vessel occlusion (ischaemic stroke/infarct) and less frequently because of a non-traumatic bleed (haemorrhagic stroke).

In 2013, the AHA/American Stroke Association proposed that advances in neurovascular imaging and pathophysiological understanding meant the focus of these definitions should switch from a time-based to a tissue-based criterion (103). A TIA had already been redefined as "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia without acute infarction" (104). Their updated definition of stroke can be summarized as "an acute episode of focal dysfunction of the brain, retina, or spinal cord lasting longer than 24 hours, or of any duration if imaging (CT or MRI) or autopsy show focal infarction or haemorrhage relevant to the symptoms" (105), and includes silent infarcts or haemorrhages "without a history of acute neurological dysfunction attributable to the lesion" (103).

However, the new definitions have not been endorsed by European and World Stroke Organization experts (106), and are yet to be adopted, particularly in less developed parts of the world where access to imaging is less universal. Moreover, for studies prospectively following stroke epidemiology, the clinical time-based definition of stroke events remains central (2).

2.2.2 Stroke Aetiology

The two main stroke pathologies - ischaemic strokes (IS) and haemorrhagic strokes (HS), can be further classified based on aetiology. It is important to briefly highlight

these distinctions because, as will be elaborated later, stroke subtypes differ between population sub-groups, which in turn implies that impact of related risk factors and prevention strategies can also be variable.

IS can have a variety of underlying mechanisms. A number of classification systems have developed over time (107); ranging from chiefly clinical, site and size based categories as proposed by the Oxfordshire Community Stroke Project Subtype Classification (108), to 'likely-cause' (causative) systems such as TOAST (Trial of Org 10172 in Acute Stroke Treatment) and its modifications (109-111), to phenotypic classifications that record any and all concurrent mechanisms that could underlie a stroke (112, 113). However, 3 broad subtypes, which together constitute two-thirds of IS (114), have been commonly recognized (Figure 2.1). These are **(A)** large artery atherosclerosis (LAA), **(B)** cardio-aortic embolism (CE), and **(C)** small artery occlusion (SAO) also used interchangeably with small vessel disease (SVD) (115).

Ischaemia in LAA results from either a progressive atherosclerotic plaque in a major extra/intracranial artery that causes substantial (>50%) stenosis, or complete occlusion (often due to superimposed thrombosis); or frequently from embolic occlusion of downstream vessel by breakaway fragments of the proximal plaque. In CE, material from thrombi in cardiac chambers (e.g., following myocardial infarction (MI), atrial fibrillation (AF)); or from diseased valves or atheromatous lesions on the aortic arch, embolizes to the brain impeding or blocking blood flow beyond the point at which it gets lodged. In SAO, micro-atheroma or lipohyalinosis, and less commonly micro-emboli from the heart or a parent artery block a small penetrating artery. The resulting (lacunar) infarct is deep and smaller than 20mm in diameter (115, 116).

Two further etiologic subtypes of IS include **(D)** strokes due to uncommon causes (3-7% of IS) such as sickle cell anaemia or coagulation disorders (115), and **(E)** strokes of undetermined aetiology. In the latter category, the cause remains undefined either because of lack of appropriate work-up; normal or inconclusive findings (cryptogenic stroke); or more than 1 potential cause being equally likely (unclassified). Nearly a third of IS are of undetermined cause (105). A subgroup of these which are non-lacunar and lack evidence of parent artery stenosis and evidence of a clear source of emboli, are labelled embolic stroke of undetermined source (117).

HS can be further subtyped into intracerebral haemorrhage (ICH) when the bleeding is focal and within the parenchyma of the brain; and subarachnoid haemorrhage (SAH) when bleeding occurs between the membranes that cover the brain and spinal cord i.e. the subarachnoid space (103). The most common causes are hypertension related hemodynamic stress (30–60%), cerebral amyloid angiopathy related weakening of vessel walls (10–30%), anticoagulation (1–20%), and vascular structural lesions (3–8%); the cause is undetermined in 5–20% of cases (105, 118, 119).

Underlying mechanisms also influence severity of strokes. TIAs result from smaller thrombi/emboli that spontaneously recanalize and/or move, resulting in symptoms that are time limited. However, TIAs increase the risk of future stroke (80, 120), and can lead to a full-blown event within a week for 1 in 12 people (121). In comparison, larger cardiac emboli are known to cause sudden-onset and severe ischaemic events, affecting extensive areas of the brain with little time for collateral circulation to develop (122). Both ICH and SAH also carry substantial mortality and morbidity (118).

2.2.3 Risk Factors of Stroke

Atherosclerotic processes contribute directly and indirectly to a large number of strokes (107). Stroke risk factors therefore commonly include risk factors for atherosclerosis, and additional factors predisposing to the many different stroke aetiologies. They are broadly classified as non-modifiable and modifiable.

2.2.3.1 Non-modifiable Risk Factors of Stroke

Age is the strongest independent risk factor for IS and ICH; and reflects both natural neuro-cardio-vascular decline and accumulated exposure of modifiable risk factors (123, 124). The incidence of stroke doubles for each decade after 55y (125). Section 2.2.5.2 elaborates on stroke burden and aetiology in older adults.

Biological **sex** influences stroke risk based on age. Generally, males are at higher relative risk. However, risk rises in females in association with use of oral contraceptives, pregnancy and post-pregnancy states, and menopause, such that relative risk becomes higher in women after 80-85y (12, 126). Overall, because of their longer life expectancy, women have a greater number of absolute stroke events (2, 125).

Ethnicity linked disparities in stroke are well established. Black adults – both in the US (125) and UK (127) are at high risk of stroke relative to White individuals. Stroke

mortality is especially higher among younger Black adults who have a higher incidence of ICH and SAH (128). Similarly, SAs both within native lands and beyond experience higher stroke burdens (11). This is discussed further in section 2.2.4.3.

Low birth weight is also associated with increased risk of stroke and CVD in general, and may be related to geographical differences in birth or maternal health disparities (128)

Stroke risk is also increased by a **parental/family history** of stroke, **gene disorders** such as sickle cell disease, and rarer gene defects that structurally affect blood vessels e.g., Fabry's disease and polycystic kidney disease. Common **gene variants** that affect development of well-known risk factors (as listed below) have also been identified. However, these explain a small amount of variation in stroke risk (128). Promisingly, modification of lifestyle factors, such as smoking and diet, can potentially benefit all levels of genetic risk (129).

2.2.3.2 Modifiable Risk Factors of Stroke

Traditional Biological & Lifestyle Factors

Hypertension – high BP is a universal risk factor for stroke (128). The association is strong and incremental across the BP range starting from 115mmHg systolic and 75mmHg diastolic. It is similar in men and women, and for fatal and non-fatal events, although weakens with age (130). Between 60-69y of age, a difference of 20mmHg in usual systolic BP (SBP) or 10mmHg in usual diastolic BP (DBP) throughout this range is associated with slightly more than a twofold difference in the risk of stroke death (128, 131). Data from multiple randomised controlled trials indicates that the association is causal for both IS and HS (128, 130).

Diabetes – diabetes has been consistently found to independently increase the risk of IS by at least two folds (132), and especially that of lacunar strokes i.e. SAO/SVD (133). Some of this association can be explained by the simultaneous susceptibility to atherogenesis and atherogenic risk factors like high BP and dyslipidaemia (128). The duration of diabetes also has a positive association with IS (134), with risk increasing markedly for a diabetic history of 10y or more. Prediabetics are also at increased risk (135), with evidence that glucose levels may be incrementally associated with stroke risk (136). In contrast, diabetes is reported to be associated with a reduced risk of SAH (137).

Dyslipidaemia - when measured as raised total cholesterol (TC) or low-density lipoprotein (LDL)-cholesterol, dyslipidaemia is associated with an increasing risk of IS, particularly LAA. The protection given by higher high-density lipoprotein (HDL)-cholesterol levels against IS is not as clear cut as that given against CHD (128). The role of triglycerides is similarly unsettled. Higher levels of Lipoprotein(a), with chemical properties similar to LDL-cholesterol, have also been linked with increased IS risk in prospective studies (138, 139). However, association of TC or LDL-cholesterol with HS is inverse (125) and likely related to its effects on vessel wall structure (140).

Overweight and obesity. Body weight and measures of general and central obesity such as BMI (weight in kg/height in m²) (2), waist circumference and waist hip ratio (27) are associated with greater stroke risk although most of this effect appears to be mediated by other stroke risk factors with which obesity is also linked such as hypertension and glucose and cholesterol levels (141). There is also evidence of raised risk of HS at BMI <22kg/m² implying a U-shaped association (142).

Cigarette smoking. Smoking is associated with a doubling of IS risk, in an established dose response relationship with number of cigarettes smoked (143), likely through its short-term thrombogenic potential and long-term promotion of atherosclerosis (128). Smoking also raises markedly the risk of SAH (144), and likely ICH (137) although this is less established. Second hand smoke or passive smoking is also linked to strokes (2).

Physical inactivity. Being physically active is generally associated with reduced risk of stroke, ischaemic and haemorrhagic (145) through effects such as lowering of BP, reduced body fat, better glucose metabolism and reduced inflammation (128, 146). However, the influence of reverse causality due to poor baseline general health has also been highlighted (137).

Diet and nutrition. Diet and dietary components influence several stroke risk factors, most importantly BP, which is raised by a high salt, low potassium intake (128). Evidence indicates an overall inverse dose response association between consumption of fresh fruits and vegetables (FFV) and stroke risk, including citrus fruit (147). Observational studies also provide evidence for an inverse association with Mediterranean style diet which in addition to fruit and vegetable includes whole grains, cereals, nuts, legumes, seafood and unsaturated fats (148, 149); and with Dietary Approach To Stop Hypertension or DASH (additionally low fat) diet (150). However, it is unclear if this applies similarly to both IS and HS.

Alcohol consumption – alcohol use of any degree linearly increases the risk of HS. The association with IS however is more J shaped with moderate drinking associated with lower risk of stroke. Light-to-moderate alcohol consumption is associated with higher levels of HDL-cholesterol, reduced platelet aggregation, lower fibrinogen concentrations, increased insulin sensitivity and glucose metabolism (128). Heavy alcohol consumption is associated with hypertension and poor BP control, hypercoagulability, and AF. (125)

Cardiovascular and Renal Pathologies

Heart disease – cardiac conditions promoting blood stasis/coagulation and thrombus formation within the heart are important causes of CE strokes. AF is the most recognized of these (125), and especially relevant in older adults as discussed later (section 2.2.4.2). Other conditions include ventricular dysfunction associated with MI, cardiomyopathies, and HF; and valvular heart diseases such as mitral stenosis, as well as prosthetic or infected valvular structures that can serve as nidus for thrombi (128). Congestive HF is also associated with increased risk of LAA and SVD due to diabetes and hypertension being shared risk factors (151). A higher risk of HS among those with HF has also been noted and likely associated with the use blood thinning medication (152).

Carotid stenosis – stenosis or the narrowing of the lumen of the carotid artery by an atherosclerotic plaque is responsible for about 15% of (LAA) IS (153). Rupture of, thrombosis and embolism from the plaque can result in symptoms of TIA or a full-blown stroke.

Renal function – kidney dysfunction both acute and chronic is independently associated with almost all subtypes of stroke especially in Asian and African populations (154). Mechanisms beyond shared traditional risk factors, in particular hypertension, include increased endothelial dysfunction and carotid plaque burden, increased prevalence of AF, uraemic platelet dysfunction and chronic inflammation and anticoagulant use during dialysis (155).

Other risk factors

Economic and psychosocial factors – poor socioeconomic status (156), stress at work/home (27), loneliness and isolation (157) appear to be associated with increased

stroke risk. However, much of this seems to be explained by the greater burden of traditional risk factors associated with social or early-life disadvantage (156, 157).

Inflammation and infections – inflammation and infection have been linked to higher stroke risk. Atherosclerosis has an inflammatory component (158). Higher levels of inflammatory markers such as C-reactive protein (CRP) (159) and interleukin-6 (IL-6) (160), reflecting the burden of atherosclerosis, have been associated with modestly increased stroke risks independent of other risk factors. For CRP however, genetic studies have failed to confirm a causal association (125). Similarly, chronic inflammatory states such as rheumatoid arthritis and systemic lupus erythematosus (SLE) have also been associated with increased atherosclerotic burden and CVD including stroke (128). Infection also necessitates inflammation, and exposure to acute (respiratory illnesses requiring hospitalization) and chronic infections (such as HIV) has been linked respectively with higher short- and long-term risk of strokes (128, 161).

Living or working in areas with air pollution – gaseous and particulate air pollution has been confirmed as a short-term risk factor for hospital admission due to stroke and/or stroke mortality (162), particularly IS and especially robustly in low and middle income countries, possibly through effects on vascular endothelial function. The association of long-term exposure to air pollution is less clear (125) although, the latest Global Burden of Disease (GBD) study ranks ambient air pollution and house-hold air pollution through use of solid fuels among the top 10 causes of DALYs due to strokes globally (2).

Ambient temperature – prevailing temperature has an acute, nonlinear (U-shaped) effect on stroke risk in vulnerable populations such as the very old. Extreme hot temperatures (with resulting vasodilation, dehydration, and increased viscosity) particularly increase the risk of IS; while excessively low temperatures (associated with vasoconstriction and high BP) raise chances of ICH (163).

Less well documented risk factors include coagulopathies both inherited (such as factor V Leiden mutation, deficiencies of protein C or S) and acquired (such as malignancy, orthopaedic surgery, medications), and antiphospholipid syndromes (128); migraine particularly in women <55y (128); and sleep disordered breathing (sleep apnoea or sleep hypopnoea) particularly in men (164). Raised homocysteine resulting from genetic enzyme deficiencies or decreased renal clearance (128) or

inadequate intake of the B-vitamins (B12, folate and pyridoxine) has been noted to increase the risk of atherosclerotic CVD including stroke particularly in SAs (10, 18, 165).

2.2.4 Stroke Epidemiology

The latest GBD study concludes that despite reductions in the age-standardized incidence of stroke between 1990 and 2019 in nearly all countries, the absolute number of strokes over this period has continued to increase, being 70% higher at 12.2 million new cases in 2019 worldwide (2). Considering age-specific stroke incidence begins to rise in middle age and continues rising into old age (more steeply for men compared to women) (9); the increase in stroke numbers signify population growth and aging population structures (105), as well as inadequate prevention strategies across many parts of the world (2).

Globally 62% of all new strokes are ischaemic, 27% are ICH and 9% are SAH. These proportions, however, vary according to population characteristics, GBD region and income level. The bulk of global stroke burden, including higher rates of ICH, resides outside of the high-income countries (2).

2.2.4.1 Stroke Trends in the UK

Stroke burden in the UK aligns with the global trend. The GBD study estimates that UK experienced a 45% decrease in the age-standardized incidence of all new strokes over 3 decades, to 62.6/100,000 inhabitants in 2019, which is almost half the global incidence and compares favourably with the other countries of the GBD Western European region (2). Despite this, event numbers for UK in 2019 stand at 74,187 strokes (67% IS), and 50,633 stroke deaths (66% IS) (2).

UK statistics collated from official sources in the British Heart Foundation's Statistical Compendium reveal declining stroke mortality, with stroke morbidity remaining high. In 2018, the UK had a total of 36,046 stroke deaths (cerebrovascular diseases ICD codes I60-I69) with mortality due to stroke being 6%, nearly halved from 11% in 2001 (5, 13). There were 135,670 hospital admissions for stroke in 2019/2020, and nearly 25,000 admissions due to TIA and related syndromes (ICD 10 G45), representing a small recent increase in morbidity due to stroke that was mostly steady since 2011 (13). General practice register based prevalence of stroke/TIA in the UK was 1.7% in 2006/2007 and rose slightly to 1.9% in 2019/2020 (66).

Two main reasons can potentially explain the falling stroke mortality along with stable/rising morbidity. Firstly, demographic aging. The number of people ≥ 65 y in the UK has gone up from 16% in 1998, to 18% in 2018 and is projected to be 24% i.e. 1 in every 4 persons by 2038 (15). Secondly, evidence from England between 2001 and 2011 suggests that more (two-thirds) of the reduction in stroke mortality may be attributable to reduced case fatality than to falling stroke event rates (166). In support, Public Health England (PHE), using general practice data from The Health Improvement Network, similarly estimated that although the crude incidence rate of first strokes fell slightly from 1.16 per 1000 English population to 1.07 over the period 2007-2016, this was because of an increase in the population over time, as absolute numbers of stroke events remained at around 57,000 at the beginning and at the end of this period (12).

Forecasts for the number of new strokes in the UK have only been incremental. Li et al (2020) applied age-specific incidence rates from the Oxford Vascular prospective study to UK population projections, and concluded that a current decline of 6% every 5y would still lead to a 13% increase in the number of first-ever strokes in the UK between 2015 and 2045 (167). In a similar exercise conducted by King et al, expert consensus regarding future incidence of stroke leaned towards steady or rising rates, with authors suggesting a 60% rise in new strokes between 2015 and 2035; trebling related health, social care and productivity costs from £26 billion to £76 billion over the two decades (16).

Between 80 and 90% of all incident strokes in the UK are ischaemic (168). Among identifiable IS subtypes, and in keeping with reports from majority White high income countries (114), CE strokes form the highest proportion followed by SAO and LAA, and have lately shown a rise in incidence (169).

The following sections elaborate on stroke burden, stroke subtypes and risk factors specifically in older adults and SAs.

2.2.4.2 Burden, Risk Factors, and Subtypes of Stroke in Old Age

The world population of persons aged 65y and older is expected to reach 994 million by 2030 and 1.6 billion by 2050 (170). Nearly two-thirds of stroke cases occur among this age group (7).

UK statistics confirm that incidence of stroke/TIA increases with age, more steeply compared to that of MI, doubling for each decade after 55y (see Figure 2.2). Based on general practice data, incidence rates for stroke/TIA in 2017, among those 55-64y, 65-74y and 75y+ were 2.8, 5.6 and 13.2/1000 population respectively (171). In England, the median age of stroke is 70y in males and 76y in females (12).

The risk of having a fatal stroke also increases with age. In European adults free of major CVD (19-77y at baseline and followed for a mean of 13y), the risk of having a fatal stroke increased by 12% per year in men and 13% per year in women (172). Stroke deaths thus form an increasingly greater proportion of CVD deaths in older adults. In the UK, 23% of all stroke and CHD deaths among those 45-54y in 2019 were due to stroke, while this proportion increased to 43% among those 85y+ (13).

Age is the strongest risk factor for stroke because natural cerebrovascular degenerative changes make the brain increasingly vulnerable to ischaemic injury (173). Cerebral amyloid angiopathy and antithrombotic use as management of other cardiovascular conditions in older adults increase the predisposition to haemorrhages (174). Together with declining general pre-stroke health and functional status, this increases the likelihood of severe deficits and of slower recovery (173).

Modifiable risk factors and their changing associations with stroke in old age

The prevalence of **traditional stroke risk factors** such as diabetes, hypertension and physical inactivity relative to recommended levels (175) increases with age; TC and BMI levels initially rise with age and then fall in the oldest old; while prevalence of smoking peaks in mid-adult life and then declines (42, 176). Associations of traditional risk factors with cardiovascular endpoints such as CHD have been found to attenuate with age (177-179). Studies examining predictors of stroke in older adults (172, 180-182) also indicate that influence of risk factors changes with ageing.

Studies with repeated long-term longitudinal follow-up of the same cohort into old age (43, 46, 183), consistently note that associations of high BP (measured continuously as SBP or as the presence or absence of hypertension), with both IS and HS attenuate with age. Similar declines have been reported for the effect of diabetes on all strokes (43), of FPG on IS (46) and of smoking on IS (46, 183). However *stronger* age-related effects have also been reported for diabetes (183) and smoking (184).

Some of these differences may be explained by regional or gender differences in the cohort characteristics, or by differences in baseline periods of recruitment. But, pooled analysis by Singh et al using data from large multi-country collaborative projects such as the Asia Pacific Cohort Studies Collaboration, the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe, the Emerging Risk Factor Collaboration, and the Prospective Studies Collaboration, conclude that the associations of key metabolic risk factors SBP and BMI with IS and HS; TC with IS, and FPG with all strokes decline with each decade from 35-44y to 85+y across Western and Asian populations (47).

A number of reasons can individually or collectively explain the weaker effects of certain traditional risk factors. Firstly, the rising prevalence of hypertension and diabetes among older adults occurs alongside a natural increase in risk of stroke in the ageing population meaning independent effects of risk factors (besides age) are difficult to identify (183). Secondly effects of a risk factor, such as deranged cholesterol, may remain/accrue in those who have been exposed at a critical period, such as midlife, despite levels normalizing in later life (183), again making it difficult to attribute outcomes to specific risk factors. Thirdly, physiological changes in older adults are thought to modify the effect of, or vulnerability to, certain risk factors (183). For example, higher blood pressures may *help* maintain blood supply to target organs including the brain, in older adults in whom age-related vascular stiffness hinders perfusion. This might also underlie some of the inverse relationships which appear among older adults such as that of higher cholesterol enhancing neuronal function; or higher BMI offsetting some vulnerabilities that come with frailty. And finally, 'depletion of susceptibles' means those most susceptible to the effects of a risk factor generally experience a serious event earlier in life, leaving as older adults a group of survivors that are inherently at low risk (43).

Interestingly, the protective effect of PA on IS in men has been reported to become stronger with age (183). In the BRHS, time spent walking was inversely associated with risk of stroke in a dose response fashion in men of mean age 68y followed for 11y (185).

In comparison, other age-linked cardiovascular conditions (section 2.2.3.2) take prominence as stroke predictors. This is especially true of **AF**, which rises in

prevalence with age (186). This rise is prominent but less ‘pervasive’, in comparison to risk factors like hypertension, such that a strong independent effect is easier to detect (183). Age (and related cerebrovascular physiology) also acts as an effect modifier such that the risk of stroke in those with AF increases up to 5 times between the ages of 50 and 80y (73).

Similarly as incidence and prevalence of **HF** rise with age (187), it becomes an important precursor in stroke aetiology (72, 173, 188). Recent evidence has broadened this risk to include age related **subclinical changes in the heart** such as those in atrial tissue substrate, increasing the chances of future strokes, particularly embolic stroke of undetermined source (189). The evidence on Natriuretic Peptides which reflect this subclinical cardiac dysfunction in predicting stroke in older adults is further discussed in section 2.5.

Age related structural and functional **changes in the kidney** result in progressively declining function, altered homoeostasis and haemodynamic states. An estimated glomerular filtration rate (eGFR) $<60\text{ml/min/1.73m}^2$ has been associated with increased risk of stroke, and the association appears more robust in old age compared to the association of traditional risk factors such as smoking and BMI (43).

Stroke subtypes in old age

Although the incidence of HS, and ICH in particular, increases with ageing (118); IS still form 80% of stroke events in older adults (25). However, the changing risk associations are reflected in the shifting distribution of ischaemic stroke subtypes. Hospital-based, population-based, and stroke registry data clearly show that proportion of CE strokes rises with age (41, 114, 169). The proportion of LAA strokes (for e.g. carotid stenosis with a clear atherosclerotic basis in hypertension) peaks to an age 70-80y and then declines; while changes in SAO/SVD strokes are less consistent (41). Data from 2000 to 2015 from the community-based South London Stroke Register shows a higher mean age of onset (74y) for first CE strokes compared to other subtypes, as well as a rising recent trend in incidence among those $>55\text{y}$ compared to declines in LAA and SVD (169).

2.2.4.3 Burden, Risk Factors, and Subtypes of Stroke in South Asians

People of SA origin (hailing from Afghanistan, India, Pakistan, Bangladesh, Maldives, Sri Lanka, Bhutan and Nepal) make up nearly a quarter of the world’s population (17).

In 2019, the GBD South Asian Region (excluding Sri Lanka and Maldives) had a total of 1,698,563 new stroke cases (14% of the global aggregate), approximating an age-standardized incidence rate of 120/100,000 population (twice the GBD study estimate of age-standardized stroke incidence in UK), of which 42% (vs 62% globally) were ischaemic, indicating a higher proportion of HS (2). Estimates also indicate that the region experienced a slower decline in stroke incidence over 1990-2019 of 10% vs 17% globally (and 42% across Western Europe) (2).

There are limited rigorously conducted population-based studies within SA countries (11, 190), although prospective cohorts have been established in the recent past (191). Available data suggest incidence rates that vary but are, in agreement with GBD study estimates, higher than incidence rates in Western countries (190, 192, 193). Stroke also forms a relatively greater proportion of all CVD compared to MI in SAs compared to Europeans (194). A recent sub-study of the PURE (Prospective Urban and Rural Epidemiology study) collaboration, using data from an 11y average follow-up of participants (including those with a history of CVD) from India, Pakistan and Bangladesh, reported an overall age and sex adjusted stroke incidence of 1.5/1000 person years (PY), with country specific rates highest in Bangladesh and lowest in India. (195).

Stroke burden in South Asians outside SA countries

Higher stroke burden is evident even among SAs outside of native lands. Communities settled in Europe and USA (196, 197) experience high stroke mortality. In the UK people of Indian, Pakistani and Bangladeshi ancestry form the largest non-White minority group (198), and in 2019 made up more than 3.5 million individuals in England and Wales (199). Based on official statistics, mortality due to stroke has been consistently higher among SAs compared to the White population, particularly among Bangladeshi men (200, 201).

Early reports from the South London Stroke Register looking at ethnic differences in stroke incidence indicated that the incidence of a first fatal/non-fatal stroke among Asians (Indian, Pakistani, Bangladeshi, Chinese) was higher than among Whites across age groups (202). In more recent analysis of data from the English primary care population, age-standardized incidence of first stroke in 2016 among Asians was 1.18/1000 population compared to 1.07/1000 in Whites (12). Findings from 8,000 SA

and 449,349 European CVD free participants of the UK Biobank followed from 2006-10 for a median of 11y indicate SAs to be at 1.3 times increased risk of IS. Longitudinal analysis of primary care data from England and Wales, with participants followed for a median of 7y over 1998-2012 also noted that compared to White women, Bangladeshi and Pakistani women were respectively at 1.3 and 1.6 times the risk of IS and TIA (20). SAs are also 25% more likely than White individuals to be diagnosed with IS as their first CVD event (203).

SAs have been observed to suffer a stroke earlier in life than Western populations (12, 190, 203-205). In the BRAINS study (Biorepository of DNA in Stroke) recruiting 4,038 participants with first IS in 2010-2019 across hospitals in UK and India; Indian and British SAs were respectively, on average 19y and 9y younger than White British cases at time of event. The younger age of onset among Indian and British SAs was evident across all subtypes of IS (23).

There is some evidence of a genetic component for the excess stroke risk among SAs (128, 190), but the bulk of stroke burden is attributable to the same modifiable risk factors as in other ethnic groups (27). The relative contribution of individual factors however differs.

Ethnic differences in distribution and associations of modifiable risk factors

The current prevalence of **hypertension** ($\geq 140\text{mmHg}$ SBP and/or $\geq 90\text{mmHg}$ DBP) at around 30% among adults in India, Pakistan and Bangladesh is broadly similar compared to Western populations (195), and is the result of opposing secular trends of increasing and decreasing BP in SA and Western countries respectively (206). According to latest ethnic-specific analyses of the Health Survey of England, the prevalence of hypertension in British SAs is similar to that in the White British population (28%) except in Pakistani adults (35%) (207). Yet, SA stroke patients are at higher odds of being hypertensive than their White counterparts (23, 204, 205). Associations of systolic and diastolic BP with stroke have been found to be stronger in SAs compared to Europeans (50).

The Indian subcontinent is experiencing an epidemic of **diabetes**. India, Pakistan and Bangladesh were ranked, and are projected to remain, among the world's top 10 countries or territories for number of people (20-79y) with diabetes, in 2019 and beyond (208). SAs abroad also demonstrate a higher prevalence compared to host

populations. British SAs have a 2 to 3 fold greater prevalence of doctor diagnosed diabetes compared to White British individuals (6%) (207). Hospital-based studies suggest that almost 50% of SA stroke patients are diabetic – significantly higher than Whites (23, 204, 205, 209). Diabetes and prediabetic hyperglycaemic states have been shown to confer an excess risk of stroke in SAs relative to Europeans, possibly through adverse effects on cerebral microvasculature and haemodynamics (210, 211), potentially underlying their greater frequency of SVD strokes (23, 205, 209).

Age-standardized prevalence of **smoking** among men in South Asia overall is 25%, and prevalence among women is low (3%). However, Bangladeshi men have exceptionally high (45%) rates of smoking (212). SAs, especially women, additionally chew tobacco in various forms (190). Among British SAs, Pakistani and Bangladeshi men also report a 25% prevalence of cigarette smoking, slightly higher than White British men. Prevalence among SA women is lower than White British women, although within SA women, Bangladeshi women have highest rates (207). SA stroke patients less frequently present with a history of smoking (23, 205, 209). When measured as the use of smoking tobacco, smoking contributes less to the attributable burden of stroke among SAs compared to European and North American ethnic groups (27).

The SA **lipid profile** is uniquely atherogenic. Compared to other ethnic groups, SAs have similar or lower levels of LDL-cholesterol, but lower than healthy levels of HDL-cholesterol, higher levels of triglycerides and Lipoprotein(a) (51, 176, 213). The prevalence of dyslipidaemia in British SA stroke cases has shown a rising trend (204). In the BRAINS study, a third of White British and Indian SA stroke patients had high cholesterol levels (≥ 5.2 mmol/l) compared to 50% of British SA patients (23). SA stroke patients in the US have also been noted to have significantly higher triglyceride and significantly lower HDL-cholesterol levels compared to African Americans (209).

SAs across the world have low levels of **PA**. In the SA region, prevalence of physical inactivity is as high as 33% (214). In England, the proportion of adults doing <30 min/week of moderate to vigorous PA ranges from 32% to 46% among SA groups (207). The independent contribution of low PA to stroke risk in SA however is variable (2, 27), and may relate to differences in how PA is measured and in methods using which its impact is calculated.

Prevalence of **obesity** in SA countries when estimated using the standard 30kg/m^2 cut-off ranges from 4-9% (195, 214), and is lower than most other regions of the world (215). British SA adults (except for Pakistani women) also show similar or lower prevalence of obesity compared to White adults using the same threshold (207). However, SAs are known to carry greater (central and ectopic) body fat and have lower muscle mass at similar BMI levels compared to White ethnic groups. The associated insulin resistance and derangements in lipids raise their cardiometabolic risk (10, 216), and lower BMI thresholds have been recommended in particular to classify diabetes risk (increased risk $23\text{--}27.5\text{ kg/m}^2$, high risk $\geq 27.5\text{kg/m}^2$) (217). Earlier comparisons between ethnic groups have noted that Pakistani and Bangladeshi adults are at increased odds of having higher waist hip ratio relative to the general population (176). Both high BMI ($>23\text{kg/m}^2$) and higher waist hip ratio (>0.91 in men and >0.86 in women) have been noted as risk factors for stroke in SAs (2, 27).

SAs have varied **dietary habits**. With increased urbanization of SA countries and migration of many SAs to developed nations, SA diet has become progressively westernised with lower intake of whole grains, FFV and greater consumption of red meats (195, 214). Even among SA vegetarians, the associated intake of refined carbohydrates and fats; and high heat cooking methods are thought to lead to adverse cardiovascular effects (10, 214). In the INTERSTROKE study (27), a healthier diet score was surprisingly associated with higher odds of stroke in SAs, while daily fruit and vegetable intake was not associated with reduced odds of stroke – reflecting a qualitative difference in diet and cooking.

Interestingly despite having a higher burden of conventional risk factors for **AF**, the prevalence of AF in the general SA population (27, 186, 218) and among stroke cases (18, 23, 205) is lower than in White ethnic groups. Evidence suggests this may be due to smaller left atrial size in SAs which reduces the chances for re-entry circuits like AF (219). However for SAs with AF, the risk of stroke is 1.6 times higher, and again related to their higher prevalence of diabetes hypertension and vascular diseases (218).

Although **drinking habits** vary between SA subgroups; alcohol intake is generally lower among SAs than Caucasians, and alcohol ranks lower among modifiable risk factors for stroke (27). Other risk factors linked to stroke burden in the SA region, but

less relevant for SAs elsewhere include ambient air pollution, household solid fuel use and lead exposure (27).

Ethnic differences in stroke subtypes

HS form a higher percentage of all strokes in SAs, with figures between 19 and 46% reported (27, 190, 205), and potentially linked to their increasing prevalence/poor control of high BP.

Among IS, hospital-based studies from within and outside South Asia indicate that both LAA and SVD strokes are more frequent than CE strokes (only 6-16% of IS) (23, 190, 205, 209, 220). Additionally, temporal trends in IS subtypes (1993-2015) suggest that while among Whites in high income countries, the proportion of IS due to CE increased (2% annually) and that due to SAO and LAA decreased (4% and 3% respectively); Asians in low-middle income countries (India, Pakistan and China) saw an 8% annual rise in proportions of IS due to LAA. These trends may be driven among Whites by population aging and better implementation of preventive strategies for atherosclerotic risk factors; and among SAs by increased urban/western lifestyles with disproportionately high burdens of hypertension and diabetes. (114). This also supports the higher prevalence of diffuse intracranial atherosclerosis patterns among SAs (197).

2.2.5 Primary Prevention of Stroke

While improved comprehensive acute stroke care is vital, and reducing stroke related fatalities critical, these strategies are not enough because many are still likely to be left with lifelong complex disability. The mainstay of reducing the wide-ranging burden of stroke is to reduce the occurrence of new strokes i.e., primary prevention, by risk factor modification (25). This is based on the combination of two well-known approaches. Population-wide strategies such as those related to tobacco consumption and salt intake, where small changes in risk factor distributions can result in large reductions in overall incidence; and the high-risk approach which directs aggressive

intervention towards the relatively fewer individuals found to be at high absolute risk through personal risk assessment (see section 2.4 for further details) (221, 222).

The success of prevention strategies at a population-level will depend on the proportion of the stroke burden that is attributable to the risk factors being modified (223). This is captured by the Population Attributable Fraction or PAF, a single quantity which takes into account both the prevalence of risk factors and their associations with disease/outcomes (explained further in Chapter 3 Methods section 3.8.5) (224).

The preceding sections have emphasized how both risk factor distributions and associations with stroke vary for older adults and for SAs compared to the general population. This suggests variable PAFs of stroke for different risk factors in these groups, hence variable benefits of risk factor modification. Only a limited number of studies have estimated PAFs of stroke specifically among older adults or SAs. These differ in design, methodology used to calculate PAF including the level of adjustment, in the risk factors chosen, and in the definitions of risk factors and 'older' subgroups; and are summarised below.

2.2.5.1 Attributable Burden of Stroke in Older Adults

The few studies (27, 225-229) reporting PAFs of stroke in older adults or in age-stratified subgroups are compared in Table 2.1 and Table 2.2.

The Rotterdam study reported PAFs of stroke in 6844 stroke free Dutch participants followed for a mean of 13y for factors that had associations with stroke in study specific Cox models in expected directions (225). The joint PAF for hypertension, smoking, diabetes, AF, CHD and BMI ($>25\text{kg/m}^2$) was reported as 51% [95% CI 41-62] (Table 2.1). Although the study has an advantage of comprising mainly older adults (median age 68y); and identifies strokes by multiple pathways including primary care records that capture strokes not admitted to hospitals, the PAFs reported are lower in comparison to other estimates both because of the method used (230) and because of the middle-high income setting, with greater preventive health services and low prevalence of nutrition related factors such as overweight/obesity. For some risk factors such as fruit and vegetable intake, inflammatory and subclinical markers (CRP and carotid intima-media thickness) data was only collected in a subgroup and indicated a slightly raised joint PAF. The study did not collect information on PA.

The INTERSTROKE is an inter-continental case-control study that recruited acute first strokes (defined according to WHO criteria) from 32 countries, matched 1:1 to similar age-sex hospital and community controls (27). Ten potentially modifiable risk factors, also explored in the earlier similarly designed INTERHEART study looking at acute MI (28), were measured using questionnaires and clinical exams. PAFs were estimated overall and in several subgroups including adults ≤ 55 y ($n=4216$) and >55 y ($n=9231$), using multivariable adjusted logistic regression models. While PAF for all risk factors combined was similar in those >55 y (90%) compared to the younger group (92%) (Table 2.1), PAFs for most individual risk factors except diet and cardiac causes were lower in the older group. Statistically significant age interactions were reported for hypertension (PAF 50% in ≤ 55 y vs 46% in >55 y), waist hip ratio, diet and cardiac causes.

This study was conducted using standardized protocols, almost all cases had neuroimaging within a week, and clinical exam and labs within 72h. Recruitment demographics suggest that the older group included more people from the 'cultural' West. However, a cut-off age of 55y means the older subgroup included adults in late-middle age and is not uniformly an old age group. But the main drawback of the INTERSTROKE, and other case control studies referenced in Table 2.1 (228, 231), is the bias associated with measuring risk factors in cases. This is related to the effect of the acute condition (here stroke for example affecting BP, although the INTERSTROKE authors did adjust for admission BP), to recall bias, and to more aggressive work-up compared to controls. The recruitment of hospital-based controls can also lead to higher prevalence of certain risk factors compared to the general population.

The GBD study published an age-stratified analysis of the proportion of stroke related DALYs attributable to 17 risk factors based on 2013 data (Table 2.2) (226). Comparing the oldest age group (70+y) to 15-49y and 50-69y adults globally, PAFs of low PA and reduced kidney function were higher. Proportion of DALYs due to stroke related to the remaining risk factors were all lower, although high SBP (55%) and low fruit (24%) and vegetable (14%) still accounted for prominent amounts. The study did not measure cardiac causes. Joint PAFs across the oldest to youngest group of participants were 87%, 98% and 90% respectively.

GBD studies use complex statistical methodology to arrive at PAFs (2, 226). PAFs are estimated using the counterfactual method, comparing the burden of disease associated with the real or factual level of risk exposure with what would be expected with a hypothetical (safer/healthier) counterfactual risk level (40). The Theoretical Minimum Risk Exposure Level or TMREL used as the counterfactual (minimum level of risk factor which is theoretically possible but not necessarily practically achievable or affordable) is defined by expert consensus based on best available epidemiological evidence. For traditional risk factors of stroke, TMRELs used in the GBD study analyses are slightly different to thresholds used in most epidemiological studies for e.g. TMREL for SBP is $\geq 119\text{mmHg}$ while the definition of hypertension in most studies including INTERSTROKE is $140\text{mmHg}/90\text{mmHg}$ (27). Similarly, TMREL for BMI has been defined as $>23\text{kg}/\text{m}^2$ compared to the standard definition of obesity ($>30\text{kg}/\text{m}^2$). Additionally, GBD PAF analyses focus on DALYs due stroke – a broader outcome inclusive of events, mortality and disability as opposed to PAF of stroke incidence.

To sum up, the evidence available on population level impact of risk factors on stroke in older adults provides a range of estimates. Moreover, there is little to no evidence on how PAFs change across mid to late adult life in the same cohort.

2.2.5.2 Attributable Burden of Stroke in South Asians

Among SAs, the few prospective estimations of risk factor impacts have been limited to PAFs of overall CVD (21, 49), and evidence regarding PAFs of stroke is scant (2, 27, 232). The INTERSTROKE and GBD studies provide subgroup analyses by region (Table 2.3) but are limited by the same inconsistencies as described above (2, 27). Although both point to hypertension as the main contributor to stroke burden ($\sim 50\%$), individual PAFs of other risk factors markedly differ in magnitude as well as rankings. A single hospital-based age and gender matched case-control study from Pakistan (232) looks specifically at intracranial atherosclerotic stroke and reports only on a limited number of independent risk factors.

2.2.5.3 Stroke Prevention as Part of Wider CVD Prevention

CVD affects three main vascular territories – coronary, cerebrovascular and peripheral. Coronary and cerebrovascular events both have an element of acute (on chronic) vascular injury (103), and share the atherogenic risk factors which drive

atherosclerotic processes underlying the classical presentations of stable/unstable angina and MI, and *ischaemic* strokes (233).

Similarly, peripheral arterial disease which refers to atherosclerotic narrowing of the peripheral arteries, predominantly in the lower limbs (progressively leading to intermittent claudication, resting limb pain and tissue death), shares many of the same atherosclerotic risk factors as stroke. It is strongly age-related and linked with smoking, diabetes, hypertension, hyperlipidaemia, renal dysfunction as well as hypercoagulation states and hyperhomocysteinemia (234).

Peripheral arterial disease often co-exists with cerebrovascular disease. And in those without prior stroke, can itself increase the risk and severity of future stroke and TIA events, possibly through associations with increased carotid artery stenosis and blood pressure variability (33). Aggressive risk factor management of such individuals may therefore help prevent first time strokes. However, peripheral arterial disease has received less attention in CVD prevention strategies, and evidence to screen for it using (low) ankle-brachial pressure index as a means of preventing CVD is as yet insufficient (235). Further, although ankle-brachial pressure index has been noted to improve prediction of cardiovascular mortality (236), whether it can meaningfully add to stroke-specific risk prediction is as yet unclear.

For now, most national public health strategies for primary prevention of stroke are embedded within broader prevention strategies which focus on risk assessment of stroke and CHD, and modification of shared traditional risk factors that are common between the two CVD event types (29-31).

However, involvement of smaller vessels, structural and functional features unique to the brain, the role of endothelial cells in maintaining neurovascular health and collateral circulation, as well as the important role of embolisms make stroke pathophysiology somewhat distinct from CHD.

Aetiological Similarities and Differences between Stroke and CHD

- Both events follow a circadian rhythm with occurrences peaking between 6 am and noon (237-239).

- Aging is relevant to both types of events, although strokes are predominantly a disease of older adults. In the Dubbo prospective study of Australian adults 60y and older, age was a stronger predictor of IS compared to CHD (240).
- Atherosclerosis in both IS and CHD is driven by concurrent loss of endothelial function (normally protective against inflammation); deposition of oxidized lipoproteins in arterial walls promoting immune and inflammatory responses resulting in fatty streaks or xanthomas; and smooth muscle proliferation and transformation leading to fibrotic and/or calcified plaques causing luminal stenosis. Rupture of unstable plaques exposes underlying elements to blood, triggers platelet activation and thrombus formation (241, 242) and results in downstream ischaemia. There is some evidence however that the composition of coronary (more fatty) and cerebral (more fibrous) plaques differs (243), with unstable plaque rupture being more frequent as a precursor to MI as opposed to stroke (107, 237).
- Atherosclerosis underlying MI almost always affects large coronary arteries (125), while vascular involvement in IS spans large vessels, both extra and intracranial such as the carotid artery and its branches, as well as small vessel disease, with some unique features (244). Intracranial atherosclerosis, more commonly seen in non-European ethnic groups such as Blacks and Asians, advances at a slower rate than extracranial atherosclerosis but is especially hastened by diabetes and hypertension. In contrast to coronary vessels, intracranial arteries have also been found to be less influenced by the effects of oxidized LDL-cholesterol and chronic hypercholesterolemia (244), and tobacco smoking (245).
- Hypertension predisposes to both IS and CHD but is noted to be a more important risk factor for stroke (62, 242, 246). This may be related to its effects on size structure and function of both larger and smaller cerebral vessels and hence cerebral hemodynamics. Hypertension related wall stress triggers vessel wall hypertrophy reducing luminal diameters and is associated with reduced vessel distensibility resulting in higher vascular resistance. It also leads to loss of smaller collateral vessels of the brain at a rate faster than which occurs with normal aging, in turn influencing severity of and recovery from ischaemic injury (244).

- The role of AF and HF has been highlighted (section 2.2.3.2) with regards to CE strokes, which form nearly a fifth of IS (114). In comparison, embolism and HF less commonly trigger the non-classical non-coronary artery disease type 2 MI (247). AF is also noted to be a stronger predictor of IS than of CHD (240)
- More broadly, HS (as explained in section 2.2.2), are also associated with hypertension (and alcohol) related structural/aneurysmal abnormalities in vessel walls. But in contrast to IS and CHD, HS are inversely associated with high cholesterol/LDL levels (248) presumably through protective strengthening of vessel endothelial cell membranes (140).

2.2.5.4 Burden of Stroke vs Coronary Heart Disease Attributable to Shared Risk Factors

In accordance with these observations, the relative contributions of specific risk factors to stroke and CHD i.e., respective PAFs have been found to vary. In the EPIC Potsdam study which followed 27,000 participants (35-65y) without a history of MI and stroke for an average of 6y; 88% of MI compared to 55% of stroke (IS & non-IS) events were attributable to the combined presence of diabetes, smoking, hypertension and raised LDL-cholesterol (249). Similarly, in the INTERHEART (28) and INTERSTROKE (27) studies, PAFs of acute MI due to hypertension, raised lipids and smoking were 18%, 50% and 36% respectively, while the respective fractions for IS were 46%, 34% and 15%. This in turn means that strategies targeting traditional modifiable risk factors shared between stroke and CHD may not be equally beneficial for each outcome.

In summary, primary prevention of stroke may need to be customised towards risk factors more appropriate to a population's stroke burden. To assess guide and prioritise strategies among *older adults and SAs*, it would be useful to separately establish the *fractions specifically of stroke*, attributable to risk factors which commonly form the focus of general CVD prevention strategies, *unique to their own populations*. A useful model for this is that of Cardiovascular Health, described next.

2.3 Overview of Cardiovascular Health

2.3.1 The Concept of Cardiovascular Health

The concept of 'cardiovascular health' or CVH was introduced by the AHA in 2010 (52). Prior to that, in the early 2000s, reductions in stroke and CHD mortality had been achieved to set goals but reductions in risk factors' prevalences especially diabetes and obesity were less successful. The CVH model was developed using 7 cardiovascular risk factors, to drive down heart disease and stroke both by primary prevention i.e. preventing disease from occurring in those with risk factors; and with particular emphasis on primordial prevention i.e. preventing risk factors from emerging altogether (250).

The AHA chose 3 health factors (BP, TC, and FPG) and 4 health behaviours (smoking, PA, diet and BMI), which had sufficient evidence available in terms of associations with heart disease, stroke, CVD free survival; and wider health aspects such as longevity, quality of life and health care costs. Most of this evidence came from prospective studies of middle-aged adults or focused on a composite of CVD (52). The AHA utilized literature reviews and recommendations from national guidelines to classify each of the 7 factors into 3 levels: ideal, intermediate, and poor (Table 2.4). The model shifted focus from adverse outcomes and illness to wellness and health, promoting the factors as Life's Simple 7 (LS7); with *ideal* CVH being the collection of *ideal* levels of *all* LS7 - in the absence of drug treatment, in those without CVD. The framework meant LS7 metrics could be scored, and CVH measured and monitored in individuals and populations (251). Population-level data could then facilitate targeted health promotion and CVD prevention programs.

Since then, a number of studies have reported prevalences of and trends in LS7 and CVH in US and non-US populations (54, 252-255). Indicators have varied from measuring CVH as ideal/non ideal; to using number of ideal LS7 (score 0-7); to incorporating all three levels of each LS7, by assigning 0, 1, and 2 points to poor intermediate and ideal levels respectively, for a composite CVH score of 0-14 that allows for measuring small changes.

A systematic review of 50 studies (published over 2010-2015) concluded that the prevalence of ideal CVH (here taken as having 6 or 7 metrics at an ideal level) was generally low across populations, ranging from 0.5-12% in US and 0.3-15% in non-US

studies (54). Ideal level of smoking was most commonly reported as having the highest, and ideal diet most commonly reported as having the lowest prevalence across studies. There was no significant change in the prevalence of ideal CVH over calendar years, although individual metrics showed increasing and decreasing trends in prevalences of ideal levels. A later review based on 88 studies (published over 2010-2018) albeit with significant levels heterogeneity, confirmed smoking and diet as the best and worst metrics, and added that men and older adults ≥ 60 y had higher prevalences of poor CVH (254).

Relationships of LS7 and CVH have been explored with a range of health and disease outcomes. Expectedly, inverse (protective) trends have been noted between better CVH and all cause and CVD mortality (256, 257); CHD, HF, stroke and composite-CVD (53); diabetes, cancer, depression and cognitive impairment (54). However, few studies have reported on stroke as the primary outcome. Meta-analyses covering similar publication periods (53, 256, 257) and including a handful of overlapping stroke-specific studies (56, 258-262) estimated that compared to those with the least number of ideal LS7 metrics (or <5 on a 0-14 score), those with the greatest number of ideal LS7 (or score ≥ 10) had nearly 70% lower risk of incident stroke. The meta-analyses described high levels of heterogeneity, studies differing with respect to follow-up duration, adjustments for covariates, measures for diet and PA, and CVH scoring. Importantly the pooled sample was dominated by middle-aged participants, and none of the studies were conducted among SAs.

2.3.2 Studies on Cardiovascular Health and Stroke at Older Ages

The potential impact of promoting CVH as a primary prevention strategy among older adults can best be studied among those without a history of CVD. However, only a limited number of prospective studies have examined associations of CVH with stroke in CVD-free older populations (Table 2.5).

Dong et al followed a US urban cohort of White, Black, and Caribbean Hispanic adults free of MI and stroke, mean age 68y (± 10) and recruited between 1993-2001, for a median (max) of 11y (16y) (258). None of the adults had all 7 metrics at ideal level and only 4% had 5-6 ideal metrics. Inverse trends between the number of ideal LS7 metrics and stroke were noted in the total cohort. However, there were just 43 strokes events among 619 White older adults and effect estimates did not reach statistical

significance. HR of stroke among those with ≥ 5 ideal LS7 vs those with 0-1 was 0.73 [0.21–2.51].

In the REasons for Geographic and Racial Differences in Stroke-REGARDS multi-ethnic cohort recruited between 2003-2007, mean age 65y, free of self-reported stroke, peripheral vascular disease, and CHD; and followed for 5y, there were 232 strokes among 13361 US White older adults (263). A fifth of the adults had a CVH score of ≥ 10 . A statistically significant inverse trend was noted between CVH score and stroke. With reference to inadequate CVH (score 0-4), HR of stroke among those with average (5-9) and optimum (10-14) CVH were 0.71 [0.46-1.10] and 0.49 [0.29-0.89] respectively. Among individual LS7 metrics BMI PA and diet had null associations with stroke. This study had a relatively short follow-up and defined PA and diet different to AHA LS7 guidelines. Additionally, although recruitment was attempted nationally, the cooperation rate was only 50%.

Gaye et al recruited non-institutionalised French men and women ≥ 65 y (mean 74y) without prevalent CVD and followed them from 1999-2001 for a median of 8.6y for stroke and CHD events (56). There were 257 stroke events among 7371 participants with complete data. Only 5% of the adults had ≥ 5 metrics at ideal level. HRs for intermediate (3-4 ideal LS7) and ideal (5-7 Ideal LS7) global CVH were respectively 0.82 [0.64-1.06] and 0.45 [0.20-1.03], p for trend 0.03. The authors found behavioural CVH (smoking, BMI, PA, diet) and biological CVH (smoking, BP, TC, FPG) to be similarly inversely associated with stroke. The study also explored a combined outcome of CHD and stroke and noted no significant interaction between global CVH and age tertiles (≤ 71 , 72—76, ≥ 76 y) although the magnitude of effect weakened towards null with increasing age. This is one of the few studies with a large sample of older adults, yet ~1000 participants were excluded due to missing data who were noted to be older, with greater prevalence of hypertension and functional disability. Overall, the recruited population was healthier and socioeconomically better off than the general population, so ideal CVH levels may have been overestimated.

All 3 studies report ideal (non) smoking status and FPG to be the two most prevalent, and diet and BP to be the two least prevalent ideal metrics. All 3 suggest incremental benefits of CVH even in old age. But effect estimates appear smaller than those reported by the above-mentioned meta-analyses and in studies among middle-aged

participants (Table 2.5). This is further supported by a more recent study among 350,000 UK Biobank participants free of CVD, 40-70y (mean 56y) and followed for 11y, which stratified effect of CVH by age-groups. HRs of stroke for both ideal and intermediate levels of CVH reduced in magnitude across 45-59y and ≥ 60 y (264). Additionally in a retrospective analysis based on national claims data from more than 2 million Japanese adults, the association of number of LS7 metrics with stroke over a mean follow up of 3y attenuated across 20-49y, 50-59y and 60-75y age groups with p for interaction <0.001 (265). However, this was limited to the employed adult population and so those >75 y were excluded.

2.3.2.1 Impact of Less Than Ideal or Sub-Optimal CVH in Old Age

The observation that associations of CVH with stroke are stronger in younger age groups is not unexpected (see section 2.2.4.2 on stroke risk factors in older adults) but smaller effect sizes along with low prevalence of good-ideal CVH would together influence the overall impact or burden of stroke that could be avoided by achieving optimal CVH. To my knowledge, PAFs of *stroke* associated with less than ideal or sub-optimal CVH have not been explored in European older adults.

Based on prevalence of low (score 0-8, 59%) moderate (score 9-11, 34%) and high (score 12-14, 7%) CVH among 12,000 participants of the US National Health and Nutrition Examination Surveys (NHANES) conducted between 2011 and 2016; combined with age-stratified incidence rates and HR of CVD derived from 7 cohorts (30,000 CVD free adults) in the Lifetime Risk Pooling Project, Bundy et al calculated the PAF of *composite-CVD* (stroke, CHD and HF) (55). Estimates were adjusted for age, sex and race but not for wider factors that affect both CVH and CVD such as socioeconomic status. It was reported that 2 million CVD events could be avoided or postponed if all US adults (≥ 20 y) achieved high CVH, PAF due to score <12 being 70%. The prevalence of high CVH (1.8%) and the PAF of CVD events (64%) were lower among those ≥ 60 y, but estimates were not provided for CVD subtypes.

In the China-PAR project (Prediction for Atherosclerotic CVD Risk in China), pooling data on CVH and CVD events from 90,000 participants of 3 nationwide cohorts, Chao Han et al (266) did report multivariable adjusted PAFs of stroke, estimating that if all adult participants had all LS7 at the ideal level, 66% of stroke events may have been averted. Significant interaction with age, indicating weaker protection by ideal CVH in

older adults was noted although age-specific PAFs of stroke were not provided. However, this study was specific to the Chinese population, and used a definition of diet tailored to Chinese food habits. Authors also reported a selection bias in that participating adults were on average less healthy than those lost to follow-up although this was a small proportion 7%.

2.3.2.2 Association of Change in CVH over Adult Life with Stroke Risk in Later Life

Although overall CVH declines with age (267) this is not an inevitable part of aging or heredity (268). People begin life with good CVH but some experience a decline in levels of metrics on the way to adulthood and beyond (251). Data from Framingham Offspring Study participants (mean 60y) indicates that each 5y period lived with intermediate or ideal CVH is associated with a 24% reduced risk of first stroke in later life (269). But work exploring how change in (i.e., worsening and more importantly improving) CVH over adult life affects risk of future events has mostly been restricted to a composite-CVD outcome (270, 271) or to short follow-up time (270, 272). Whether change in CVH between mid-life and older age can influence stroke incidence in later life remains uncertain.

A Chinese study among 75,000 CVD free middle-aged urban employees noted 5 CVH trajectories based on CVH scores over 4y through latent mixture models (272). During 5 yrs of follow up, 1852 CVD including 1401 stroke cases were identified. Relative to the low-stable group, the moderate-increasing, moderate-decreasing, high-stable I and high-stable II all had progressively lower risks of incident CVD and specifically stroke. HR of stroke in high-stable II group (mean CVH score 11) was 0.23 [0.17-0.30]. Effect sizes for composite-CVD were larger in those <60y compared to ≥60y (p for interaction 0.01). However, the transition period for change in CVH spanned only 2-4y and follow-up was limited to a maximum of 5y.

Middle-aged participants of the Framingham Heart Study (n=2774) were assigned to one of four CVH trajectory groups based on CVH scores (rang 0-14, cut-off for high taken as ≥8 and low ≤7) at first and last of ≥2 exams that were attended over 4 exam cycles between 1991 and 2008 (270). Over a median follow-up of 5 years starting from the latest exam, 428 first CVD events were recorded. In comparison to participants belonging to the high-high CVH group (i.e., those who maintained a score ≥8 through

the study period) all other participants (high-low, low-low, low-high) had a higher risk of CVD. In particular, those who started with low CVH and improved had similar age-sex adjusted HR to those who started off low and remained in low CVH (low-high 1.73 [1.26-2.38] and low-low 1.90 [1.51-2.39]). This potentially suggests limited utility of modifying CVH in adult life. However, the study used a very broad CVD outcome (stroke, TIA, CHD, HF and intermittent claudication) and had a relatively short median follow-up making it hard to draw conclusions regarding stroke prevention in older adults.

In another analysis among middle-aged civil servants (mean 44y at baseline) who participated in multiple waves of the Whitehall study, authors created more precise trajectories by using high (5-7 ideal metrics) moderate (3-4) and low (0-2) CVH categories to make 9 groups based on change in CVH over 10y. Over a median follow up of 19y, 1114 first CVD events occurred in 6326 participants. But no consistent associations were seen between direction of change in CVH and incident CVD. However, when 4 trajectory groups were created based on a cut-off score of 8 (as in the Framingham Heart Study above), with reference to the high-high group those among the low-low category were at twice the risk of CVD, and HRs for low-high (1.38 [1.14-1.67]) and high-low (1.50 [1.26-1.67]) were similar. This analysis with a much longer follow up and multivariable adjustment for age, sex, race/ethnicity, depression, education, occupation, and family history of CVD suggests some benefit of improving CVH. However, the bulk of incident CVD events were made up of CHD (MI, angina, and coronary procedures) and inferences regarding stroke are less certain. In the same study, additional analyses among 9256 participants followed for 30y found time-varying CVH to be inversely associated with stroke (n= 295 IS, HS, TIA) with HR per unit increase in 0-14 score 0.89 [0.84-0.95]; and for moderate and high categories with ref to low category: 0.77 [0.60-0.98] and 0.58 [0.33-1.01] respectively.

2.3.3 Studies on Cardiovascular Health and Stroke in South Asians

Few reports are available regarding the prevalence of CVH and related LS7 metrics among SAs, and to my knowledge there are no prospective studies examining associations of CVH with or its population level impact on stroke, or even CVD.

2.3.3.1 Studies Estimating CVH in South Asia

Cross-sectional studies from Nepal (n=2) and India (n=2) provide some estimates of CVH profiles (273-276), however authors do not always clarify if participating adults are CVD free (Table 2.6).

In a population-based study of middle-aged semi-urban Nepalese adults, CVH was estimated using validated WHO-STEPS surveys and examination in 2017 using 6 of the 7 AHA metrics, and replacing TC with alcohol consumption (276). Diet was measured only using portions of FFV consumed per day and ideal BMI was taken as $<23\text{kg/m}^2$. Ideal CVH (6-7 ideal metrics) was noted in 14.3% of the participants, intermediate CVH (4-5 ideal metrics) in 67.0% and poor CVH (1-3 ideal metrics) in 18.7%.

In the 2013 nationally representative household survey in Nepal LS7 metrics were measured in adults 15-69y as per AHA definitions except for PA (defined by twice the cut-offs for minutes spent in moderate/vigorous activity per week) (275). Prevalence of ideal CVH (5-7 ideal metrics) was 52%, intermediate (3-4 metrics) 44% and poor (0-2 metrics) 5%. The unusually high prevalence of ideal CVH related to the younger sample (~60% of the participants were 15-44y), despite which the prevalence of ideal BP was considerably low, and no participants had ideal levels of all LS7. The high prevalence of ideal PA (despite the higher cut-off) was due possibly to widespread labour intensive occupational physical activities.

Notwithstanding the differences in how the studies estimated CVH, both reported ideal PA as the most common and ideal BP and diet as the least common metrics; and being female and younger was associated with higher odds of having ideal CVH.

The India Heart Watch study was a multi-city cross-sectional survey that used cluster sampling to recruit 6198 urban middle-class adults 20-75y (62% response rate) in 2006-10 (273). Authors used AHA definitions for all metrics except diet and tobacco use (cigarettes, bidis and smokeless tobacco), and calculated CVH based on number of ideal LS7 as good ≥ 6 , average 4-5 and poor 1-3. Less than 1% of the sample had all 7 metrics at ideal level. Age adjusted prevalence of good CVH was 4% in men and women. CVH declined with age, and this appeared to be related more to declining prevalence of ideal health factors as opposed to ideal health behaviours. In age-adjusted analyses, nil use of tobacco was the best ideal metric, but only a fifth or less

of the sample had ideal BP and PA, with prevalence of ideal diet 10%. The study is limited to an urban setting but a good reflection of the cardiovascular risk profile of localities with higher prevalence of CVD.

Prevalence of CVH was also estimated among adults ≥ 30 y from cross-sectional surveys over 2010–14 in metropolitan cities, smaller cities and rural areas of India (274). Participants were free of CVD. Age-sex standardized prevalence of individual metrics indicated ideal smoking best (77%) and ideal diet (4%) and BP (35%) worst metrics overall. Good, moderate, and poor CVH were 9.9%, 48.9%, and 41.2% respectively. Women, younger adults, the least wealthy, and rural residents had significantly higher achievement of good CVH compared to their counterparts. But LS7 definitions disregarded medication use, diet was based only on FFV, and authors acknowledge that instruments used for measuring PA were known to overestimate PA.

2.3.3.2 Studies Estimating CVH among South Asians outside South Asia

Measures of CVH across ethnic groups and subgroups in Western lands are sparse, and disaggregated data is just beginning to emerge (277). This shows that the prevalence of CVH and its component metrics is variable and differs from general population estimates. In the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study, CVH was measured among 875 CVD free adults (mean age 55y) between 2010 and 2013 (278). Adapted definitions for diet and PA were used. Almost 42% percent of the cohort had ≥ 4 ideal LS7, 27.9% had 3 and 30% ≤ 2 ideal metrics. Those with ≥ 4 ideal LS7 were likely to be female, younger, more acculturated, have private health insurance, and university educated. No participant had all LS7 metrics at the ideal level.

Compared to Non-Hispanic White adults that took part in the 2011-2016 NHANES (279), fewer MASALA SAs (30% vs 34%) had poor CVH (≤ 2 ideal metrics). This was driven by a similarly high prevalence of not smoking (80% in MASALA SAs vs 79% in Non-Hispanic Whites) and a similarly poor prevalence of ideal diet ($< 3\%$); better PA (65% vs 41%) and BMI (44% vs 30%); and lower prevalence of ideal FPG (56% vs 74%), TC (40% vs 54%) and BP (33% vs 40%).

CVH among British SA has not been estimated. However, comparisons of cardiovascular risk factors available from survey data and cohort studies (as described

in 2.2.4.3) indicate that compared to White British adults, British SAs have a higher prevalence of diabetes and sedentary behaviour, lower smoking, obesity, and LDL-cholesterol, and generally similar or higher use of BP medication and fruit and vegetable consumption. How these metrics collectively impact stroke risk remains to be seen.

2.3.4 Life's Essential 8 – the Revised CVH Model

In August 2022, the CVH model was updated from LS7 to Life's Essential 8 or LE8 (280), including sleep as a new metric, replacing TC by non-HDL cholesterol and smoking with nicotine exposure which additionally accounts for second hand smoke, recommending ethnicity-specific BMI criteria for obesity, and using a more granular points system (scale of 0-100) for all metrics to account for even smaller changes. The LE8-CVH score (also ranging 0-100) is calculated as an unweighted average of the 8 items. Examining this upgraded model requires data on sleep and sufficient information on other metrics to apply updated definitions. Evidence is only beginning to emerge supporting its expected inverse relationship with all-cause and CVD mortality (281).

Despite being superseded by LE8, the LS7 metrics are well known and easily measured. Although methods by which diet and PA are quantified can vary and have an element of reporting bias, they have generally been left out of risk assessment tools, while within the CVH model they can inform risk of CVD and stroke to some extent. Greater number of ideal CVH metrics have also found to be associated with lower levels of biomarkers of subclinical CVD (253, 282), and evidence suggests that CVH works through additional as yet unmeasured pathways or aspects of lifestyle that improve health (251).

The CVH score is easy to understand, calculate and track both by electronic health record systems and by individuals if they are made aware (283). Estimating prevalence of CVH metrics and impact of CVH on stroke in groups with a high stroke burden such as older adults and SA individuals, could have the potential to motivate targeted behaviour change as part of patient clinician discussions and to inform population-wide public health campaigns focused on stroke prevention.

The next section discusses assessment of stroke risk as the high-risk prevention approach, available and recommended risk tools, and the evidence on their applicability to older adults and SAs.

2.4 Assessing Stroke Risk

Identification of individuals with high risk of stroke, followed by appropriate therapeutic intervention is complementary to population-wide stroke prevention strategies that shift the distribution of risk factors and risk overall (222). Estimating absolute risks of a clinical outcome is possible through risk prediction tools which statistically incorporate weighted key risk factors to provide an individual-specific probability over a period of time (e.g., 10yr risk of stroke being x%).

The development of risk prediction tools is an elaborate statistical process. A good quality model will have (1) been developed using data from an appropriately designed and sized study which can provide reliably measured predictor and outcome variables relevant to the prediction question (284, 285); (2) appropriate model specification including coding and selection of key clinically relevant effect variables; (3) appropriately handled missing data; and (4) correction for over-fitting and performance checks (including internal validation using techniques such as bootstrapping and k-fold cross validation) in the development data. Models then need to be fit as proposed in new data to assess their applicability beyond the development cohort (286).

2.4.1 Stroke Specific Risk Tools

The most well-known of stroke risk tools is the Framingham Stroke Risk Profile (FSRP), developed using data collected from the Framingham Heart Study in the 1960s and 70s (69, 287). Later tools developed in the USA include the Cardiovascular Health Study (CHS) tool using data from older adults (288), a Revised form of the FSRP (R-FSRP) using more recent waves of the Framingham Heart Study to take into account changing risk factor prevalences and stroke trends (289), and the REGARDS tool based entirely on self-reported data from the prospective bi-racial (White and Black) REasons for Geographic and Racial Differences in Stroke cohort (290). In the UK, QStroke (20) has been derived from large electronic primary care datasets (Table 2.7).

Tools are either sex-specific or include sex as a predictor variable. Included in all models are core risk factors: age, diabetes, some measure of BP and/or antihypertensive use, AF, and past CVD although the components making up the latter predictor vary. Tools differ with respect to other predictors e.g., a measure of walking

time and creatinine in CHS, race in REGARDS, and updated interaction terms in R-FSRP. QStroke is a particularly complex model, containing in addition to the core set: cholesterol, BMI, ethnicity, a measure of socioeconomic status, family history of CHD and various interactions. Most tools calculate the 10y risk of all strokes (IS and HS), although QStroke is limited to IS and includes TIA.

Risk prediction models are expected to perform well in populations that closely resemble those using whose data they have been developed (the development cohort) in terms of baseline risk, risk factor distributions and risk associations. The performance of risk tools in 'plausibly related' populations i.e. their generalizability to individuals from a geographically/ethnically diverse background or from different epochs associated with differentially evolved clinical/preventive practices, is examined through 'external validation' studies (286). These specifically assess the applicability of tools in the new setting using two indicators, (1) discrimination – how well a model separates participants that go on to have the event from those that do not (ranging from as good as chance, a C-index of 0.5, to perfect discrimination, a C-index of 1) (286), a value <0.7 is considered suboptimal (291); and (2) calibration - the accuracy with which predicted risk of the event agrees with observed risk measured as a ratio of predicted to observed risk overall and/or graphical comparisons across the range of predicted risk. Section 3.8.6 has further details.

Performance of risk prediction tools in populations beyond the development set can be limited firstly by the quality of the original model, and additionally, by features of the new data. These include case-mix i.e., the distribution of predictors (e.g., age range, blood pressure, proportion of smokers) as well as risk in the validation setting (-a model may not be able to discriminate well between individuals who are all at high risk); sample size; the availability of and congruency of definitions of predictors/outcomes which comprise the model in new data; and by differences in healthcare provision between the development and validation cohorts (286).

Thorough evaluation of model performance in data that is representative of the population in which the model is going to be implemented, including in key groups based on sex, race etc is hence critical (292). This is because even though external validation cannot by itself capture the clinical impact of using a risk prediction model, it is only through external validation that models can be considered for this

assessment. Transparent reporting of both development and validation procedures helps ensure this is done in a scientifically sound way (293).

2.4.1.1 Studies Validating Stroke Specific Tools in Older Adults

External validation studies have mainly been conducted on the Framingham stroke tools (Table 2.8). In a recent examination of the original FSRP among US older adults of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, stroke risk was overestimated by 1.74 times with suboptimal discrimination (C-index 0.653) (294). Few assessments have been conducted in the older European population, and findings remain inconclusive. In adults (55-74y) from Rotterdam, the FSRP and CHS predicted the probability of having a stroke well in those at intermediate risk, but overestimated probabilities for those at higher risk. Discrimination for both tools was acceptable at C-index 0.75 but fell to 0.69 in the subgroup $\geq 65y$ (295).

In validation among French older adults (65-85y), the FSRP was massively mis-calibrated, overpredicting the risk of stroke in both men and women by almost 4 times, with discrimination 0.70 in women and 0.67 in men (296). The Rotterdam and French cohorts began much later than the original Framingham study and validations were conducted over a shorter 5-6y follow-up.

In a 10y follow up of the same French cohort (289), external validation of the R-FSRP (with a more contemporaneous development sample) indicated it was well calibrated, but C-indices were 0.72 in women and 0.70 in men. Yet, performance of both FSRP and R-FSRP in a later wave of the Rotterdam study (mean age 70y) was inadequate - showing significant mis-calibration, with discrimination C-indices 0.74 in women and lower at 0.68-0.69 in men (297).

To my knowledge external validation among British adults has only been conducted for an earlier Framingham stroke equation (pre-dating the FSRP) (298). Among International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment-INSIGHT trial participants (55-74y, mean 64y) with a limited number of events and a very short follow up of 4y, this was found to underestimate stroke risk (299). A later validation among QResearch participants 35-74y similarly noted underprediction beyond the 6th decile of predicted risk and lower discrimination in comparison to QStroke (20).

Validation of QStroke conducted in the Clinical Practice Research Datalink, a parallel general practice data independent of the derivation sample, showed generally good calibration and discrimination: C-indices 0.882 in women and 0.869 in men. However, restricting analyses to complete cases (only a third of the eligible participants) reduced discrimination to 0.794 in women and 0.771 in men (300). Additionally, 80% of participants in both the development and validation samples were <65y in age and QStroke remains to be validated in an independent prospective cohort of older British adults.

2.4.2 Composite CVD Risk Tools

Current clinical guidelines recommend assessing stroke risk in combination with the risk of CHD using composite-CVD risk tools such as QRISK3 developed in England and Wales (32), PCE in USA (30), and Systematic COronary Risk Evaluation-2 tool, SCORE2 in Europe (31) (Table 2.9). Thresholds of risk are defined based on evidence of clinical- and cost-effectiveness analyses, beyond which individuals become eligible for lifestyle and pharmacological interventions for example, >10% 10y risk of CVD estimated by QRISK3, leading to offer of lipid lowering medication (32).

Composite-CVD risk assessment was deemed appropriate because of the similar aetiology of, and hence preventive approaches to, CHD and (ischaemic) stroke (301); because including stroke in the risk outcome of prediction tools often meant individuals (especially in intermediate risk category) crossed the threshold for preventive intervention (302) that was likely beneficial for global vascular risk (303); and because of the social, economic and public health burden of stroke and its greater prevalence in certain populations (304). Although it was acknowledged that HS had a different underlying pathophysiology, most composite-CVD risk tools (except QRISK) did/do not differentiate between stroke subtypes, on account of hypertension being an important risk factor of both IS and HS, and of the smaller proportion of HS unlikely to have a bearing on the risk estimates of aggregating the two types (304).

2.4.2.1 Methodological Issues in Use of Composite Risk Tools in Older Adults

However, some methodological questions remain regarding the use of composite-CVD tools. As described in section 2.2.5.4, despite the overlap of risk factors, their relative contributions towards CHD and stroke are different. More recent work using large primary care electronic health records linked to hospital and mortality data, has

further supported the heterogeneity in associations of BP, smoking and diabetes with CVD subtypes as opposed to composite-CVD and raised interest in disaggregating CVD risk to inform clinical discussions and decisions (61-63). This is particularly relevant if outcomes are differentially meaningful to individuals (62) - a disabling stroke may impact quality of life more dramatically than a cardiac event (305).

Although there is allowance for finding the risk of component outcomes by scaling total predicted risk by the proportion of the composite outcome formed by that component, whether this captures the true risk of stroke in older adults remains unclear. This is related to two concerns.

Firstly, most CVD risk tools (57, 58, 306), except the recently developed SCORE2 for Older Persons, SCORE2-OP (307) have been developed from predominantly middle-aged cohorts (Table 2.9). As described in section 2.2.4.2, ageing is accompanied not only by attenuation (46, 47, 177) but also reversal (44) in risk factor CVD associations. And the accuracy of even composite-CVD risk prediction becomes questionable in older adults (291, 308, 309). For example, in an almost complete national dataset, Mehta et al used equations derived from 30-74y adults in New Zealand to predict 5y risk of CVD among nearly 125000 adults 75-89y (mean 80y) (309). Discrimination overall was 0.62 at best, and worsened with increasing 5y age bands. The equations underpredicted risks in women, especially in older groups, and overpredicted risks in men, especially among higher deciles in the oldest men.

Secondly, as adults move from middle to older age, stroke forms a greater proportion of CVD compared to heart disease (13, 67, 171). Most tools are developed using time-to-event models in which follow-up stops at the first event irrespective of type, discounting any future events. In the predominantly middle-aged cohorts from which the tools are developed, more events are likely to be CHD. Scaling factors from these cohorts may therefore be inaccurate for older populations.

So far, very few studies (Table 2.8) have validated composite-CVD risk tools for predicting *stroke* as a specific outcome in old age.

2.4.2.2 Studies Validating Composite CVD Risk Tools for Stroke Risk Prediction

D'Agostino et al noted that the Framingham General CVD risk profile derived to predict the combined risk of CHD, IS, HS, TIA, HF and intermittent claudication, discriminated well when used for predicting the 10y risk of a first stroke, especially in men (C-statistic

0.826), with little miscalibration (Table 2.8). However, this assessment was done in the same middle-aged cohort (mean age 49y) from which the function was developed and expected to be optimistic. The number of stroke events was also limited (306).

When the same risk function was examined in 9638 middle-aged French and Irish men free of CVD, discrimination for stroke was found to be modest (C-index 0.68) and the risk of stroke noted to be overestimated by two folds (310). In the authors' opinion this resulted from different risk factor distributions and baseline risk of European vs US men.

Flueckiger et al (294) externally validated the PCE for predicting strokes in CVD free MESA participants of mean age 62y. However, this was applied without scaling. The discrimination was 0.716, but PCE was as a result found to massively over-predict (by four folds) the risk of stroke.

A report published while this literature review was being updated (311) compared R-FSRP, PCE and the REGRADS self-reported tools for prediction of stroke risk in more than 62,000 individuals from pooled US cohorts. Authors described very similar discrimination among the tools (~0.72), but over-estimation of risk by (scaled) PCE and R-FSRP overall, and worse discrimination and calibration in those 60y and older.

2.4.3 Competing Deaths and CVD Risk

A further consideration in old age is the risk of death from non-stroke or non-CVD causes, which precludes the occurrence of stroke. Ignoring the probability of death can assign individuals a higher than 'realistic' probability of experiencing stroke (124). The modelling of most tools does not account for this eventuality. When risk predictions from such tools have been validated externally against observed risks that consider competing deaths, varied results have been reported. However, studies are limited to having examined the effect of competing risks on the prediction of composite-CVD risk (Table 2.10).

In a large primary care electronic health record data set linked to hospital and mortality data, Livingstone et al noted systematic over-estimation of CVD risk by QRISK3 in adults >65y when using validation models that adjust for competing non-CVD deaths (312). However, this was accompanied by large amounts of missing data which necessitated imputation, significant loss to follow-up, and an index date almost 6y later

than the QRISK development cohort which may partly be underlying the overprediction.

Nana et al (313) compared the 5y performance of PCE in a pooled sample of 4 well-known US cohorts, among adults >75y vs 40-74y. Both discrimination and calibration were poor in older men and women, with PCE overestimating risk particularly when accounting for competing deaths. However, the fact that the cohorts were used in developing PCE and that the validation waves were aligned with more recent preventive practices than the development waves may both be influencing performance and utility.

Interestingly, in a 10y external validation study among older adults (mean age 72y) free of CVD from the CHS cohort, PCE had an overall discrimination of 0.68-0.69, and was generally well calibrated even when competing risks were adjusted, except for over-prediction in the highest risk categories (314).

2.4.4 Summary of Evidence on Stroke Risk Prediction in Older Adults

Stroke risk prediction is possible using stroke-specific and composite-CVD risk prediction tools. The few studies that have examined validity of stroke-specific risk tools in older adults in prospective cohorts indicate modest discrimination and generally over-estimation of risk. Evidence is insufficient to support or reject the accuracy of commonly used CVD risk tools for predicting stroke risk in old age.

Nevertheless, if different subtypes of CVD events drive risk in different age-groups, knowing the absolute risk of stroke in old age becomes even more important when we consider that (1) the ratio of harm vs benefit of interventions such as statins is less clear for primary prevention of stroke among older people (315, 316); and (2) preventive work up and interventions unique to stroke such as cardiac/carotid imaging, anticoagulation and revascularization may be more worthy of consideration in older adults (27, 65).

2.4.5 Stroke Risk Assessment in South Asians

Starting with the Framingham models, CVD risk prediction tools have been developed from predominantly Caucasian cohorts. With SAs having different risk factor distributions and vulnerability to these risk factors, such tools are likely to be inaccurate. Further, age being a dominant predictor in CVD models, and SAs being younger at the time of a first CVD event, tools are likely to underpredict risk (317).

Stroke forms a greater proportion of CVD in SAs compared to MI and WHO risk prediction charts estimating the combined risk of fatal or non-fatal acute MI and stroke have recently been updated to reflect the risk factor levels and CVD incidence of the 21 GBD regions, including South Asia (194). However, these models have also been developed using prospective cohorts from the Emerging Risk Factors Collaboration from mostly high-income countries. There are no models developed exclusively from or for SAs.

Notably, there are no stroke-specific models for SAs and no formal validation studies of existing stroke-specific tools. Very early work based on risk factor levels from 700 SA and 800 European men and women from the Newcastle Heart Project noted indirectly that the Framingham stroke model predicted lower stroke mortality risk among SAs relative to Europeans when compared to national mortality data which indicated otherwise (318). The FSRP and R-FSRP have been examined in mixed race cohorts in the USA, but none have included SAs (289, 294, 319). And although QStroke (20) includes ethnicity as a predictor, it has not been independently validated among SA cohorts.

Composite-CVD risk tools are being examined in SA countries, but focus is limited to comparing performance on classifying participants regarding statin eligibility cross-sectionally, and prospective validation studies for both composite-CVD and stroke risk prediction have yet to emerge. So far agreement between tools has been poor when examined among acute CHD patients (320, 321) and in primary prevention cohorts (322, 323), with the WHO risk calculators also performing poorly (321).

In the UK, prior to the QRISK models now in use, a multiplication factor of 1.4 was applied to the estimate given by the Framingham model in use for CVD risk prediction for SA men (324). However, this was criticised for being based more on expert agreement than individual-level data, and for ignoring the higher risk in SA women (325). Earlier, a modified Framingham risk calculator for ethnic minorities – ETHRISK, had also been developed using primary care data in the UK in 2006 but this excluded diabetes as a risk factor and remained unvalidated (326).

The initial QRISK model was then updated, and SA ethnicity was incorporated into QRISK2 as a predictor. The model performed better than the modified Framingham score among SAs in a validation exercise using primary care health records (325). But

external validation of QRISK2 in SABRE SAs (220 events among 1317 participants) without baseline CVD, mean age 51y (327), indicated underestimation of risk in both men (ratio of predicted to observed risk: 0.71 [0.64-0.78]), and especially in women (0.52 [0.34-0.72]), mainly because of underprediction in the mid-high deciles. Discrimination was acceptable (C-index 0.73-0.75), but lower than that reported in the primary care validation (325).

However, the SABRE validation was limited by number of events in the 10y follow-up especially in women and in having assumed null values for some of the QRISK2 variables. The current recommendations from National Institute For Health And Care Excellence (NICE) (32) suggest using the updated QRISK3 model for CVD risk assessment in SAs, which retains SA subgroups as predictors.

In the US, performance of CVD risk tools in migrant SAs has not been tested prospectively. In cross-sectional analysis among SA participants of the MASALA cohort, PCE predicted risks were found to be discordant with indicators of subclinical atherosclerosis (328). In a retrospective analysis of a cohort of SAs (30-70y) without CVD who were members of a US health management organization, the PCE was found to underestimate 10y CVD risk across all risk categories and *significantly in low and borderline* risk groups, and in all patterns of statin use (329). Current US guidelines recognize this underprediction and recommend considering SA ancestry as a risk enhancer (30).

In summary, the lack of prospective SA cohorts with sufficient follow-up and events has not made it possible to develop or extensively validate stroke-specific or scaled CVD prediction tools. However, the indication is that risk prediction in SAs needs to be improved.

2.4.6 Alternate Models for Risk Prediction

Lifetime Risk

Lifetime risk estimates the chance of developing a disease before the end of life, and is based on statistical methods that factor in the chance of dying from causes other than the cause of interest across the ages. As such lifetime risk of CVD has been endorsed as a helpful tool for improving risk communication and behaviour change. But its main utility is understood to be among younger individuals (330, 331). This is because with age playing a key predictor role in CVD risk estimation models,

conventional 10y predicted risks for younger individuals often fail to cross set intervention thresholds, even while their risk factor burden would indicate otherwise.

Given this, lifetime risk tools may be appropriate for predicting stroke risk among SAs, who often experience events at comparatively younger ages and for whom 10y risk prediction tools can underestimate risk. Thus, lifetime risk models should be examined once enough prospective data for SAs is available.

However, it has been noted that 10y risk prediction generally performs well for individuals in whom life expectancy approaches 10y (332) and lifetime risk models may have limited applicability among older adults. Additionally, lifetime risk alone cannot be used for decision making regarding drug therapy (330-332). Considering older age can be associated with rapid fluctuations in health states, and the impending need is for short-term decision making to be better informed; providing older adults more frequently with more precise estimation of even shorter-term risk (3-5y) for composite-CVD as well as individual components of CVD events, may lead to more meaningful physician-patient discussions on (achievable) short term lifestyle goals as well as decisions on the risks and benefits of initiation, up titration or stepping down of drug therapy (70, 333).

Dynamic vs Static Risk Prediction

The conventional way of predicting CVD risk, including all of the tools described so far, is through a 'static' model i.e., one that uses a single time point measurement of the predictor values. In comparison, a 'dynamic' risk prediction model makes use of repeat longitudinal measurements and gets 'updated' with this information. Dynamic risk prediction models have been considered based on simpler strategies such as last observation carried forward or cumulative mean of a time varying predictor (Sweeting et al, 2017), as well as more complex methods. The latter refit models (334, 335) with predictor values estimated using linear mixed effects at each new 'landmark' point in time, including only data (risk set) for individuals who have survived to the landmark time; followed by fitting a Cox model to each risk set at each landmark time. Such dynamic risk prediction models take account of change in predictor(s), survival up to landmark time and have a separate set of effect size estimates (beta coefficients) for each time point. As a result, their prediction accuracy is thought to improve, leading to more clinically relevant decisions. Research into development and comparisons of

dynamic CVD risk prediction is evolving (334, 336, 337). Moreover, landmarking dynamic models may be a computationally efficient way of utilizing the large amounts of sequential data available in electronic health records. It remains to be established however if dynamic models that predict updated risk over shorter time frames are able to change clinical outcomes for older adults.

2.4.7 Use of Biomarkers in Improving Risk Prediction for Stroke

The use of novel predictors in addition to traditional risk factors, to refine CVD risk prediction has been increasingly explored. This is done with the aim of improving identification of those most (at high risk and) likely to experience an event and hence most likely to benefit from allocation of (often resource limited) interventions, as well as those in whom unnecessary intervention (and its associated adverse effects) can be avoided. The next section discusses Natriuretic Peptides as blood markers of stroke risk and the limitations in evidence for their potential use in stroke risk prediction in older adults and SAs.

2.5 Blood Markers of Cardiac Strain/Injury and Stroke

A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention' (338). Biomarkers can be measured in blood or assessed through means such as imaging; and are associated with the disease outcome statistically although may not be causally linked.

For a biomarker to be of practical use, it should be inexpensive and easy to measure, reliable, acceptable and harmless to individuals, applicable to different age groups, sexes and ethnicities and add value to known prediction models enough to change or guide management (339). Assessing the added value of a biomarker begins by establishing independent associations with the outcome of interest. But further key criteria include ability to improve model discrimination (as measured by Area Under the Receiver Operating Curve-AUROC or C-indices) and importantly to reclassify individuals to more appropriate risk categories defined ideally by clinically relevant risk thresholds (as measured by net reclassification indices-NRI) (71). Section 3.8.7 has further elaboration.

Examples of biomarkers examined for CVD risk prediction include CRP as a marker of inflammation, albuminuria as a marker of renal function, coronary artery calcium (CAC) as a risk marker of subclinical atherosclerosis, and Natriuretic Peptides (NPs) and Troponins as indicators of compromised cardiac structure and function (340). Evidence indicates that the added value of CRP in improving CVD risk classification is minimal (341), and CAC is limited by availability, cost-effectiveness (342), uncertainty in its role with respect to stroke (343) and potential risk of radiation exposure (341). In comparison NP testing is cheap, safe and already forms part of standard clinical practice for HF diagnosis and management (344, 345). NPs have shown promise for improving composite-CVD risk prediction (346). The sections ahead discuss mechanisms linking NPs to stroke and the gaps in evidence regarding their role in improving stratification specifically of stroke risk.

2.5.1 Natriuretic Peptides: Physiology and Factors Affecting Distribution

Natriuretic peptides (A-, B- and C-NP) are a class of proteins released by cardiac muscle cells in response to volume and pressure overload/stretch and ischaemia (74, 347). Synthesis of BNP initially takes place as a pro-peptide which undergoes

cleavage into the active hormone BNP and the amino-terminal inactive fragment or NT-proBNP. Synthesis takes place predominantly in ventricular muscles although atrial muscle cells can also produce BNP under pathological states. BNP in turn reduces blood pressure, volume, and sodium levels through renal and cardiovascular effects (74). Although BNP and NT-proBNP levels correlate well, BNP has a shorter half-life of 20 min as opposed to 1-2hrs of NT-proBNP, which is therefore less likely to show fluctuations and more reflective of chronic disease states (74).

BNP is cleared predominantly through enzymatic degradation, membrane receptors and by passive renal excretion, and NT-proBNP mainly through renal clearance. Apart from disease states such as HF and coronary artery disease, levels are also influenced by age, gender and obesity such that higher mean values are present in women, older adults and non-obese adults (74, 348).

Clinical thresholds of NT-proBNP are widely used for diagnosis and prognosis of symptomatic HF and prognosis of stable coronary artery disease and acute coronary syndromes. Cut-offs can be age-dependent, such as those recommended by US Food and Drug Administration—a threshold of <125 pg/mL among individuals younger than 75 years and of <450pg/mL among individuals 75 years or older, commonly used to rule out chronic HF (349). NICE suggests 400pg/ml as cut-off for chronic HF (345), and 300pg/ml for new presentation of acute symptoms to rule out HF (344). In primary care for screening of asymptomatic ventricular dysfunction, levels lower than those seen in acute presentations of dyspnoea, such as 125pg/ml are recommended for all ages (350). Epidemiological studies have also taken 100pg/ml as a cut-off for elevated NT-proBNP among CVD free middle-aged adults (351).

2.5.2 Mechanisms Linking NT-proBNP to Stroke Risk

NP levels *below* clinical cut-points and indicating subclinical heart disease have also been linked to future CVD events including strokes (346, 352). Mechanisms underlying this association include valvular heart disease, paroxysmal AF, atrial cardiopathy or age-related atrial substrate changes predisposing to CE strokes (353, 354). The association may also reflect shared risk factors between coronary and cerebrovascular pathologies although in many cases adjustment for these factors does not entirely attenuate the link. Apart from residual confounding, there may be other pathways such as inflammatory conditions which trigger NT-proBNP release and atherosclerosis

(355), the effect of NPs on endothelial permeability (356) or its long-term association with development of hypertension (357) which can predispose to both atherosclerosis, and vascular bleeding.

However, NPs also mediate lipolysis in adipose tissue and induce regeneration of blood vessels in vascular tissue (358). Studies have additionally noted a lower risk of incident diabetes associated with higher NT-proBNP levels (359, 360) indicating that the relationship between NPs and stroke risk may be more complex.

2.5.3 Studies Exploring NT-proBNP and Stroke Risk Prediction in Older Adults

As age attenuates associations between traditional risk factors and cardiovascular outcomes, markers which remain robust/consistent such as NT-proBNP (43, 361) are likely to show more incremental value for risk prediction. However, the utility of NT-proBNP as an added biomarker has mostly been examined in middle-aged cohorts (76, 362, 363) or limited to prediction of combined events if in older adults, often in combination with other biomarkers (333, 364-366). Few studies have quantified long-term associations between NT-proBNP and stroke in older adults, and even fewer have reported on the ability of NT-proBNP to reclassify stroke risk.

In an early meta-analysis, associations of NPs with CVD were estimated as pooled risk ratios comparing the top third of the NP distribution with the bottom third using published estimates from 40 unique cohorts up to 2009 (352). Only 13 studies (6 being part of clinical trials) reported separately on stroke (2063 events in 567764 individuals), giving a pooled RR of 1.93 [1.58-2.37]. Most of these were short with only 3 reporting a median follow-up of 9-10y, and degree of confounder adjustment varied although all adjusted for core risk factors. It is also unclear how many of these participants were CVD free at baseline. Improvement in discrimination on adding NP was available only for the composite-CVD outcome and reported to be modest (0.01-0.1 increment in AUROC or C-index). Sufficient data on the performance of NPs in risk stratification for specific CVD subtypes among low and intermediate risk groups (i.e., primary prevention groups) was lacking.

These findings were updated in an individual-participant data meta-analysis based on evidence published until 2014 (346). With 3768 stroke events in 76839 individuals free from a broad range of CVD conditions, the pooled risk ratio of stroke (adjusted for age, smoking, diabetes, SBP, TC and HDL and stratified by sex) among those with NT-

proBNP levels in the top third vs the bottom third of the distribution was of a similar magnitude 1.81 [1.58-2.07], and as strong as the association with CHD. NT-proBNP improved C-index of stroke beyond the base model by +0.011. Reclassification was only reported for the combined risk of stroke, CHD and HF. NT-proBNP improved specificity of the composite outcome by about 4%. Studies were from Europe and USA except for 1 study from Japan. Although this pooled sample included older adults (mean 61y±10) and had median follow-up of 8y, subgroup analyses indicated (non-significant) weakening of the NT-proBNP stroke association with increasing age, and with increasing follow-up ($p=0.083$). Although prevalent CVD was excluded, participants with incident cardiovascular events such as HF, AF and MI during follow-up were also censored.

The main studies examining the NP-stroke association in older adults from this meta-analysis and studies published since 2014 are summarised in Table 2.11.

In the Atherosclerosis Risk in Communities (ARIC) study, Folsom et al (77) reported increased risk of all strokes across quintiles of NT-proBNP as a significant trend. This was especially true for CE strokes although numbers were small and CIs wide. Trends persisted after adjusting for prevalent and intervening CHD, HF and AF. NTproBNP caused a modest increase in discrimination (+0.01) for 10y predicted risks of total strokes. However, this analysis included participants with prevalent CVD, adjusting for prevalent conditions in models. It can be argued however that such individuals are a group under surveillance and likely in receipt of various preventive managements, the influence of which may not be accounted for by simple adjustment. The study also reported a sum NRI which is uninformative (71).

In a later analysis of the same participants (367) excluding those with prevalent stroke and CHD, and followed for a median of 15y, log-NT-proBNP was found to be associated with IS with HR 1.55 [1.40-1.71], across all levels of subclinical atherosclerosis as measured by combinations of carotid intima media thickness and presence of plaque. However intervening events were ignored, and incremental performance was not examined.

In the biracial REGARDS study (263), positive trends were also reported between NT-proBNP and IS and all IS subtypes. These were weak for SVD and strongest for CE (9-fold risk in top vs bottom quartile). Excluding those with HF, left ventricular

hypertrophy (LVH), chronic kidney disease (CKD), and AF caused little change. This analysis did not find significant interactions with age, sex or race. However, event numbers were small in some quartiles and follow-up limited to 5y. Improvement in category-less NRI was reported but the clinical importance of category free reclassification is unclear. The study did not carry out adjustment for incident AF and did not include HS as part of its outcome.

Recently, Zhu et al (368) used 14y follow-up of the Rotterdam 1997-2001 cohort of CVD free older men and women to examine prediction of stroke events by NT-proBNP, and also reported stroke-specific reclassification for events and non-events separately. HRs per SD-log NT-proBNP were similar at ~1.4 in both sexes. NT-proBNP also modestly improved 10y risk discrimination of stroke and was noted to correctly upgrade 4% and 9% of stroke cases in women and men respectively to higher risk categories based on AHA recommended CVD risk thresholds, while also leading to smaller amounts of statistically non-significant misclassification of non-cases.

2.5.4 Studies Examining Associations of NT-proBNP with TIAs in Older Adults

Stroke presentations range in severity from TIAs, to non-fatal strokes to death. Risk tools such as QStroke (20), QRISK3 (58) and FSRP (287) predict the collective probability of these events. Given the incidence of TIAs also increases with age (79), risk tools could benefit from integrating blood biomarkers that relate subclinical cardiac malfunction at older age to all relevant endpoints, to improve risk assessment and modification in older adults. But evidence on prospective associations of markers of subclinical cardiac dysfunction with TIA as an outcome separate to stroke, is limited.

Portegies et al (81) examined associations of NT-proBNP with TIA included as a stroke event and separately. In participants of the Rotterdam study, they noted that associations of the biomarker with a composite stroke and TIA outcome were present in both men and women, but this was driven by IS and HS in men and IS and TIA in women. These patterns did not change with exclusion of and censoring those with heart disease (CHD, AF, HF) except for attenuation of risk of HS in men. The study has a reasonable follow-up but does not look at prediction performance with respect to these outcomes. And whether subclinical heart disease leads to more severe presentations in men compared to women remains to be confirmed.

In the UK, 75% greater risk of a first stroke or TIA in the top vs bottom tertile of BNP distribution has been reported among older (mean age 62y) CVD free Welsh men of the Caerphilly cohort. The men were followed for an average of 10y, and competing risk methods adjusted for non-stroke CHD and HF occurring prior to strokes (369). However, improvement in discrimination was not reported because a p value <0.01 was not achieved for the association.

Associations of biomarkers with a composite of stroke and TIA events were also examined in a mostly older age sample of community dwelling CVD free adults in New Zealand (370). Multivariable adjusted risks were 4 times higher for the 4th and 5th quintile of NTproBNP distribution. However, for clinically defined thresholds, a threefold higher risk was present for levels >1000pg/ml but did not reach statistical significance. This may be related to the small number of events in the short 5y follow-up. Improvement in discrimination was not reported for stroke events separately and was small for composite-CVD. Incident events were not adjusted. A parallel examination conducted in CVD free adults (mean age 65y) recruited from the Vitamin D Assessment (ViDA) trial yielded slightly better performance indices but was similarly limited by number of events as well as a healthy volunteer bias.

2.5.5 NT-proBNP and Stroke Associations in SA

Formal comparisons between ethnic groups in multi-ethnic cohort studies indicate that Chinese and Black populations have lower average levels of NT-proBNP compared to their Caucasian counterparts (371). Black groups especially have been noted to have 30-40% lower levels and it has been suggested that this may be the reason underlying their greater risk of hypertension (82). However, positive prospective associations between NT-proBNP and stroke have been reported in expected directions among Blacks (77, 263), and among Japanese adults (372).

To my knowledge, the only report of a comparative association for NT-proBNP among SAs is for older participants of the SABRE follow-up visit 2, including those with clinical CVD. In this analysis hyperglycaemia (measured by HbA1c levels) was associated with worse global cardiac dysfunction (measured by NT-proBNP) cross-sectionally only in SAs and not Europeans; the association being abolished by adjustment for cardiometabolic risk factors. SAs were found to have higher mean NT-proBNP levels compared to Europeans when adjusted for left ventricular mass (373). It has not

however been investigated if levels of subclinical cardiac dysfunction measured by NT-proBNP are prospectively linked to CVD and especially stroke risk in SAs.

2.5.6 NT-proBNP as a Stroke Risk Predictor Independent of Troponins

Troponins (isoforms T and I) are contractile protein fragments that leak into the general circulation with cardiac muscle stress and damage (374), and universally used for diagnosis of acute coronary syndromes (375). Minor stable elevations, detected by highly sensitive assays have, like NTproBNP, been linked with early cardiac structural and functional changes (376) and to future CVD, including stroke (376-382).

It is thought that mechanisms triggering the release of Troponins and NPs are slightly different (348), and the physiological roles of NPs broader (358), hence plausible that the biomarkers contribute different information regarding CVD or stroke risk. There is some indication that NT-proBNP may be a stronger predictor of stroke mortality than Troponin-T (78), however hardly any studies have examined if NT-proBNP remains associated with the range of fatal/non-fatal stroke and TIA events when adjusted for Troponin, in CVD free older adults and none to my knowledge in CVD free SAs. Examining this may help identify which of the 2 biomarkers is a better candidate for improving stroke risk prediction and potentially has a greater role in informing primary prevention of stroke in these population sub-groups.

2.6 Summary of Literature Review and Gaps in Evidence

This literature review has

- Highlighted the greater burden and differing subtypes of stroke in older adults, and in SAs compared to Western Caucasian populations.
- Elaborated on the different distributions, risk factor-stroke associations and hence the differing impact (PAFs) of traditional risk factors in these groups.
- Described the CVH model, and how it is as yet an unexplored construct to study the collective impact of traditional risk factors on stroke, and hence the benefit of their modification for population-level primary prevention of stroke in older adults and especially in SAs.
- Described the overlapping yet distinct pathologies of stroke and CHD. And argued why the current norm of stroke risk to be estimated as part of CVD risk needs to be re-examined in older adults, particularly given (1) most risk tools have been developed using data from middle-aged individuals, (2) stroke forms an increasingly greater proportion of CVD relative to heart disease in old age, and (3) old age is associated with altered risk benefit ratios of preventive interventions and with competing causes of death.
- Summarised the established positive associations of NT-proBNP with stroke generally, while emphasizing the limited evidence on long term associations of NT-proBNP with the spectrum of stroke events (inclusive of TIAs) in older adults, and its unconfirmed utility in improving individual-level stroke risk classification and guiding stroke prevention in old age.
- Underscored the lack of dedicated stroke/CVD risk tools for SAs, and the lack of prospective SA cohorts that would allow validation of current Western prediction models in SAs, with the indication that risk with available tools is generally underestimated.
- Described how associations between NT-proBNP and stroke events in SAs remain to be confirmed; and proposed that until risk tools can be developed from SA populations, the role of NT-proBNP in improving individual level prediction and reclassification of stroke risk beyond traditional risk factors is worth examining.

The thesis will address these gaps through the 4 specific objectives enumerated earlier in Chapter 1; and listed here again.

1. Examine the prevalence of CVH (and its component modifiable metrics), its associations with and its impact on, stroke risk in older age; and among SAs.
2. Externally validate and compare the performance of stroke-specific (FSRP and QSTROKE) and composite-CVD risk tools (QRISK3 and PCE) in predicting stroke risk in older age.
3. Examine independent long-term associations of NT-proBNP with stroke events (TIAs, non-fatal and fatal strokes) in older age; and with total stroke among SAs.
4. Examine if addition of NT-proBNP to models containing traditional risk factors improves stroke risk stratification in older age; and for SAs.

2 Literature Review

Table 2.1 Studies estimating Population Attributable Fractions (PAF%) [95% CI] of stroke events in older adults

Author, Year Location	Nakayama, 2000 Japan (227)		Bos, 2014 Rotterdam (225)	Park, 2015 Korea (228)		Hussein, 2016 Indonesia (229)		O' Donnell, 2016 INTERSTROKE* (27)	
Type of study	Prospective		Prospective	Case control		Survey prevalence linked to literature-based Relative Risks		Case control	
Outcome	All strokes		All strokes	Ischaemic Strokes		All strokes		All strokes	
Methodology for PAF	Miettinen's Equation		Exclusive attributable risk	Levin's Formula		Levin's Formula		Confounding/Multivariable adjusted modification of Levin's formula	
Age (y)	40-64	≥65	Median 68	46-65	≥66	<55	≥55	≤55	>55
Risk factors									
High blood pressure	Untreated 13.5 [6.3-20.1]	Untreated 4.9 [-2.5-11.7]	36 [26-49]	Men 22.7 [14.9-30.4] Women 22.7 [11.6-34.0]	Men 23.7 [14.7-32.2] Women 23.4 [11.4-34.3]	49.0 [46.5-51.6]	52.9 [49.6-56.3]	49.7 [46.0-53.4]	46.0 [42.2-49.8]
Diabetes			4 [2-7]	Men 14.6 [9.5-20.1] Women 7.8 [2.5-14.5]	Men 12.5 [7.3-18.1] Women 15.1 [9.4-21.1]	6.3 [4.8-7.9]	5.8 [2.8-8.8]	5.6 [2.5-12.1]	3.6 [1.4-8.8]
Dyslipidaemia				Men 2.5 [-0.7-6.3] Women -2.9 [-8.0-3.4]	Men 5.8 [2.6-9.5] Women 3.8 [-1.2-9.3]	10.3 [7.0-13.7]	2.2 [-3.7-7.5]	30.8 [22.6-40.5]	25.6 [20.1-31.9]
Obesity-Body Mass Index			1 [0-92]	Men -0.9 [-1.8-0.7] Women -0.6 [-2.8-4.0]	Men -0.3 [-0.8-0.7] Women -1.3 [-2.6-0.6]	14.6 [11.1-17.9]	0.4 [-1.8-2.8]		
Obesity-Waist Hip Ratio								23.5 [15.2-34.5]	16.0 [9.7-25.2]
Current Smoking	14.9 [2.3-26.0]	0 [-9.3-8.5]	16 [10-26]	Men 37.4 [28.9-45.2] Women 7.7 [1.9-17.0]	Men 16.7 [12.6-27.0] Women -1.0 [-2.8-1.6]	11.1 [6.2-15.4]	3.7 [0.5-6.7]	16.3 [11.6-22.3]	10.9 [8.6-13.7]
Physical Inactivity								35.3 [21.0-52.8]	35.9 [26.4-46.7]

2 Literature Review

Author, Year Location	Nakayama, 2000 Japan (227)		Bos, 2014 Rotterdam (225)	Park, 2015 Korea (228)		Hussein, 2016 Indonesia (229)	O' Donnell, 2016 INTERSTROKE* (27)	
Diet			4 [1-13]^				16.4 [7.9-30.9]	26.5 [20.9-33.0]
Cardiac causes							4.9 [3.8-6.3]	10.8 [9.4-12.4]
Atrial Fibrillation	3.6 [0.3-6.7]	6.0 [1.5-10.3]	2 [1-5]					
Coronary disease			1 [0-8]	Men 2.3 [0.6-4.9] Women 2.4 [-0.1-7.0]	Men 4.1 [1.4-7.5] Women 9.5 [5.1-15.3]			
Alcohol intake							10.9 [6.1-18.7]	4.1 [1.7-9.4]
Stroke history				Men 11.6 [7.3-17.4] Women 10.6 [4.6-21.1]	Men 19.7 [14.5-25.5] Women 17.3 [12.0-23.8]			
Psychosocial factors							22.8 [14.8-33.3]	15.3 [10.5-21.8]
C-Reactive Protein			6 [0-54]^					
Carotid Intima Media Thickness			14 [4-40]^					
Composite PAF			51 [41-62]				92.2 [88.8-94.6]	90.0 [87.3-92.1]

*Uncertainty limits are 99% CI.

^in subset with data on these factors, composite PAF changes from 59 [47-71] (without) to 65 [51-77] (with them).

Definitions of risk factors vary by study.

Table 2.2 Global Burden of Disease Study age stratified Population Attributable Fractions (PAF% - 95% CI) of stroke related disability adjusted life years attributable to 17 risk factors based on 2013 data

Risk factors and clusters	15-49 years	50-69 years	70+ years
Air pollution & environmental risks			
Ambient PM2.5 pollution	23.4% (23.0-23.7%)	19.4% (19-19.7%)	12.4% (12.0-12.4%)
Household air pollution from solid fuels	25.3% (23.6-26.3%)	18.6% (17.2-19.5%)	9.5% (8.7-9.9%)
Lead exposure	5.2% (3.3-7.4%)	8.2% (5.9-10.4%)	5.8% (4.1-7.7%)
Dietary risks			
Diet high in sodium	20% (10.7-31.6%)	28.3% (15.7-41.6%)	18.7% (10.4-27.9%)
Diet high in sugar-sweetened beverages	0.8% (0.5-1.1%)	0.3% (0.2-0.4%)	0.1% (0.0-0.1%)
Diet low in fruits	52.1% (41.5-59.4%)	41.8% (31.8-49.7%)	24.0% (16.4-29.8%)
Diet low in vegetables	32% (28.0-35.3%)	22.5% (19.0-25.7%)	13.5% (11.2-15.4%)
Diet low in whole grains	21.4% (18.3-23.9%)	16.9% (14.2-19.1%)	11.0% (9.0-12.4%)
Alcohol use	8.6% (6.6-9.7%)	8.0% (6.4-9.1%)	5.6% (4.6-6.5%)
Physical activity			
Low physical activity	3.8% (2.8-4.7%)	7.4% (5.4-8.9%)	9.9% (7.3-11.7%)
Tobacco smoke			
Smoking	28.8% (26.2-31.5%)	26.7% (23.7-29.3%)	12.1% (10.6-13.2%)
Second-hand smoke	3.1% (2.9-3.1%)	2.5% (2.4-2.5%)	1.5% (1.5-1.6%)
Physiological factors			
High Body Mass Index	40.8% (36.4-44.8%)	29.2% (25.6-32.4%)	11.7% (9.4-13.9%)
High fasting plasma glucose	14.4% (6.2-22.6%)	13.7% (7.2-19.8%)	9.0% (4.2-14.4%)
High systolic blood pressure	64.6% (60.7-67.7%)	75.2% (70.6-76.3%)	55.2% (49.2-58.8%)
High total cholesterol	6.2% (5.0-7.2%)	6.0% (3.2-8.6%)	2.5% (0.2-6.8%)
Low glomerular filtration rate	5.5% (4.6-6.4%)	6.9% (6.0-8.2%)	8.3% (7.2-9.2%)
Clusters of risk factors			
Air pollution*	41.7% (40.9-42.3%)	34.1% (33.1-34.6%)	20.5% (19.8-20.7%)
Tobacco smoke\$	31.9% (29.7-34.3%)	29.1% (26.5-31.6%)	13.6% (12.3-14.6%)
Dietary risks**	75.3% (71.1-78.7%)	72.7% (66-77.9%)	51.7% (43.2-58%)
Behavioural risks§	82.5% (80.9-84.4%)	83.6% (80.8-85.8%)	64.4% (59.5-67.7%)
Environmental risks¶	44.2% (43.5-45%)	39.1% (37.7-39.9%)	24.7% (23.6-25.3%)
Metabolic risks¶¶	74% (71.6-76.1%)	82.8% (80.1-83.3%)	64.1% (59.2-66.8%)
All risk factors combined	89.6% (88.4-90.6%)	97.7% (96.6-98.5%)	87.4% (83.5-90.6%)

2 Literature Review

*Air pollution cluster includes ambient PM pollution, and household air pollution

\$Tobacco smoke includes smoking and second-hand smoke exposure

**Dietary risks cluster includes diet high in sodium and sugar-sweetened beverages, and diet low in fruits vegetables and whole grains

§Behavioural risks cluster includes smoking (including second-hand smoking), dietary risks (diet high in sodium, diet high in sugar sweetened beverages, diet low in fruits, diet low in vegetables, diet low in whole grains, alcohol use), low physical activity

¶Environmental risks cluster includes air pollution cluster, and lead exposure

¶¶Metabolic risks cluster includes high fasting plasma glucose, high total cholesterol, high systolic blood pressure, high body-mass index, and low glomerular filtration rate

Percentages are not mutually exclusive. The sum of percentages in the columns exceeds the total for all risk factors combined because of overlap between various risk factors. Zero percentage indicates very low numbers

Table adapted from *Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016;15(9):913-24. (226)*

2 Literature Review

Table 2.3 Studies estimating Population Attributable Fractions (PAF%) [95% CI] of stroke for risk factors among South Asian adults

Author, Year Location	Kamal, 2013 Pakistan (232)	O' Donnell, 2016 INTERSTROKE* (27)	Feigin, 2021 GBD South Asia 2019 (2)
Type of study	Case control	Case control	Prevalence from surveys linked to literature-based Relative Risks
Outcome	Ischaemic Stroke (Intracranial atherosclerotic disease)	All strokes	Disability Adjusted Life Years due to all strokes
Methodology for PAF	Not specified	Confounding/Multivariable adjusted modification of Levin's formula	Counterfactual Method
Risk Factors			
High blood pressure	48.7 [33.1-53.5]	47.2 [41.9-52.5]	55.8 [47.7-62.4]
Diabetes	10.7 [9.6-11.8]	-0.1 [-10.0-9.8]	24.7 [17.1-34.4]
Dyslipidaemia		20.4 [9.2-39.4]	5.9 [3.4-9.8]
Obesity-Body Mass Index			22.1 [13.3-31.3]
Obesity-Waist Hip Ratio		32.1 [12.1-45.4]	
Current Smoking		8.0 [2.8-21.1]	13.1 [11.8-14.5]
Second-hand smoking			3.7 [2.7-4.8]
Physical Inactivity		44.7 [21.7-70.2]	1.1 [0.2-2.9]
Diet		-28.0 [-54.4 - -2.0]	
Diet low in vegetables			5.7 [1.8-9.6]
Diet low in fruits			12.8 [7.7-18.2]
Diet low in whole grains			1.6 [0.5-2.4]
Diet high in red meat			1.5 [0.6-2.4]
Diet high in sodium			7.1 [0.6-19.0]
Low glomerular filtration rate			8.4 [7.0-9.8]
Cardiac causes		5.2 [3.9-7.0]	
Atrial Fibrillation		3.1 [1.9-5.0]	
Alcohol intake		10.7 [7.4-15.4]	3.4 [2.1-4.9]
Family history	10.7 [8.8-12.5]		
Education			
Psychosocial factors		8.1 [1.3-36.9]	

2 Literature Review

Author, Year Location	Kamal, 2013 Pakistan (232)	O' Donnell, 2016 INTERSTROKE* (27)	Feigin, 2021 GBD South Asia 2019 (2)
Un/Employment	23.8 [18.7-26.2]		
Income	10.5 [8.7-12.3]		
Chronic Stress	3.1 [2.6-3.9]		
Ambient particulate matter pollution			23.9 [18.4-29.0]
Household air pollution			18.2 [13.0-24.3]
Low ambient temperature			2.4 [-0.2-4.7]
Composite PAF		85.1	84-88%^

*Uncertainty limits are 99% CI.

^Includes high ambient temperature and lead exposure, reported for low to upper middle-income countries.
Definitions of risk factors vary by study.

2 Literature Review

Table 2.4 Definitions for Poor Intermediate and Ideal levels of Life's Simple 7 metrics in adults

Metric	Poor	Intermediate	Ideal
Current Smoking	Yes	Former ≤12 months	Never or quit > 12 months ago
Body Mass Index, kg/m ²	≥30	25-29.9	<25
Physical Activity	None	1-149 min/week of moderate activity or 1-74 min/week of vigorous activity or 1-149 min/week of moderate & vigorous activity	≥150 min/week of moderate activity or ≥75 min/week of vigorous activity or ≥150 min/week of moderate & vigorous activity
Diet pattern score	0-1	2-3	4-5
Total Cholesterol, mg/dl	≥240	200-239 or treated to goal	<200
Blood pressure, mmHg	SBP≥140 or DBP ≥90	SBP 120-139 or DBP 80-89 or treated to goal	SBP<120 and DBP<80
Fasting plasma glucose, mg/dl	≥126	100-125 or treated to goal	<100

Adapted from Lloyd-Jones DM, Hong YL, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction The American Heart Association's Strategic Impact Goal Through 2020 and Beyond. *Circulation*. 2010;121(4):586-613. (52)

DBP: diastolic blood pressure, SBP: systolic blood pressure.

Each of the following dietary components is assigned 1 point: Fruits and vegetables ≥4.5 cups per day, Fish ≥two 3.5-oz servings per week (preferably oily fish), Fiber-rich whole grains (1.1g of fibre/10g of carbohydrate) ≥three 1-oz-equivalent servings per day, Sodium ≤1500 mg per day, Sugar-sweetened beverages ≤450 kcal (36 oz) per week.

Table 2.5 Prospective studies reporting associations of Cardiovascular Health (CVH) and Life's Simple 7 (LS7) metrics with stroke events

Author, Year	Study Design (Location)	Population	LS7 and CVH measures	Stroke Outcome and follow-up	Adjustments	Key Findings
Dong, 2012* (258)	Prospective (Northern Manhattan Study)	N=2981 White 21%, Black 25%, Caribbean Hispanic 54% Adults ≥40y (mean 69y) No history of stroke or MI	LS7 as per AHA definitions. Grouped by number of metrics 0-1, 2, 3, 4, and 5-6	WHO criteria, Neuroimaging, verified by adjudicators Median follow-up 11y	Age, sex (and ethnicity for total cohort effects)	0 with 7 ideal metrics, 4.4% with 5-6 (higher among Whites) Ideal non-smoking behaviour high, and diet component poor, across ethnic groups Inverse gradient between number of LS7 and HR of stroke, though trend statistically not significant in Whites
Kulshreshtha, 2013* (259)	Prospective (REGARDS, US-National)	N=22,914 Adults ≥45y (mean 65y) White 58%, Black 42% No history of stroke, peripheral vascular disease and CHD	LS7 as per AHA except diet and PA LS7 scored 0 (poor), 1 (intermediate), 2 (ideal) Composite score 0-14. Categorical CVH: inadequate 0-4, average 5-9, optimum 10-14	WHO criteria or positive neuroimaging if symptoms <24hrs, verified by adjudicators Follow-up 4.9y	Age, sex, ethnicity, region of residence, alcohol intake, income, education	Optimum CVH higher in Whites (19%) vs Blacks (7%) Smoking and diet best and worst metrics Among Whites, with ref to inadequate CVH, HR of stroke for average 0.71 [0.46-1.10] and optimum 0.49 [0.29-0.89] (p for trend 0.04); HR per unit rise in composite score 0.91 [0.86-0.96]
Gaye, 2017* (56)	Prospective (3C-France)	N=7371 Adults ≥65y (mean 74y), non-institutionalised and without prevalent CVD	LS7 as per AHA except diet and PA Global CVH: Ideal if 5-7 ideal metrics, Intermediate if 3-4, Poor if 0-2. Behavioural CVH (smoking, BMI, PA, diet) and Biological	WHO criteria, Neuroimaging, verified by adjudicators Median follow-up 8.6y	Age, centre, sex, education and living alone. Analyses by metric also adjusted for other metrics. Also for time-	1 person had all ideal LS7, 5% had ideal global CVH Smoking and BP best and worst metrics HRs for intermediate and ideal global CVH: 0.82 [0.64-1.06] and 0.45 [0.20-1.03] p for trend 0.03; and similar magnitudes for Behavioural

2 Literature Review

Author, Year	Study Design (Location)	Population	LS7 and CVH measures	Stroke Outcome and follow-up	Adjustments	Key Findings
			CVH (smoking, BP, TC, FPG) also defined as Ideal, Intermediate and Poor if 3-4, 2 or 0-1 relevant metrics at ideal level		dependent functional disability and depression to test for mediation	and Biological CVH categories Time-dependent functional disability and depression did not mediate the association between global CVH and combined CVD
Itoh, 2022 (265)	Retrospective (Japan)	N=2,728,427 Adults ≥20y (as 20-49y, 50-59y and 60-75y), Without history of MI, angina, HF, stroke or hemodialysis	LS7 as per AHA except diet and PA, measured as number of non-ideal metrics (0-7)	National employees' claims database with ICD10-linked outcomes Mean follow-up 3.3y	Age and gender	Across age-groups, mean no. of non-ideal LS7 increased, % non-ideal BP, FPG and TC increased and % PA, smoking and diet decreased Increasing risk of stroke with number of non-ideal metrics, association attenuated with age, p interaction <0.001 Relative risk reduction on improvement in LS7 also decreased with age.
Chao Han, 2018 (266)	Prospective (China-PAR)	N=93987 Adults ≥20y (mean 52y) Without ASCVD on entry	LS7 as per AHA except diet 6 groups based on number of ideal LS7 ≤2, 3, 4, 5, 6 and 7	WHO criteria, hospital and death records verified by study adjudicators Median follow up of 6, 13 and 15y in the three cohort sources	Age, sex, region, urbanization, alcohol, education, family history of ASCVD, and cohort sources	7% with 7 ideal metrics BP worst, FPG best metric Significant inverse trend between number of LS7 and HR of stroke With ref to ≤2, HR for all LS7 ideal 0.20 [0.15-0.28], and PAR 66.4% [54.1-75.9] Greater protection among younger participants
Zhang, 2013 (260)	Prospective (Kailuan-China)	N=91,698 Adults ≥18y (mean 52y), Without history of MI or stroke	Ideal LS7 with modified definitions for PA, smoking, diet (salt intake)	WHO criteria confirmed by neuroimaging, verified by	Age, sex, education, income. Analyses by metric also	1% with 6-7 ideal metrics Significant inverse trend between number of LS7 and HR of total stroke, IS, ICH

2 Literature Review

Author, Year	Study Design (Location)	Population	LS7 and CVH measures	Stroke Outcome and follow-up	Adjustments	Key Findings
			Grouped by number of metrics 0, 1, 2, 3, 4, 5 and 6-7	arbitration committee Maximum follow-up 4y	adjusted for other metrics.	All ideal metrics (esp BP) inversely associated with total stroke and IS. For ICH only BP reached significance and TC had null association. No interaction between CVH and age $\geq 60y$
Miao, 2015 (261)	Prospective (Kailuan-China)	N=91,598 Adults $\geq 18y$ (mean 52y), Without history of MI or stroke	LS7 with modified definitions for PA, diet (salt intake), smoking LS7 scored 0 (poor), 1 (intermediate), 2 (ideal) Composite score 0-14. Categorical CVH: inadequate 0-4, average 5-9, optimum 10-14	WHO criteria confirmed by neuroimaging, verified by arbitration committee Mean follow-up 6.8y	Age, gender, alcohol, income, education; heart rate, uric acid, and CRP	Mean CVH score 8.6, 35% with optimum CVH With ref to inadequate CVH, HR of stroke for average 0.57 [0.48-0.69] and optimum 0.30 [0.24-0.37] (p for trend 0.01); HR per unit rise in composite score 0.82 [0.81-0.84]
Lachman, 2015 (262)	Prospective (Norfolk, UK)	N=10,043 Adults 39-79y (mean 57y) Without prevalent CVD	Some LS7 definitions modified, HbA1c replacing FPG. LS7 scored 0 (poor), 1 (intermediate), 2 (ideal) Composite score 0-14. Categorical CVH: 0-2, 3-5, 6-8, 9-11 & 12-14	Hospital/mortality linked ICD-10 codes I60-62 Mean follow-up 10y	Age and sex	3% with score 12-14 HbA1c and smoking best, and diet worst metrics. Inverse trend between categorical CVH and stroke, HR in healthiest (12-14) vs least healthy (0-2) 0.16 [0.02-1.37] p=0.09
Gaye 2017 (383)	Prospective (PRIME-France and N.Ireland)	N=9312 Men 50-59y (mean 55y) Without history of CHD and stroke	LS7 as per AHA except diet and treated diabetes Global CVH: Ideal 5-7 ideal LS7, Intermediate 3-4, Poor 0-2. Composite CVH score 0-14. Behavioural CVH (smoking, BMI, PA,	WHO MONICA criteria, reports linked to hospital or primary care records, adjudicated by committee Median follow-up 10y	Age, education, study centre, social status, living alone, marital status, family history of CHD, fibrinogen	7% with ideal global CVH. Non-diabetes status best and diet worst metrics. HR stroke in ideal 0.24 [0.06-0.98] and intermediate 0.84 [0.58-1.21] vs poor global CVH; per unit increase 0.80 [0.74-0.89]

2 Literature Review

Author, Year	Study Design (Location)	Population	LS7 and CVH measures	Stroke Outcome and follow-up	Adjustments	Key Findings
			diet) and Health factor CVH (BP, TC, FPG) defined as Ideal, Intermediate and Poor if ≥ 3 , 2 or 0-1 relevant metrics at ideal level			
Cao, 2021 (264)	Prospective (UK Biobank)	N=354976 Adults 40-70y (mean 56y) Without history of stroke and CHD	Diet, glucose metrics modified, HDL cholesterol used. Poor, intermediate and ideal levels of Behavioural CVH: 0-3, 4-6, and 7-8 Biological CVH: 0-2, 3-4, and 5-6 Global CVH: 0-7, 8-11, and 12-14	Data linked to hospital and mortality records, using ICD-10 (I60-I64) Median follow-up 11y	Age, sex, ethnicity, socioeconomic status, alcohol, employment, education, family history of stroke, CRP Analyses by metric also adjusted for other metrics.	14.5% Optimal CVH (12-14) Glucose and smoking best and BP poorest metric Each metric inversely associated with total strokes (except BMI, PA on adjustment for other LS7) HR in intermediate 0.69 [0.65-0.73] and optimal CVH 0.48 [0.43-0.53] vs inadequate. HR per unit rise in composite score 0.89 [0.88-0.90]
Isiozor, 2021 (384)	Prospective (KIHD-Finland)	N=2520 Men 42-60y (mean 53y) Without history of stroke	LS7 diet modified; LS7 metrics low (0-2), medium (3-4), high (≥ 5) Global CVH (0-14) poor (0-6), intermediate (7-8), ideal (9-14)	WHO criteria, FINMONICA registry and hospital and mortality linked ICD9/10 codes. ~100% with neuroimaging Median follow-up 26y	Age, alcohol, socioeconomic status, medications for BP and TC, diabetes	5.5% with high LS7 score FPG and PA best metrics, diet worst With ref to low LS7, HR of stroke for medium 0.68 [0.56-0.83] and high 0.52 [0.32-0.86] With ref to poor CVH, HR of stroke for intermediate 0.66 [0.53-0.83] and ideal 0.50 [0.39-0.64] HR per unit rise in composite score 0.86 [0.81-0.90]

*Studies with a majority older population in sample

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Table 2.6 Cross sectional studies on prevalence of Cardiovascular Health (CVH) and Life's Simple 7 (LS7) metrics in South Asians

Author, Year	Location	Population	LS7 and CVH measures	Key Findings
Gyawali, 2018 (276)	Nepal	N=2310 Adults ≥25y (mean 47y) Semi urban	Ideal metrics as per AHA except diet, BMI (cut-off 23kg/m ²) and harmful alcohol use instead of TC. CVH based on number of ideal LS7: Ideal 6-7, intermediate 4-5, poor 1-3	Ideal CVH 14.3%, intermediate CVH 67.0%, poor CVH 18.7%. Prevalence of ideal CVH lower in men. Ideal PA (98%) most common ideal BP (65%) and diet (5%) least common. Ideal Smoking 72%, BMI 70%, alcohol intake 87% and FPG 88%. Being female and younger associated with higher odds of ideal CVH
Ghimire, 2020 (275)	Nepal	N=3238 Adults 15-69y Nationwide	LS7 as per AHA except higher cut-offs for ideal PA CVH based on number of ideal LS7: Ideal 5-7, intermediate 3-4, poor 0-2	Ideal CVH 52%, intermediate 44%, poor 5%; mean CVH score 4.4 (range 0-7); 0 participants with all LS7 ideal. Diet (0.1%) and BP (29%) worst and PA (95%) best metric. FPG (83%), TC (84%), BMI (76%) & Smoking (77%). Being female and younger associated with higher odds of ideal CVH
Gupta, 2017 (273)	India Heart Watch	N=6198 Adults 20-75y Urban middle-class	Ideal LS7 as per AHA, except diet and tobacco use (cigarettes, bidis and smokeless tobacco). CVH based on number of ideal LS7: good ≥6, average 4-5 and poor 1-3	Less than 1% with all 7 ideal metrics. Poor CVH 62.4% men and 54.9% women, average in 34.1% and 41.5%, good in 3.5% men, 3.6% women In men and women, respectively, age-adjusted prevalence of no tobacco use 72.0% and 89.6%; ideal PA 20.1% and 20.6%; diet 10.6% and 10.6%; BMI 57.7% and 52.8%; BP 17.1% and 22.4%; TC 72.4% and 72.7%; and FPG 57.4% and 59.5%
Shivashankar, 2022 (274)	India	N=22144 Adults ≥30y (mean 47y) Urban and rural Excluding prior CHD or stroke	LS7 definitions disregarding medication use. Diet based on FFV ≥6, 4 to 5, and ≤3 ideal LS7 metrics as having good, moderate, and poor CVH, respectively.	Overall 0.2% with all LS7 ideal, mean CVH score 3.8. Good, moderate, poor CVH: 9.9%, 48.9%, 41.2% respectively Ideal smoking best and ideal diet and BP worst metrics overall, but rural settings having higher prevalence of most metrics except smoking, and of good CVH
Talegawkar, 2018 (278)	US South Asians MASALA	N=875 Adults 40-84y (mean 55y) Free from CVD	LS7 adapted for SA diet and intentional PA Ideal CVH score 0-7	No participants with all LS7 ideal. A fifth had 5-6 ideal. 42% with ≥4 ideal LS7, 27.9% with 3 & 30% with ≤2. Ideal smoking best and diet and BP worst metrics

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Table 2.7 Predictors and outcome event definitions in stroke-specific risk tools

	FSRP (287)	CHS (288)	REGARDS (290)	QStroke (20)	REVISED FSRP (289)
Outcome Event	All types of fatal and non-fatal strokes and TIA	All types of fatal and non-fatal stroke	All types of fatal and non-fatal stroke	Ischaemic fatal and non-fatal strokes and TIA	All types of fatal and non-fatal stroke
Exclusions	Prevalent stroke	Prevalent stroke	Prevalent stroke and TIA	Prevalent stroke, TIA and use of anticoagulant medication	Prevalent stroke
Age of development sample	55-84y	≥65y	≥45y	25-84y	55-84y
Examination periods	1964-68 & 1975-78	1988-90, 1992	2003-2007	1998-2012	1988-92 & 1999-2001 1987-91 & 1998-2001
Prediction horizon	10y	5y	10y	10y	10y
Predictors					
Age	✓	✓	✓	✓	✓
Age 65+y	-	-	-	-	✓
Socioeconomic status	-	-	-	✓	-
Education	-	-	✓	-	-
Ethnicity	-	-	✓	✓	-
Self-reported general health	-	-	✓	-	-
Family h/o of premature coronary heart disease	-	-	-	✓	-
Type 1 Diabetes	-	-	-	✓	-
Type 2 Diabetes	-	-	-	✓	-
Diabetes	✓	✓	✓	-	-
Diabetes if Age <65y	-	-	-	-	✓
Diabetes if Age 65+y	-	-	-	-	✓
Rheumatoid Arthritis	-	-	-	✓	-
Chronic Kidney Disease	-	-	-	✓	-
Coronary Heart Disease	-	✓	✓	✓	-
Heart Failure	-	-	-	✓	-
Cardiovascular Disease	✓*	-	-	-	✓*
Valvular Heart Disease	-	-	-	✓	-
Total Choll: HDL Chol Ratio	-	-	-	✓	-
Creatinine	-	✓	-	-	-
Impaired fasting glucose	-	✓	-	-	-
Self-reported hypertension	-	-	✓	-	-
Hypertension Treatment	✓	-	-	✓	✓

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	FSRP (287)	CHS (288)	REGARDS (290)	QStroke (20)	REVISED FSRP (289)
Systolic BP	✓	✓	-	✓	-
Systolic BP if on hypertension treatment	-	-	-	-	✓
Systolic BP if no hypertension treatment	-	-	-	-	✓
Body Mass Index	-	-	-	✓	-
Cigarette Smoking	✓	-	✓	✓	✓
Time to walk 15ft	-	✓	-	-	-
Atrial Fibrillation	✓	✓	✓	✓	✓
Left Ventricular Hypertrophy	✓	✓	-	-	-

*Aggregate of CHD, HF, Intermittent claudication. Risk tools are either sex-specific or incorporate sex as a predictor.

Table 2.8 Studies validating stroke-specific and composite-CVD risk tools for stroke prediction

Author, Year	Location (Baseline Exam)	Population	Risk Tool	Outcomes	Key Findings
Chatellier, 2002 (299)	Europe (INSIGHT Trial 1994-1996)	N=4407 Adults 55-74y, (mean 64y) Free of CHD, stroke, PAD	Framingham Stroke Equation (Anderson et al)	Fatal/Non-fatal stroke, TIA, SAH from trial endpoints 3.7y follow up	96 stroke events Mean Calibration 1.0 overall but overestimating in some countries and underestimating in UK.
Voko, 2004 (295)	Netherlands (Rotterdam 1990-1993)	N=3862 Adults 55-74y (mean 69y in women and 67y in men) Free of stroke at baseline	FSRP (without adjustment for antihypertensive medication), and CHS	Probable and definite strokes verified from primary care, municipal authorities, and hospital records. No TIA. 5y follow up	171 strokes in all Mean calibration: FSRP 1.16, CHS 1.22 Decile-Based calibration: both overestimating risk from 8 th decile onwards but generally well calibrated below that Discrimination: AUROC 0.75 for both, for those ≥65y falls to 0.69
Bineau, 2009 (296)	France (3C-1999-2001)	N=6913 Adults 65-84y (mean 66y in women, 65y in men) Free of stroke at baseline	FSRP (with adjustment for antihypertensive medication)	Self-report verified by adjudicators through GP, hospital and death records. 6y follow-up	110 strokes in all Mean calibration: Men 3.7, Women 4.35 Decile-Based calibration: systematic overestimation across all deciles in men and women. Recalibration improved these. Discrimination: AUROC 0.67 for men and 0.70 for women
McClure, 2014 (319)	USA (REGARDS 2003-2007)	N=27748 Adults ≥45y (mean 65y) White (60%), Black (40%) No history of stroke	FSRP (with adjustment for antihypertensive medication)	WHO criteria or positive neuroimaging if symptoms <24hrs, verified by adjudicators from medical records on participant report of event. Follow-up 5.6y	Number of events not reported. Calibration assessed by ratio of annualized FSRP predicted rate to observed (calculated by Poisson regression) FSRP overestimated (generally x2) annualized risk across all sex-race strata and quintiles of risk, esp. highest Discrimination not reported

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Author, Year	Location (Baseline Exam)	Population	Risk Tool	Outcomes	Key Findings
Dufouil, 2017 (289)	USA (REGARDS 2003-2007)	N=23691 Adults ≥55y (mean 66y)	Revised FSRP	All strokes-As above REGARDS follow-up 5y	629 strokes in REGARDS. Revised FSRP overestimated risk in REGARDS, esp. among Black men C-statistic 0.62-0.66 in Blacks, 0.68-0.75 in Whites
	France (3C-1999-2001)	N=7601 Adults ≥65y (mean 73y) No history of stroke	Revised FSRP	3C follow-up 10y	262 strokes in 3C Revised FSRP well calibrated in 3C C-statistic 0.72 in women, 0.70 in men
Bos, 2017 (297)	Netherlands (Rotterdam 2002-2006)	N=7966 Adults ≥55y (mean 70y in women and 69y in men) Free of stroke at baseline; additional analysis in CVD and AF free subgroup	FSRP & Revised FSRP	All strokes from medical records and hospital discharged, adjudicated, 10y follow-up	Stroke incidence 8.7/1000PY Both FSRP & R-FSRP were mis-calibrated, R-FSRP less so. R-FSRP calibrated better in men without CVD and AF, but overestimated in women C-statistic in women FSRP 0.74 [0.72-0.77], R-FSRP 0.74 [0.71-0.76]; C-statistic in men FSRP 0.69 [0.66-0.73], R-FSRP 0.68 [0.65-0.72]
Hippisley-Cox, 2014 (300)	UK (Clinical Practice Research Datalink 1998-2012)	N=3,106,231 Adults 25-84y Free of stroke, TIA and anticoagulant use	QSTROKE	Ischaemic stroke and TIA, recorded in primary care (CPRD), secondary care and mortality linked data	70,060 events Generally well calibrated; Discrimination 0.882 (0.794) in women and 0.869 (0.771) in men (complete cases)
Flueckiger, 2018 (294)	USA (MESA 2000-2002)	N=6712 Adults 45-84y (mean 62y) Free of Atherosclerotic CVD	FSRP, Revised FSRP & PCE (no calibration described)	Adjudicated fatal/non-fatal ischaemic or haemorrhagic stroke Mean follow up 11y	231 Strokes Mean calibration: R-FSRP 1.38, FSRP 1.74, PCE 3.97 C-statistic: R-FSRP 0.716, FSRP 0.653, PCE 0.716
D'Agostino, 2008 (306)	USA (Framingham 1968-1971, 1971-1975 & 1984-1987)	N=8491 Adults 30-74y, mean 49y Free of all CVD	Framingham CVD Risk Profile for predicting stroke using calibration factor 0.2385 in women and 0.1590 in men	Strokes & TIA Adjudicated from medical histories, hospital records; 10y follow-up	In women 84/4522, C-index 0.769 [0.715-0.822], well calibrated In men 93/3969, C-index 0.826 [0.789-0.863], slight miscalibration

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Author, Year	Location (Baseline Exam)	Population	Risk Tool	Outcomes	Key Findings
Majed, 2013 (310)	Europe (France and Ireland, 1991-1993)	N=9638 Men 50-59y Free of CHD and stroke	Framingham CVD Risk Profile using calibration factor 0.1590	Stroke as per WHO definition validated by committee, from medical records. TIA excluded. 10y follow-up	138 strokes Discrimination poor 0.68 in French and 0.62 in Irish men Two-fold overestimation overall, higher in French, somewhat less in Irish men.
Hong, 2023 (311)	USA (Framingham Offspring, ARIC, MESA & REGARDS - pooled and subgroups-multiple examinations)	N=62842 Adults ≥45, median age 61y Free of stroke and TIA	Revised Framingham, REGARDS self-report and PCE (using race specific calibration factors)	Strokes (IS and HS) 10y performance	2199 strokes Discrimination: PCE 0.72 [0.71-0.73]; R-FSRP 0.72 [0.72-0.73]; and REGARDS self-report 0.73 [0.72-0.74]; better among Whites, women and <60y (PCE & R-FSRP discrimination 0.67 in Whites 60y+) Calibration as global ratio of observed vs expected events Overall: REGARDS self-report 1.05, R-FSRP 0.86, PCE 0.74 White <60y: REGARDS self-report 0.95, R-FSRP 0.85, PCE 0.75 White ≥60y: REGARDS self-report 1.02, R-FSRP 0.79, PCE 0.79

PAD: peripheral arterial disease

Table 2.9 Predictors and outcome event definitions in composite CVD risk tools

	Framingham General CVD Risk Profile (306)	PCE (57)	QRISK3 (58)	SCORE2/ SCORE2-OP (59, 307)
Outcome Event	CVD (CHD, Ischaemic stroke, Haemorrhagic stroke, TIA, HF, Intermittent claudication)	First hard Atherosclerotic CVD – coronary death or fatal stroke or non-fatal MI or stroke.	Coronary Heart Disease (angina, acute MI, subsequent MI, complications after MI, other acute IHD, chronic IHD), Ischaemic Stroke and TIA	Fatal and non-fatal CVD
Exclusions	Free of all CVD (as above)	Prevalent MI, stroke, congestive heart failure, percutaneous coronary intervention, coronary bypass surgery, AF and > 79y	Prevalent CVD (heart attack, angina, stroke or TIA) & use of statins	Prevalent CVD
Age of Development Samples	30-74y, mean 49y	40-79y, mean 55y	25-84y, mean 43y	Mean age 57y/73y
Prediction horizon	10	10y	10y	10y
Predictors				
Age	✓	✓	✓	✓
Townsend Score	-	-	✓	-
Ethnicity	-	-	✓	-
Atrial Fibrillation or Flutter	-	-	✓	-
Family h/o of premature coronary heart disease	-	-	✓	-
Type 1 Diabetes	-	-	✓	-
Type 2 Diabetes	-	-	✓	-
Diabetes	✓	✓	-	✓
Rheumatoid Arthritis/related syndromes	-	-	✓	-
Chronic Kidney Disease	-	-	✓	-
Hypertension Treatment	-	-	✓	-
Migraine	-	-	✓	-
Corticosteroid use	-	-	✓	-
Atypical antipsychotic use	-	-	✓	-
Systemic Lupus Erythematosus	-	-	✓	-
Severe Mental Illness	-	-	✓	-
Erectile dysfunction or treatment	-	-	✓	-
Cigarette Smoking	✓	✓	✓	✓

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	Framingham General CVD Risk Profile (306)	PCE (57)	QRISK3 (58)	SCORE2/ SCORE2-OP (59, 307)
Body Mass Index	-	-	✓	
Total Cholesterol	✓	✓	-	✓
HDL-Cholesterol	✓	✓	-	✓
Total Chol:HDL Chol Ratio	-	-	✓	-
Systolic BP	-	-	✓	✓
Systolic BP not treated	✓	✓	-	-
Systolic BP treated	✓	✓	-	-
Variability in Systolic BP	-	-	✓	-

Risk tools are sex specific.

Table 2.10 Studies examining performance of CVD prediction tools in older adults while adjusting for competing risks

Author, Year	Location (Baseline Exam)	Population	Risk Tool	Outcomes	Key Findings
Livingstone, 2021 (312)	UK (CPRD 2004-2016)	Adults 25-84y without previous CVD and statin use N=1484597 women, N= 1420176 men	QRISK3	Fatal and non-fatal CHD, Stroke or TIA through primary care Read codes, HES and ONS death registration 10y follow-up, ~2/3 rd censored due to de-registration or end of follow up<10y so median follow-up 5y.	39048 events in women, 49146 in men Censoring due to statin initiation more common than non-CVD death generally. But censoring due to non-CVD death more common in older adults. Overall C-index 0.865 in women, 0.834 in men But <0.65 in all above ≥65y Calibration excellent for men and women overall, but overprediction in older adults especially >75y When competing mortality accounted for, overprediction evident at higher predicted risk overall, and systematically in >65y for both men and women
Nanna, 2019 (313)	USA (CHS, MESA, Framingham Original & Offspring; exams ranging from 1992 to 2002)	N=2663, ≥75y, median 78y N=9864, 40-74y, median 62y Free of Atherosclerotic CVD	PCE	Hard CVD (fatal and non-fatal MI, stroke and CHD death) 5y follow-up	Discrimination: C-index 0.62 [0.60-0.65] in ≥75y, 0.75 [0.73-0.76] in 40-74y Calibration: poor in both groups; over-prediction at higher risks, esp. in older group on adjusting competing deaths HR in older group weaker for female sex, HDL, smoking
Nguyen, 2020 (314)	USA (CHS 1988-89, 1992-1993)	N=4249, ≥75y mean 72y Without Atherosclerotic CVD	PCE	Hard CVD (fatal and non-fatal MI, stroke and CHD death) 10y follow-up	917 Atherosclerotic CVD and 706 competing events. No loss to follow-up Discrimination: 0.68 in men, 0.69 in women Calibration overall reported as difference rather than ratio between predicted and observed risk: well calibrated globally. Competing risks adjustment shows a 2-3% higher predicted risk. Risk-category based miscalibration at higher predicted risk and improved slightly when competing risks adjusted, although overestimation remains at highest risk
Mehta, 2020 (309)	New Zealand (National cohort 2006)	N=124358 75-89y, mean 80y With CVD and HF	VARIANZ	Broad fatal or non-fatal CVD through linked national	30152 CVD events

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Author, Year	Location (Baseline Exam)	Population	Risk Tool	Outcomes	Key Findings
				hospital and death administrative datasets 5y follow-up	Discrimination: 0.617 overall in women, 0.591 in men. Poorer discrimination in increasing 5yr age-bands Calibration: underprediction in women in middle 8 deciles, becoming more evident with increasing age. Overprediction in men in upper 2 deciles. In older ages, underprediction in lower and marked over prediction in upper deciles of risk

Table 2.11 Studies reporting associations of Natriuretic Peptides with stroke and incremental performance of NT-proBNP for stroke risk prediction

Author, Year	Study Design (Location)	Population	Natriuretic Peptide	Stroke Outcome	Adjustments	Key Findings
Di Angelantonio, 2009 (352)	Systematic Review and Meta-analysis of prospective studies spanning Europe, N. America, Asia-Pacific	N=87474 individuals N=40 studies 1) general population 11; 5 excluding baseline CVD (2) people with elevated CVD risk factors 11 (3) people with stable CVD at entry 18 13 studies reporting separately on stroke, N=56764 individuals	BNP n=7, NT-proBNP n=30, both n=3	10625 CVD events (fatal/non-fatal MI, stroke, TIA, HF) 2063 stroke events Weighted mean follow-up 5y	Age, sex, smoking, diabetes, BP, lipids plus additional characteristics variably	Pooled RR comparing top third to bottom third of NP distribution of CVD 2.82 [2.4-3.33], of stroke 1.93 [1.58-2.37]. Considerable heterogeneity not explained by study characteristics except those with <250 events reporting larger RR. 14 studies (2684 CVD events/25696 individuals) reported modest improvements (of 0.01-0.1 in AUROC or C-index) in discrimination of CVD Smaller increments in larger and general population studies.
Natriuretic Peptide Studies Collaboration, 2016 (346)	Systematic Review and Meta-analysis of individual participant data from prospective studies from Japan, Europe and USA	N=95617 participants, mean age 61y(SD10) N=40 studies in all Adults without history of CVD (CHD, stroke, TIA, peripheral vascular disease, AF, HF, cardiovascular surgery, & pulmonary heart disease)	NT-proBNP in main analysis	3768 stroke events in 76839 individuals from 30 cohorts along 8y of median follow-up	Age, smoking, diabetes, SBP, TC and HDL; models stratified by sex	RR for stroke comparing top to bottom third of NP distribution 1.81 [1.58-2.07], similar for IS, HS. RR per SD-log 1.43 [1.34, 1.53] RR weaker for 60-70y and >70y vs <60y; with diabetes vs without; taking statins and BP medication but interactions not statistically significant. NT-proBNP increased stroke discrimination of base model from 0.669 to 0.681 (delta C 0.011, p<0.0001). For combined outcome (CHD, stroke, HF) NT-proBNP improved

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Author, Year	Study Design (Location)	Population	Natriuretic Peptide	Stroke Outcome	Adjustments	Key Findings
						reclassification of non-cases by ~3-4%
Rutten, 2010 (385)	Prospective (Rotterdam 1997-1999, 2000-2001)	N=5063 Adults mean age 68y Without CHD, HF, stroke	NT-proBNP	IS verified by study physicians through linkage to primary care data; coded as ICD10 I63 Follow-up to 2007 only	Age, smoking, diabetes, SBP, TC and HDL; models run by sex [Plus MDRD GFR, BMI and BP medicine use- did not alter findings]	54 IS in men, 70 IS in women HR top vs bottom tertile Men: 2.06 [0.91-3.18], women: 2.07 [1.00-2.97] HR per SD-log NT-proBNP in men: 1.49 [1.13-1.69], women: 1.39 [1.08-1.79] C-statistics on adding NT-proBNP in Men: 0.699→0.714 Women: 0.721→0.734
Folsom, 2013 (77)	Prospective (USA-ARIC 1996-1998)	N=10902 Adult 55-75y Without stroke	NT-proBNP	IS (lacunar, non-lacunar and CE) and HS verified after self-reports, through hospital and death records using computer algorithm and physician reviewer. Mean follow-up 11y	Age, sex, race, BMI, smoking, diabetes, SBP, TC, HDL, Lp-PLA2, lipid lowering & antihypertensive drugs, CRP, prevalent CHD, HF, AF Plus CHD, HF, AF as time-varying events No significant interactions between NT-proBNP and race, sex or hypertension status	63 HS, 444 IS (87 lacunar, 232 non-lacunar, 125 CE) For all strokes, significant trend in HR across quintiles, topmost 2.88 [2.05-4.05] small attenuation with incident CHD, AF, HF. Similar associations with IS and non-lacunar strokes, and especially strong associations with CE 9.01 [3.11-26.1]. With HS, 2-fold higher risk across all quintiles but does not reach statistical significance. For all strokes, NT-proBNP increased C-index from 0.743→0.753, IDI 0.005
Cushman, 2014 (263)	Case-cohort (USA-REGARDS 2003-2007)	Adults 60-70y without baseline stroke 546 cases, 956 remaining stroke free	NT-proBNP	Ischaemic Strokes based on WHO definition supplemented by imaging and verified by stroke physicians	Main: age, race, age×race, sex, income, education, SBP, diabetes, LVH, BP medication, smoking, CHD, AF.	HR in top vs bottom quartile for IS 2.9 [1.9-4.5]. Trend weaker with SVD, strongest with cardioembolic (although large CIs). Age, sex, race and NT-proBNP interactions not significant. Excluding those

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Author, Year	Study Design (Location)	Population	Natriuretic Peptide	Stroke Outcome	Adjustments	Key Findings
				5y of follow up	Additional: GFR, HF, albuminuria	with HF, LVH, CKD, AF caused little change. Category free net reclassification for IS in addition to Framingham risk factors improved in 27%
Portegies, 2015 (81)	Prospective (Rotterdam 1997-2001)	N=5611 Mean age 68y in men, 69y in women Without stroke, TIA, HF	NT-proBNP	IS, ICH, TIA through primary care linkage with study, verified through hospital records by study neurologist; Mean follow-up 9.3y in men, 9.8y in women.	Sex-specific models. Adjusted for age, SBP, DBP, smoking, diabetes, TC, HDL, creatinine, drugs for BP, lipids & antithrombotic use	HR of combined strokes/TIA per SD-In-NT-proBNP ~1.3 in men and women. HR of <i>stroke only</i> stronger in men (not statistically significant). Associated with IS, HS but not TIA in men. Only IS and TIA in women (statistically significant). Similar findings for tertiles. Risk of combined stroke/TIA ~ x2 in top vs bottom for men/women. Excluding & censoring CHD, HF, AF: HR for combined strokes/TIA unaffected, in men HR for HS attenuated. Association for any cerebrovascular disease weaker in those taking any antithrombotic vs taking none.
Elkind, 2013 (386)	Prospective (USA-CHS)	N=4198 Older adults Without Stroke	NT-proBNP	Ischaemic stroke, Total strokes Follow up not specified	Demographic, Traditional CVD risk factors Mediation by AF, HF, LVH	For IS each doubling of levels, HR 1.13 [1.07-1.19], top quintile vs bottom 1.66 [1.26-2.18]. Adjusting for AF, HF, LVH caused minimal change. Results similar for total strokes.
Agarwala, 2016 (367)	Prospective (USA-ARIC 1996-1998)	N=8172 Adults 55-75y, mean 63y Without stroke or CHD	NT-proBNP	Ischaemic Strokes Median follow-up 15y	Age, sex, race, ARIC 10y stroke risk score; overall and stratified by min, mild, substantial subclinical	366 IS events; Log-NT-proBNP HR 1.55 [1.40-1.71] overall, with similar magnitude across degrees of atherosclerosis

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Author, Year	Study Design (Location)	Population	Natriuretic Peptide	Stroke Outcome	Adjustments	Key Findings
Patterson, 2018 (369)	Prospective (Caerphilly 1989-1993)	N=1112 Men 55-69y, mean 62y Without CVD	BNP	Strokes, TIA except SAH. Verified through mortality, primary care and hospital records by study committee Mean follow-up 10y	atherosclerosis based on carotid intima media thickness ± plaque Age, BMI, smoking, diabetes, SBP, TC, Triglycerides, Family history of premature CHD	115 events SubHR increased across tertiles, top third 1.75 [1.06-2.88] p trend >0.01; per third 1.33 [1.04-1.70], p > 0.01 Discrimination not estimated
Saeed, 2018 (333)	Prospective (USA-ARIC 2011-2013)	N=4760 Adults 69-88y, mean age 75y Without CHD, IS, HF	NT-proBNP	Ischaemic strokes defined as validated hospitalized embolic or thrombotic strokes; Median follow-up 3.6y	Age, sex, race, SBP, TC, HDL, smoking, diabetes and antihypertensive use, plus GFR	81 stroke events. HR per unit ln-NT-proBNP 1.49 [1.17-1.91] HR for categories 100 to <300 and ≥300pg/ml vs <100pg/ml: 1.35 [0.75-2.42], 2.59 [1.36-4.94] p trend 0.01 For Global CVD (CHD, stroke & HF) C-statistics on adding NT-proBNP to PCE variables 0.647→0.739, change 0.092, IDI 0.066
Wu, 2022 (370)	Prospective (NZ-HVOLS)	N=2528 Adults 20-99y, mean 64y; 60% participants >60y Without baseline CVD	NT-proBNP	Strokes and TIA tracked from national deaths, hospital discharges and prescription ICD codes; 5y follow-up	For PREDICT variables age, sex, BMI, ethnicity, deprivation, smoking, diabetes, SBP, TC:HDL, AF, family history of CVD, medications for BP, lipids, antithrombotic use	70 events HR of top 5 th to bottom 5 th of NT-proBNP 4.70 [0.99-22.27], per ln-NT-proBNP 1.43 [1.08, 1.89] Improvement in discrimination reported only for combined CVD: 0.777 TO 0.784, a non-significant change of 0.006. NT-proBNP correctly upgraded 2% of those with CVD events and downgraded 2% of those without.

2 Literature Review

Author, Year	Study Design (Location)	Population	Natriuretic Peptide	Stroke Outcome	Adjustments	Key Findings
Zhu, 2022 (368)	Prospective (Rotterdam 1997-2001)	N=5430 Adults mean age 69y Without CHD, HF, Stroke	NT-proBNP	WHO defined strokes from primary care linkage with study, verified through hospital records by study neurologist Mean follow-up 14y	Models run by sex; Age, SBP, TC, HDL antihypertensive use, smoking, diabetes [+ GFR made no difference] Risk categories by 5%, 7.5% and 20%	HR per SD-log NT-proBNP in Women 1.40 [1.25-1.58] Men 1.38 [1.19-1.61] Change in C-index for 10yr risk of stroke in women +0.007, men +0.014. Only improves event reclassification significantly in men (9%) and non-significantly 4% in women

Figure 2.1 Subtypes of Stroke

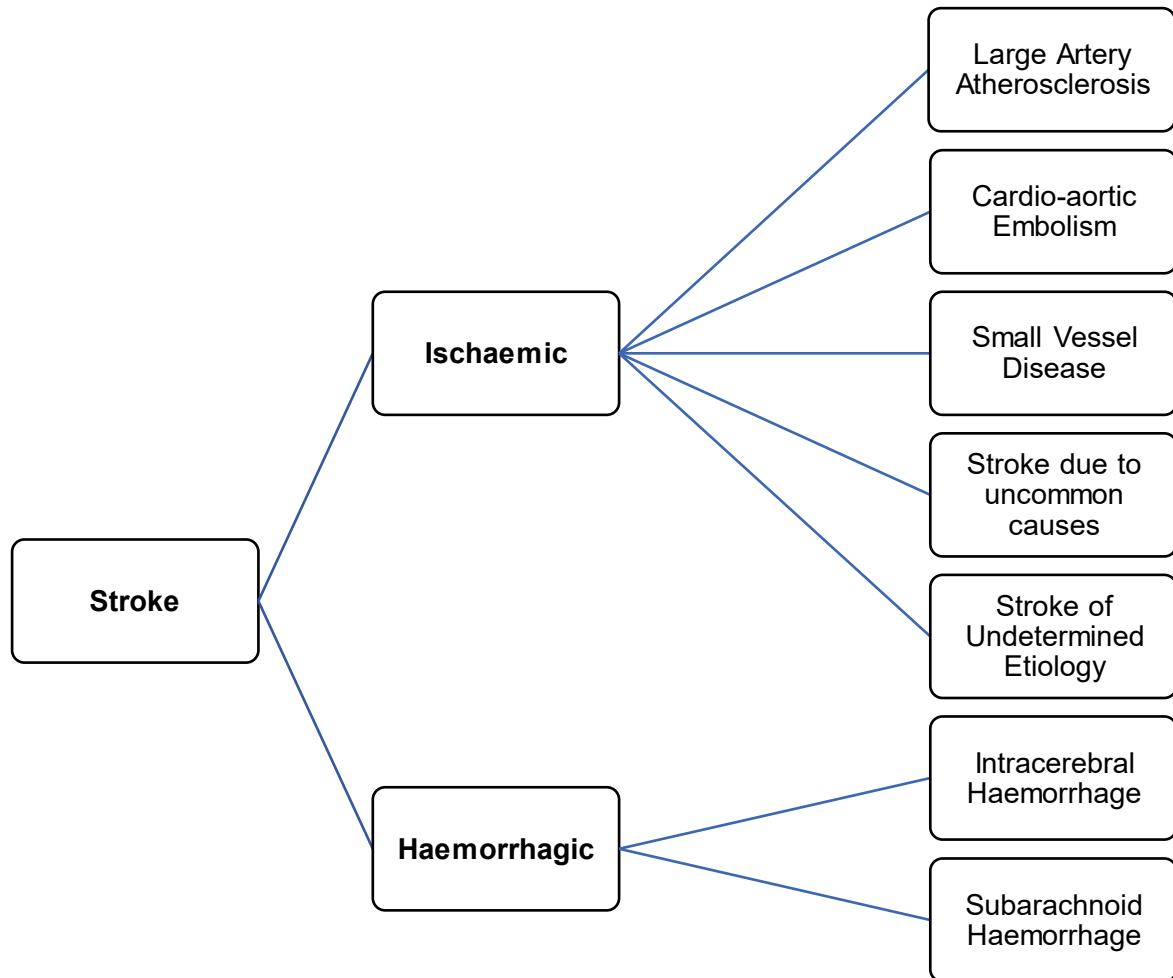


Figure 2.2 Trends in incidence of Stroke/TIA and Myocardial Infarction across age groups, UK 2017

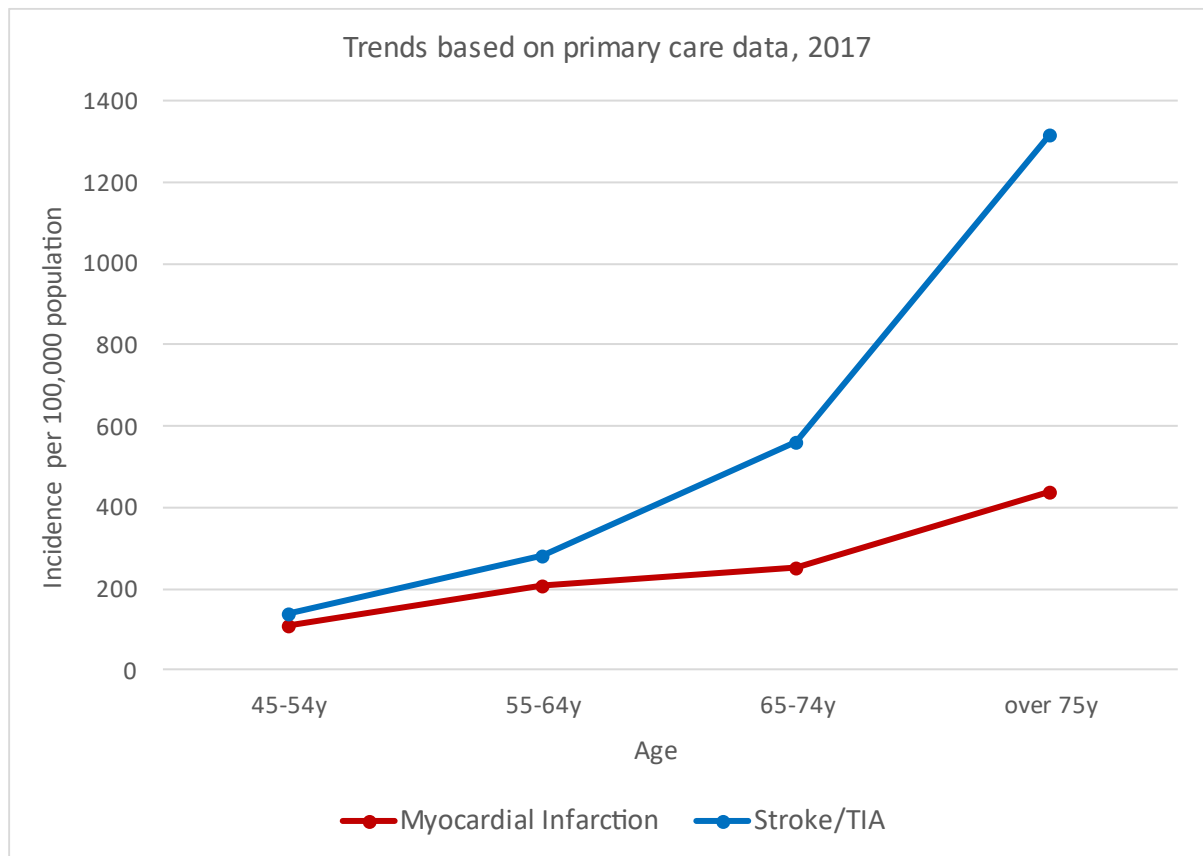


Figure based on British Heart Foundation Statistics (171)

Chapter 3. Methods

3.1 Introduction

This thesis analyses epidemiological data from two separate prospective cohorts – the British Regional Heart Study (BRHS) for objectives relating to older age; and the Southall and Brent Re-visited study (SABRE) for objectives relating to SAs. Because these are two distinct population groups, particularly in terms of age-range and ethnicity, data have not been pooled. In this chapter, I will elaborate sequentially on the study design, data collection methods, data examined, strengths and limitations for BRHS (section 3.2-3.4) and SABRE (section 3.5-7). An overview of the statistical techniques used is presented in section 3.8, with further methodological details relating to specific objectives provided in relevant chapters.

3.1.1 Defining ‘Old’ in BRHS

This thesis aims to inform primary prevention of stroke in ageing populations. While getting older is inevitable, people age variably; and chronological age may not necessarily reflect biological age. It is, however, a practical need of epidemiological ageing research to have some characterisation of old age. For the purpose of this thesis, age 60y at participation in the 20y BRHS re-examination (Q20) was chosen, based on the WHO and United Nations age cut-off for older people (387, 388). This is also the age at which stroke incidence rates are noted to rise sharply (12). In keeping with the debate around the use of the term ‘old’ (389), the thesis refers to participants 60y and above as ‘older adults’.

3.2 The British Regional Heart Study

The BRHS was originally conceived to explore Britain’s geographic variations in CVD mortality, particularly its links with water hardness (390). It began in 1978-1980 by recruiting a socially representative sample of 7,735 men aged 40-59y, from 24 primary care practices across Britain. At this baseline recruitment, men provided questionnaire-based socio-demographic, health, and lifestyle history; underwent physical examination and blood work. Using a prospective study design, participants

have been followed periodically by regular postal questionnaires for self-report on physical, physiological, mental and social aspects of health; by reports from GPs for cardiovascular morbidity; and by linkage to national mortality registers for deaths (86, 391). With data collection spanning over 40 years (392), BRHS has advanced the understanding of how many environmental, socioeconomic, behavioural, and biological factors influence CVD occurrence from mid-adulthood to later life (393). Evidence from BRHS continues to inform the aetiology and prevention of CVD at older ages (392).

The BRHS has received ongoing funding support primarily from the British Heart Foundation; and additionally, from the Department of Health, the Medical Research Council (MRC), Diabetes UK and the National Institute for Health Research (NIHR). Ethical approval for the BRHS was granted by the National Research Ethics Service (NRES) Committee, London. Written informed consent for participation has been obtained from all participants in accordance with the Declaration of Helsinki.

3.2.1 Recruitment

At inception (1978-1980), men were recruited from 24 towns to cover all major regions of Britain (including England, Scotland and Wales) based on the following 7 criteria (390, 394):

1. All standard regions should be represented.
2. Towns should be discrete entities with populations of 50,000-100,000 at the 1971 Census. In England one larger town was included (Ipswich). In Scotland, some towns below 50,000 were considered to obtain a reasonable number of suitable towns.
3. The choice of towns within regions should reflect the variations in mortality from CVD and water hardness.
4. Towns were to be socioeconomically representative of the region where possible.
5. Towns with noticeable population movement or with unusual population structure were avoided.
6. Some towns that were apparent "outliers" when CVD mortality and water hardness were plotted against each other, for example Hartlepool, Exeter, and Harrogate, should be included.

7. Between similar towns meeting these criteria, a town should be chosen by random selection.

Figure 3.1 displays a map of the 24 towns included in the BRHS. Table 3.1 shows standardised mortality ratios for CVD in 1969-73 in men aged 35-64 years, the number of men examined in each of the 24 towns and the corresponding response rate.

A single primary care general practice was selected from each town if the practice population was >7500, if it was representative of the socioeconomic composition of the town, and willing to participate. From each practice, 450 men were randomly selected from age-sex registers, stratified by four five-year age categories (40-44, 45-49, 50-54 and 55-59 years). Men with severe mental or physical disabilities (<10 per practice) were excluded. Nearly 10,000 men were sent invitations, signed by their GP, encouraging them to attend a CVD health check at a local venue, usually at the practice premises. Of these, 7735 men agreed to take part in the study, approximating 300 men per town with a mean response rate of 78% (Table 3.1) (390).

3.2.2 Baseline Data Collection (Q1)

During 1978-1980, a team of 3 trained nurses visited each town to collect baseline data from all 7735 men. At the study venue, nurses first administered a socio-demographic, health, medical, and lifestyle history questionnaire (Appendix 3.1); conducted height, weight, BP and lung function measurements (Appendix 3.2); and finally recorded an electrocardiogram (ECG) and obtained blood samples (390).

3.2.3 Follow-up Data Collection

Since Q1, participants have been followed periodically up to present day. Figure 3.2 and Figure 3.3 display methods of data collection and participant numbers across the follow-up timeline.

3.2.3.1 Follow-up Questionnaires

After Q1, regular postal questionnaires have been sent to participants, recording information on health and lifestyle factors, and personal and socioeconomic circumstances. The first follow-up questionnaire was sent out after 5-years (in 1983-85), followed by questionnaires after 12- (1992), and 16- (1996) years. At the 20-year (1998-2000) follow-up, the main questionnaire was nurse-administered, and a food frequency questionnaire was mailed separately. Postal questionnaires were also sent

in 2003, 2005 and 2007. Questionnaires were also completed at the 30-year follow-up in 2010-12. Since 2014 postal questionnaires have been sent out annually.

3.2.3.2 Mortality Follow-up

To collect information on deaths, participants have been tagged in 2 National Health Service Central Registers (now Office of National Statistics General Register Office), Southport for England and Wales, and Edinburgh for Scotland (391). Death certificates containing identification details, date and place of death, and cause of death coded using International Classification of Disease 9th and subsequently 10th (ICD-9 and ICD-10) have been provided (initially every 3 months and then) at monthly intervals. Deaths have also been verified from information supplied by participating practices on periodic review sheets (elaborated next).

3.2.3.3 Morbidity Follow-up

Information on several non-fatal events (Appendix 3.3) has been collected through GP reports and biennial reviews of participant medical records. Every two years a standard record review form (Appendix 3.4) has been mailed to participating practices requesting information on each man's continuing registration status, current address, any new CVD events (including MI, angina, stroke, TIA, AF and HF) or CVD treatments (coronary artery bypass graft, coronary angioplasty), and new diagnoses of cancer or diabetes occurring over the last two years.

New non-fatal MI and stroke events have been further confirmed via an enquiry form (Appendix 3.5) sent to the GP or hospital consultant to verify that study case criteria had been fulfilled (86). The WHO diagnostic criteria for definite MI required the presence of ≥ 2 of: typical history including chest pain, positive ECG findings and raised cardiac enzyme levels (395, 396). Non-fatal stroke events required an acute disturbance of cerebral function of vascular origin lasting >24 hours (102), including SAH, ICH or thrombosis. The criteria for a TIA was disturbance of cerebral function of vascular origin lasting <24 h and leaving no residual deficit (1).

Men re-registering with a new practice have been traced using information provided by local authorities. In addition to the original 24 practices, the study now collaborates with >1400 GPs across Britain. The study maintains continued mortality and morbidity follow-up of 98% of the cohort (393).

3.2.3.4 Twenty Year Follow up Survey in 1998-2000 (Q20)

In 1998-2000, men (aged 60-79y) were invited for a 20-year in person follow-up, Q20 (86). Of 5565 surviving men, 4252 (77%) attended. Nurses administered a questionnaire (Appendix 3.6) and conducted physical examinations (Appendix 3.7). All men were asked to provide a blood sample collected using the Sarstedt Monovette system (Sarstedt, Numbrecht, Germany). Men were asked to fast for at least 6 hours prior to a pre-arranged appointment between 08:00 and 18:00 hours. Blood samples were frozen and stored at -20°C on the day of collection and transferred in batches for storage at -70°C until analysis, performed after no >1 freeze-thaw cycle. Men also completed a separate postal dietary questionnaire (Appendix 3.8). In person re-examinations have also been conducted at 30-year (2010-12; mean age $79 \pm 5\text{y}$) and 40-year (2018-19; mean age $85 \pm 4\text{y}$) follow-ups but these measures have not been used in this thesis.

3.3 BRHS Data Used in This Thesis

This thesis examines the relationship of CVH, and of change in CVH over adult life, with stroke risk in old age using (exposure) data from Q1 (mean age $50\text{y} \pm 6$) and Q20 (mean age $68\text{y} \pm 5$). To evaluate performance of stroke and CVD risk prediction tools in old age; to study relationships of NT-proBNP with stroke; and its added value for refining risk prediction in older adults, the thesis uses (exposure) data from Q20. For CVH and NT-proBNP relationships with stroke, subsequent follow-up data on mortality and cardiovascular morbidity were included to June 2018. For risk prediction work, a 10y follow-up from Q20 was analysed to match the 10y time horizon of risk tools.

What follows are details of data collection methods of different exposures and covariates. For simplicity, these have been classified as self-reported, physical exam and blood measures. Prevalent disease and outcomes events are then described separately. The exact combination of exposure, covariates and outcomes used for each research objective are further detailed in relevant chapters.

3.3.1 Self-reported Measures

Age

Men were asked their date of birth at Q1 and Q20, from which age was derived.

Social Class

Men were asked to report their longest held occupation at Q1 (aged 40-59y). The Registrar General's Classification of Occupations (397) was used to classify subjects into six occupational social class categories: I (professional occupations e.g. barristers, physicians, engineers), II (intermediate occupations e.g. teachers, sales managers), III non-manual (skilled non-manual occupations e.g. clerks, shop assistants), III manual (skilled manual occupations e.g. bricklayers, coalminers), IV (partly skilled occupations e.g. bus conductors, postmen) and V (unskilled occupations e.g. porters, general labourers). Occupational social classes were further dichotomised into either two groups: non-manual (social classes I, II, III non-manual) and manual (social classes III manual, IV, V); or 3 groups (non-manual, manual and armed forces).

At Q20, the index of multiple deprivation (IMD) for England, Scotland and Wales was applied to BRHS based on participants' postcode of residence to capture socioeconomic status as quintiles of IMD (393).

Smoking

At both Q1 and Q20, information on current and previous smoking habits was collected via questionnaires. Participants were asked detailed questions on whether they had ever smoked, whether they smoked currently and how much, and if they had given up then at what age. From the information collected, men were classified into binary (smoker yes/no) or wider categories as defined by the criteria suited to each research objective.

Physical Activity

At Q1 and Q20, men were asked to indicate their usual pattern of physical activity, under 4 headings: regular walking, cycling, recreational activity, and sporting (vigorous) activity. Each activity was assigned a score based on type (intensity) and frequency/duration, using recommendations from the National Heart, Lung and Blood Institute workshop (398) and Minnesota intensity codes (399). Scores were heavily weighted on vigorous exercise (Table 3.2). Regular walking and cycling related to weekday journeys, including those to and from work. Recreational activity included gardening, pleasure walking, and do-it-yourself jobs. Sporting (vigorous) activity included running, golf, swimming, tennis, sailing, digging, etc. Physical activity at work was excluded from the score partly because few middle-aged men do physically

demanding work and partly because such activity is not readily amenable to modification. A Physical Activity Index (range 0-46) was derived by summing scores for each activity. This was not a measure of total time spent in physical activity, but a relative estimate of how much physical activity had been carried out or energy expended. The index has been validated against heart rate and forced expiratory volume in 1 second (FEV1) and objectively measured physical activity in the same sample (400, 401).

This index was used to classify men into 6 physical activity states: **inactive** (0-2), minimal activity across all types; **occasional** (3-5), regular walking or recreational activity only, or sporting activity less than once a week only; **light** (6-8), more frequent recreational activities plus sporting activity less than once a week, or regular walking plus some recreational activity; **moderate** (9-12), cycling very frequently only, or very frequent recreational activities plus regular walking, or sporting activity once a week; **moderately vigorous** (13-20), sporting activity 2-4 times a week, or sporting activity once a week plus regular walking/cycling and recreational activity; or **vigorous** (>21), sporting activity more than 4 times a week, or less frequent sporting activity plus frequent walking/cycling and recreational activities. Derivation of the of the LS7 physical activity metric is described in Chapter 4.

Diet

Dietary intake was only measured at Q20 with a self-administered food frequency questionnaire that was developed for use in the WHO's Monitoring Trends and Determinants in Cardiovascular Disease Survey (402) and has been validated against weighed food intake in British populations (403). Participants reported how frequently they usually consumed 86 different food and drink items per week, in 9 categories: 1, 2, 3, 4, 5, 6, or 7 d/week, monthly, or rarely/never. Diet quality was assessed using the Elderly Diet Index (EDI) developed by Kourlaba et al (404) specifically to address adherence to nutritional recommendations for older adults on the basis of the frequency of consumption of specific foods/food groups in the Modified MyPyramid for Older Adults. The EDI consists of 9 components (meat, fish and seafood, legumes, fruit, vegetables, cereals, bread, olive oil, and dairy), each assigned a 4-point scoring system on the basis of frequency of consumption, resulting in a total score range from 9 to 36. The frequency of olive oil consumption was not available, so the scoring of this component was modified using never/rarely consumed and tertiles of weekly

consumption (405). Higher scores on EDI indicated greater compliance with dietary recommendations and hence a healthier diet. Derivation of the LS7 diet metric was based on tertiles of EDI as elaborated in Chapter 4.

Alcohol Consumption

At Q1 and Q20, men were asked about the frequency (none; on special occasions only; once or twice a month; weekends; daily/most days) and quantity (2 drinks a day or less; 3-6 drinks a day; more than drinks a day) of their drinking. One drink was defined as 1 unit of alcohol (i.e., a single whisky, gin or brandy, a glass of wine, sherry or port or half a pint of beer). From this data, alcohol intake was classified into five groups: none (0 units/week); occasional (<1 unit/week); light (1-15 units/week, which included weekend 1-2 units, weekend 3-6 units and daily 1-2 units); moderate (16-42 units/week); heavy (>42 units/week).

Health and Medication History

At Q1 and/or Q20 men gave yes/no responses to being asked if they had ever been told by a doctor that they have or have had a range of conditions (heart attack, coronary thrombosis, MI, angina, stroke, arthritis, bronchitis, diabetes, cancer, heart failure and high blood pressure). Men were also asked whether they suffer from chest pain on exertion and breathlessness when walking. Men also reported on medications from which use of glucose lowering, anti-coagulant, anti-hypertensive, lipid-lowering, migraine and anti-psychotic drugs could be noted. At Q20, men were also asked regarding intermittent claudication using questions based on the Edinburgh Claudication Questionnaire (406).

Family History of CVD

Paternal or maternal history of premature death (<60y) from heart disease and stroke was inquired at Q1.

3.3.2 Physical Measurements

Blood Pressure

At Q1, SBP and DBP readings were recorded using the London School of Hygiene sphygmomanometer, with the subject seated and the arm supported on a cushion. DBP was recorded at disappearance of sounds (phase V). Mean of the two successive readings were used (86, 390). Blood pressure was adjusted for town and observer bias (407).

3 Methods

At the Q20 physical exam, SBP and DBP were measured twice (1-minute apart) in the right arm with a Dinamap 1846 automated blood pressure monitor (CMS Ltd, London, United Kingdom), first with the participant seated and then while standing. Average of the two seated readings were used for analyses.

Body Mass Index

At Q1, height was measured without shoes using a Harpenden Stadiometer with digital meter which recording to the nearest millimetre. Weight in trousers and socks was measured to the nearest 0.1kg on an MPS110 field survey scale (beam balance) (86, 390).

At Q20, height and weight were both measured in standing position, with shoes and bulky items off. Height was measured with a Harpenden stadiometer to the last complete 0.1 cm. Weight was measured with a Soehnle digital electronic scale to the nearest 0.1 kg. For measurements falling between two 0.1 kg marks, the lower value was recorded. Body mass index (BMI) was calculated for each man in kg/m^2 .

Further anthropometric measurements included waist circumference measured using an insertion tape (CMS Ltd, London, United Kingdom) with the participant standing, feet one foot apart on a marked template, at the mid-point between the iliac crest and lower edge of the ribs above, at the end of expiration. And hip circumference measured around the hips at the point of maximum girth with the tape horizontal and the gluteal muscles relaxed. Both measures were recorded to the last completed millimetre, twice and an average was used.

Lung Function

At Q1, the Vitalograph J49-B2 with a digital meter recorded forced vital capacity and forced expiratory volume in one second (FEV1).

Spirometric lung function including FEV1 at Q20 was assessed using the Vitalograph Compact II (Vitalograph Ltd, Buckingham, UK), calibrated before every examination session using a precision syringe (408).

ECG

At Q1 ECGs were recorded on computer tape using the three-lead orthogonal system and viewed on an oscilloscope for any major abnormalities. The completed tapes for each town were sent to a collaborating centre for analysis by computer. In cases of technical problems a 12-lead ECG was recorded on a Hewlett-Packard (1515-B) machine and sent for analysis (390).

ECG at Q20 was measured using Siemens Sicard 460- 12 lead ECG, and computer interpreted at University of Glasgow ECG core laboratory based at Glasgow Royal Infirmary, analysed, and coded in accordance with Minnesota Coding definitions.

3.3.3 Blood Measures

Blood samples were collected by trained nurses at Q1 for measuring serum glucose, TC and HDL-cholesterol, using standard procedures.

Lipids

At Q20, blood lipid concentrations were measured at the Department of Chemical Pathology, Royal Free Hospital. Serum TC and HDL-cholesterol, and triglycerides were measured using an automated analyser Hitachi 747 (Hitachi, Tokyo, Japan) (409). LDL-cholesterol was calculated using the Fredrickson-Friedewald equation (410).

$$LDL = Total\ cholesterol - (Triglyceride / 5) - HDL$$

Triglycerides and LDL-cholesterol concentrations were adjusted for period of fasting and time of sample collection (409).

Fasting Glucose

At Q20, plasma glucose was measured using a glucose oxidase method with a Falcor 600 automated analyser (A Menarini Diagnostics, Wokingham, United Kingdom) at the Department of Chemical Pathology, Royal Free Hospital. Glucose concentrations were also adjusted for period of fasting and time blood sample was taken (409).

Cardiac Biomarkers

NT-proBNP and high sensitivity cardiac Troponin-T (hs-cTnT) were measured at Q20 using an automated clinically validated immunoassay analyser (e411, Roche Diagnostics, Burgess Hill, United Kingdom) with the manufacturers' calibrators and quality control reagents. The limit of detection was 5pg/ml for NT-proBNP and 3pg/ml for hs-cTnT. Samples with hs-cTnT recorded as <3 were assigned 2.99pg/ml.

Inflammatory Markers

At Q20, CRP was assayed by ultrasensitive nephelometry (Dade Behring, Milton Keynes, UK). IL-6 was assayed using a high-sensitivity ELISA (R&D Systems).

Kidney Function

Kidney function at Q20 was assessed through estimated glomerular filtration rate (eGFR), based on participant characteristics and measured creatinine using the Modification of Diet in Renal Disease formula (411).

3.3.4 Prevalent Conditions

At Q1 (middle-age: 40-59 years), prevalent CVD was self-reported based on recall of doctor diagnosed stroke, heart attack, MI, coronary thrombosis, and angina.

At Q20 (older age: 60-79 years), prevalent stroke, TIA, MI and HF were ascertained through GP reports/record reviews. Prevalent LVH was ascertained using Minnesota ECG codes (3.1 or 3.3), and AF using both GP reports and ECG findings (Minnesota codes 8.3.1 or 8.3.3). Prevalence of diabetes was based on reported physician diagnosis and/or diabetic medication or fasting glucose >7mmol/l. Further details are provided in specific chapters.

3.3.5 Incident Events

For the purpose of this thesis, mortality and incident events' follow-up ended in June 2018 (or at 10y for external validation of risk tools).

Mortality was ascertained through National Registers as described in 3.2.3.2 with cause of death coded using ICD-9. Fatal stroke was coded 430-438 and fatal MI 410-414.

Dates of non-fatal events – MI, stroke, TIA, HF and AF were ascertained from ad hoc GP reports and biennial reviews of participants' primary care medical records. Study definitions of non-fatal MI, non-fatal stroke and TIA align with WHO criteria and have been outlined in section 3.2.3.3. For noted MI, acute coronary syndrome, HF and stroke events, GPs were asked to provide further information on clinical presentation, hospital record summaries and results of specific relevant investigations where available. A BRHS clinical assessor reviewed this material to verify diagnoses.

3.4 BRHS Strengths and Limitations

BRHS is well suited for the study of stroke in older adults by virtue of its extended follow-up of a large broadly representative sample of British men, from middle to older

age. Stroke capture has been objective and reliable - the incidence rates of stroke observed using the study protocol, during both middle and older age, have been comparable with national data (87, 88). In addition, BRHS records TIA as a specific outcome. Although this is based only on primary care records, wider evidence suggests that 90% of stroke and TIA events are captured through GP data (58, 300), making it possible to reliably examine risk tools that include TIA in their outcome, and biomarker associations. The availability of PA and dietary measures has allowed estimation of CVH at older age, and multiple biomarkers measured using validated clinical assays have made it possible to explore effects of subclinical age-related cardiac (dys)function on stroke. However, numbers of HS are few and subtype specific analyses have not been possible.

3.4.1 Selection Bias and Health Cohort Effect in BRHS

Baseline Q1 comparisons between participants (78% response rate) and non-responders indicated men who did not participate were younger, more likely to be unmarried and less skilled workers (412). In the first three years of follow-up, non-responders had higher total mortality, but this reduced to non-significant levels ($p>0.05$) subsequently, while CVD mortality was similar in both groups; making associations internally valid.

Comparison between those who attended (77%) and failed to attend (23%) the Q20 examination indicated men who did not attend were a year older, more likely to be smokers and have physical disability, and with slightly higher rates of doctor diagnosed heart conditions, hypertension and diabetes, and markedly higher rates of reported stroke (413). They also had higher total mortality within a year of the Q20 exam, but majority of these deaths were non-cardiovascular. These comparisons suggest an element of selection bias. However, this thesis explores associations between CVH/NT-proBNP and stroke in those who are free of CVD, and a priori excludes those with a history of heart disease and stroke, as well as related conditions such as AF and HF. So, while these differences important, they are unlikely to have a major influence on confounder adjusted exposure-stroke associations in a primary prevention cohort.

The healthy cohort effect relates to a selection of survivors and is a critical challenge for ageing research. All participants being recruited at or above a certain age must

have survived to that (minimum) age in order to be eligible (414). If the exposure of interest influences this survival, then survivors with that exposure will represent the healthiest of that group and potentially distort exposure-outcome associations. However, exposure-outcome associations may be relied upon if there is sufficient heterogeneity in the exposure i.e., the sample displays a range of exposure levels (415).

It could fairly be argued though that BRHS findings are relevant to the current group of older adults and may not generalize to coming generations of older adults who would have been born later and experienced different early life conditions, as well as lived through different clinical and preventive practices.

Up until 2003, 68% of the participants have responded to all communications, and attrition due to death and emigration is representative of the source population (86). Linkage to national mortality registers, collaboration with GPs and meticulous periodic review of primary care records has enabled excellent follow-up rates. For analyses with baseline in Q1, 98% follow-up was available through to Q20. For analyses with baseline in Q20, 96% of participants have been followed up to 2018 (Figure 3.4).

It is also acknowledged that the BRHS is limited to men of predominantly European ethnicity so generalizability of findings to women and the wider ethnic groups is limited. The recruitment strategy avoided inner city populations and towns with high mobility. Nevertheless, this has enabled a stable cohort with high response rates. Further analysis-specific relevant limitations and strengths are elaborated on in each chapter.

3.5 The Southall and Brent Revisited Study (SABRE)

The SABRE study is a population-based multi-ethnic cohort study of European, and first-generation migrants of SA and African-Caribbean heritage. It began in 1988-1991 as two separate cross-sectional studies conducted to identical protocols, for investigating ethnic differences in burden of CVD and associated cardiometabolic risk factors (89, 90). Participants (80% male by design) were recruited from industrial workplaces (20%) or randomly selected from primary care physician lists (80%) in neighbouring London areas of Southall and Brent. At this baseline, participants completed a socio-demographic, health, and lifestyle questionnaire; underwent clinical

examination and provided fasting blood samples. Since then, participants have been flagged for death and causes of death (via the UK Office of National Statistics). Morbidity follow up has been conducted through self-report, primary care records and/or clinical exam at 20y (V2, 2008-2011), and at 25-30y (V3, 2014-2018), and by linkage to Hospital Episode Statistics (HES) provided by NHS Digital for traced participants (90).

SABRE has been funded at baseline by the UK Medical Research Council and Diabetes UK, and at follow-up by the Wellcome Trust and British Heart Foundation. All participants gave written informed consent. Approval for the baseline study was obtained from Ealing, Hounslow and Spelthorne, and University College London research ethics committees and at follow-up from St Mary's Hospital research ethics committee (Ref.07/H0712/109).

3.5.1 Recruitment

The Southall arm of SABRE recruited SAs and Europeans. A target of 1500 men (40-69y) per ethnic group was considered to have 90% power for detecting a 1.54 relative risk of prevalent CHD in SAs compared to Europeans at 5% significance. Recruitment was done from 4 factories in West London and 16 general practices in Southall and Greenford in the London Borough of Ealing, chosen based on a good mix of South Asian and non-Asian workforce/patients. The general practice component was boosted with a target sample of 600 women (416).

Of 1141 men invited at the factories, 808 (71%) agreed to participate. Of 7320 GP signed invitations sent to men and women registered at the practices, 4713 were delivered, of which 2946 (63%) were accepted. The final sample consisted of 1711 SAs (1420 men, 291 women) and 1762 Europeans (1516 men, 246 women). A small number of African Caribbeans (209 men, 14 women) also participated. The ethnicity specific overall response rates were 62% in the SA group and 66% among non-Asians.

The Brent arm recruited Europeans and African Caribbeans from 6 general practices in the inner London Borough of Brent. A sample of 300 subjects in each sex-ethnic group (40-69y) was calculated to have 90% power for detecting a 3.2% difference in mean SBP and DBP at 5% significance. Practice staff helped assign patients to one of five ethnic groups: European, SA, African Caribbean, other, and unknown. A random sample from the combined African Caribbeans and unknown group, stratified

by 5-year age group and sex was selected, along with an equal sample of Europeans chosen similarly. Of 3178 invitations sent, 2088 were delivered and 1218 accepted for attendance at study examination (response rate 58%). The final sample consisted of 578 African Caribbeans (244 men, 334 women) and 585 Europeans (272 men, 313 women) (417). In this thesis data only from European participants of the Brent arm has been examined.

In both locations, participants with cancer, renal failure, severe disability, severe psychiatric disturbances, or pregnancy were excluded.

3.5.2 Baseline Data Collection V1

Fieldwork was conducted over 1988-1990 in Southall, and 1990-91 in Brent. Participants were invited to a factory/local health centre after an overnight fast. Beforehand, they were asked to complete a self-administered questionnaire covering sociodemographic, lifestyle, occupational and past medical history including medication use (Appendix 3.9). This was checked by a bilingual interviewer on attendance. Research staff conducted clinical measurements, ECG, and obtained blood samples as per standard protocols (89, 416).

3.5.3 Follow-up Data Collection

3.5.3.1 Mortality Follow-up

ICD-9 and 10 codes for causes of death have been provided for participants flagged in National Mortality Registers by UK Office of National Statistics since baseline. Due to withdrawal of/non-response to consent requests, and emigration from the UK, mortality data for 8% of participants (n=373) is no longer available (Figure 3.5).

3.5.3.2 Morbidity Follow-up V2 and V3

Twenty years after baseline data collection (V2, 2008-2011), surviving participants living in England and Wales were invited to take part in a follow up comprising a health and lifestyle questionnaire, primary care record review (undertaken by trained members of the research team), a clinic visit at St. Mary's Hospital London or a combination of these (89). A further follow-up visit, along with augmented recruitment of partners of index participants, at 25-30y (V3, 2014-2018) focused on physical and cardiovascular ageing through questionnaire and clinical measurements (90). This

supplemented with Hospital Episode Statistics covering admissions and procedures since 1989 form the basis of the morbidity follow-up (Figure 3.5).

3.6 SABRE Study Data Used in This Thesis

This thesis examines the long-term impact of midlife CVH on stroke; the associations of NT-proBNP with stroke, and its added value for refining risk prediction in SAs. For these objectives, and to make useful ethnic comparison, the thesis uses (exposure) data provided by both SA and European participants from the **baseline visit 1998-91**, linked to deaths and non-fatal cardiovascular events follow-up **until 2011 (V2)**.

Below I elaborate on data collection methods of different exposures and covariates. These have been classified as self-reported, physical exam and blood measures. Prevalent disease and outcomes events are defined separately. The exact combination of exposure, covariates and outcomes used for each research objective are detailed in relevant chapters.

3.6.1 Self-reported Measures

Age

Calculated from reported date of birth.

Ethnicity

Ethnicity was agreed with interviewer based on name, country of birth, appearance, parental place of origin and/or further enquiry in case of doubt. SAs were defined as having ancestral origins in India, Pakistan or Bangladesh. Most were born in the Indian subcontinent (82%), 14% were born in East Africa, all were first generation migrants. European participants were classified by country of birth as native British, Irish or other.

Social Class

Participants were asked about their current or most recent occupation, qualifications/training and supervisory status. The Registrar General's classification of Occupations was used to assign midlife social class as five main categories and further grouped as manual/non-manual (418). Participants were additionally asked about age on starting and leaving full time education and home tenure.

Smoking

Participants were categorised into 'current' or 'never' or 'ex-smokers' using yes/no responses to the questions 'do you smoke cigarettes?' and 'have you ever smoked cigarettes regularly?'.

Physical Activity

Physical activity was derived as the total megajoules per week of energy expended in sports, walking, cycling and daily activities reported using questions and energy expenditure estimates based on the habitual physical activity questionnaire in epidemiological studies (419). Derivation of the SABRE LS7 PA metric is described in Chapter 4.

Diet

'Fresh fruit' and 'fresh green vegetable' intake was assessed using questions inquiring about frequency of consumption, with response categories 'not in the last week', 'once in the last week', '2-3 times in the last week', or 'on most days in the last week'. Derivation of the SABRE LS7 diet metric is described in Chapter 4.

Alcohol Consumption

Intake was derived from a series of questions on type, frequency, and quantity of drinks as the average number of units per week. A unit of alcohol was defined as half a pint of beer or cider, a glass of wine or fortified wine, or a single unit of spirits.

Health and Medication History

Participants gave yes/no responses on being asked if they had ever been told that they have or have had a range of conditions (heart attack, angina, heart failure, high blood pressure, stroke, arthritis, asthma, diabetes and kidney stones). They were asked if they experience chest pain on exertion and breathlessness when walking. They were also asked to list major illness or operations and prescription and over the counter medications.

3.6.2 Physical Measures

Blood Pressure

Seated brachial SBP and DBP were recorded as the mean of two readings measured after a 15-min rest using a random zero sphygmomanometer (Hawksley, London, UK).

Body Mass Index

Height was measured using a stadiometer without shoes and wearing a light hospital gown. Weight was measured using a Soehnle electronic scale. BMI was calculated as weight in kilograms divided by squared height in metres. Body fat measurements were also conducted for waist circumference (as the smallest girth between the costal margin and iliac crests) hip circumference (over greater trochanter) and mid-thigh, using a fibreglass tape with a spring balance set to a constant tension of 600 g. Anthropometry was measured by four trained observers, one acted as the standard and periodic standardization measurements were made during the study to ensure good interobserver reliability.

ECG

All participants underwent resting 12-lead electrocardiography. Minnesota criteria (420) were used to identify major Q waves.

3.6.3 Blood Measures

Lipids

HDL was separated by dextran sulphate/magnesium precipitation (Technicon, USA) within 48 h. Plasma triglyceride and cholesterol were measured in a centrifugal analyser by enzymic colorimetric techniques--glycerol phosphate oxidase ('Triglyceride N', Wako, Japan) and cholesterol oxidase (C-System, Boehringer, Germany). Cholesterol readings obtained with Boehringer 'Precilip EL' as the standard were multiplied by 0.93 to recalibrate them to the reference method of the Centres for Disease Control (416).

Fasting Glucose

Glucose after overnight fast was measured by the glucose oxidase method in a Yellow Springs analyser with an aqueous standard (Southall) (416) and the hexokinase method Roche, Switzerland (Brent) (417). Subjects without diabetes also underwent a glucose tolerance test including a second blood sample 2h after the glucose load. Participants with known diabetes were not asked to fast or undergo a glucose challenge and provided a non-fasting sample.

Cardiac Biomarkers

NT-proBNP and hs-cTnT were measured as in BRHS, in plasma samples on an automated clinically validated immunoassay analyser (e411, Roche Diagnostics,

Burgess Hill UK). All assays used the manufacturer's calibration and quality control materials. The limit of detection was 5pg/ml for NT-proBNP and 2.5pg/ml for hs-cTnT. A correction formula was applied to values below the lower limit of detection for each measure i.e., lower limit divided by square root of 2, which is a frequently used although imperfect method of dealing with unreported values (421).

Inflammatory Markers

Serum CRP was measured on an automated platform (c311, Roche Diagnostics, Burgess Hill UK).

Kidney Function

Creatinine and cystatin C were measured in stored serum samples by an automated clinically validated platform (c311, Roche Diagnostics, Burgess Hill, UK) using the manufacturer's calibrators and quality control material. Coefficient of variation of the serum assays was < 3.5%. Estimated glomerular filtration rate was derived using CKD Epidemiology Collaboration (CKD-EPI) eGFR estimating equations based on serum cystatin C and creatinine separately (422).

3.6.4 Prevalent Conditions

CHD or stroke occurring prior to study participation was identified by self-report of doctor diagnosed disease from baseline questionnaire, along with presence of pathological Q waves on ECG for CHD. Baseline diabetes was identified by self-report of physician diagnosis or WHO 1999 criteria (423) for fasting and oral glucose-tolerance testing blood glucose measurements or by report of anti-diabetic medication use.

3.6.5 Incident Events

For the purpose of this thesis, follow-up for all incident events ended in 2011.

Deaths were ascertained through National Registers as described in 3.5.3.2. Fatal stroke was coded ICD-9 430-439 or ICD-10 I600 to 1698. Fatal CHD ICD-9 410-415 or ICD-10 I200 to 1259 (and included death due to angina, MI or its sequelae, or atherosclerotic heart disease). Non-fatal events were identified as follows.

Stroke

- Review of primary care data by 2 senior physicians blinded to ethnicity and participant identity for definite or probable diagnosis of stroke according to pre-

determined criteria based on symptoms and their duration, magnetic resonance imaging or computed tomography.

- Hospital Episode Statistics with diagnostic codes ICD-9 430-439 or ICD-10 I600 to 1698.
- Participant report of physician-diagnosed stroke and symptom duration exceeding 24hrs.

CHD

- Review of primary care data by 2 senior physicians blinded to ethnicity and participant identity. A CHD event was noted if both agreed on definite or probable diagnosis of myocardial infarction or acute coronary syndrome, according to predetermined criteria used in the Anglo-Scandinavian CARDIAC Outcomes Trial (based on symptoms, cardiac enzymes, ECG and hospital discharge diagnosis) (Sever et al., 2001). A third physician adjudicated if necessary. Coronary interventions and angina confirmed on exercise testing were included as incident events.
- Hospital Episode Statistics with diagnostic codes ICD-9 415-415 or ICD-10 I200 to 1259, together with operation codes K401-469, K491-504, K751-759 and U541 from the Office of Populations and Surveys classification of interventions and procedures.

3.7 SABRE Study Strengths and Limitations

The SABRE Study is unique in having two decades long prospective follow-up of a reasonably large cohort of first generation British SAs, allowing midlife health and disease markers to be examined for effects on later life outcomes. European participants have been recruited and examined using similar locations and procedures making ethnic comparisons of effects of exposures reliable and informative. For the 2011 endpoint considered in this thesis, follow-up is available for 90% of the baseline participants, and characteristics of those with/without follow-up are similar within each ethnic group (51).

Stroke events have been identified using multiple sources. However, the number of stroke events is modest and limits analysis by fatal and non-fatal events or by stroke

subtypes which as elaborated on Chapter 2 varies by ethnicity. Formal validation of risk prediction tools that have a 10y horizon has also not been possible (objective 2 is only explored in BRHS). SABRE participants are also predominantly male. Among SAs, more than 50% are of Punjabi Sikh origin which may limit the applicability of findings to other SA subgroups – although all experience increased CVD burden. Moreover, the burden of both exposures and incident events observed among first generation migrants may not hold true for subsequent generations.

Further, baseline measures were collected 30-years ago. And clinical and prevention practice will have changed over follow-up. It is likely that effect sizes are an approximate reflection of real associations. However, with limited research data available for studying the migrant SA population, findings add to the knowledge base for future work.

3.8 Statistical Methods

All statistical analyses have been conducted in STATA (versions 14-17) and are cohort specific. Research-objective specific methods have been described in detail in each chapter. Below is a general description of the main statistical techniques used.

Analyses exclude those with baseline CVD. While this is a necessity for defining ideal CVH, and of risk prediction of a first event; for exploring associations of biomarkers with stroke this is intentional because those with a positive CVD history are generally under management/surveillance strategies that would influence stroke risk and hence relevance of findings for primary prevention of stroke. This also helps avoid some degree of reverse causation that could influence poor cardiovascular health in particular health behaviours like smoking, PA and diet. Potential confounders and mediators have been selected based on literature on CVD risk factors, stroke in older adults and SAs (as described in Chapter 2).

For statistical tests, a p-value <0.05 is taken as statistically significant. For tests of interaction, the threshold is kept at $p < 0.10$. However, effect sizes and 95% confidence intervals are given due consideration in interpreting results.

3.8.1 Descriptive Statistics

Continuous variables were examined for normality using histograms and normality tests. Characteristics of participants were described using means ($\pm$ standard deviations SD) for normally distributed continuous variables such as BP; and medians (interquartile range-IQR or 25th and 75th quartiles-Q1 and Q3) for non-normally distributed variables such as physical activity. Biomarkers with skewed distributions such as NT-proBNP were log transformed and standardized. Categorical variables were summarised as proportions (%).

Statistical comparisons between groups (for e.g., European and SAs, or across quantiles of biomarker values) were conducted using parametric (t-tests/one-way ANOVA) and non-parametric tests (Mann-Whitney U/Kruskal Wallis/Chi-squared/Fisher exact) as appropriate.

3.8.2 Multivariable Linear Regression

Linear regression is a common statistical method for examining associations between a normally distributed outcome variable y and an exposure variable x . In multivariable linear regression additional confounding variables x_n are added to get as accurate as possible an estimate of the association between y and the exposure of interest, allowing for the effects of these other variables (424).

The cross-sectional association between ethnicity and log-transformed NT-proBNP was assessed using multivariable linear regression models (Chapter 6).

3.8.3 Survival Analysis

In longitudinal studies following individuals over time, the outcome variable is the continuous survival time T , from beginning of follow-up (e.g., entry into study BRHS Q1, or new data collection such as BRHS Q20), to the occurrence of a binary event of interest (e.g., stroke). For individuals who are lost to follow-up, who die from a cause other than the event of interest during follow-up, or who do not experience an event up until the end of follow-up, T ends at these points and is considered censored (425).

While accounting for incompletely observed or censored survival times, a survival function S estimates the probability that a subject selected at random will have a survival time T greater than some stated value t ; in other words, will survive (i.e., not have experienced the event of interest) up to and including t , given by

$$S(t) = \Pr(T > t)$$

Most commonly, estimation of this survival function is by the Kaplan-Meier (KM) method, which was used across the 4 thesis objectives to plot and compare survival curves across exposure groups (using the log rank test) over the respective follow-up periods (t) and calculate incidence rates.

The KM method was also used to estimate the failure function F or *observed risk* by time t , using the survival estimate in

$$F(t) = 1 - S(t)$$

for comparison with predicted risk in external validation of risk prediction tools (Chapter 5).

3.8.4 Cox Proportional Hazards Regression

Studying the effect of exposures/covariates on survival requires modelling how they influence the probability of an event occurring during any given time assuming it has not already occurred. This probability is given by the hazard function h which may or may not be constant over the follow up period. The Cox Proportional Hazards model is a semi-parametric regression modelling approach which allows estimation of the effect of exposures on the hazard function without specifying its shape. Instead its key assumption is that the ratio of the hazards in exposed and unexposed groups remains constant even if the underlying hazards change over time (424). Using Cox models, the hazard function for those with a positive exposure is given by:

$$h(t) = h_0(t) \times \exp(\beta_1 x_1)$$

where $h(t)$ is the hazard at time t , $h_0(t)$ is the baseline hazard (the hazard for an unexposed individual in whom exposure = 0) at time t , and x_1 a binary exposure variable (here taking the value of 1).

The hazards ratio (HR) comparing hazards in exposed and unexposed individuals at time t is then given by:

$$\begin{aligned} HR(t) &= \frac{h_0(t) \times \exp(\beta_1)}{h_0(t)} \\ &= \exp(\beta_1) \end{aligned}$$

Informally, it can be interpreted similarly to an odds ratio or relative risk.

The assumption that the hazards (whatever their underlying shape) are proportional is assessed visually by near parallel log cumulative hazards/survival plots, and/or formally by tests based on Schoenfeld residuals.

The model can be extended to include x_n covariates, including those that change over time.

Cox models were used to assess the covariate adjusted associations between CVH and stroke events (Chapter 4), for external validation of risk tools (Chapter 5), and for examining associations of biomarkers with stroke (with adjustment for intervening cardiac events as time-varying covariates, Chapter 6) as well as added values of biomarkers for risk prediction (Chapter 7).

3.8.5 Population Attributable Fraction

The impact of an exposure on disease at the population level depends on the risk ratio associated with the exposure as well as its prevalence.

The population attributable fraction (PAF) is the excess burden of disease in the population associated with an exposure; and assuming a causal relationship, also the fraction of disease that could be eliminated if the exposure was removed/reduced.

There are multiple methods to calculate PAFs. The simplest formula for PAF is given by Levin's equation:

$$PAF = \frac{Prevalence(RR - 1)}{1 + Prevalence(RR - 1)}$$

where prevalence is the population prevalence of exposure, and RR the relative risk of disease associated with exposure. Covariate adjusted RRs can be used to account for confounding. This method is limited to finding the PAF for a single risk factor.

In this thesis, PAF was calculated using the scenario-based `punafcc` Stata post estimation command described by Newson (426), and based on the method of Greenland and Drescher (427). This compares the mean hazards between a fantasy scenario where values of one or more of the exposure variables are assumed to be nil, and a baseline scenario with real world exposure (keeping other predictors constant). It thus first estimates as a ratio (and 95% CIs) how much hazard would have

remained if the exposure was eliminated known as the population unattributable fraction or PUF. This is then subtracted from 1 to get the fraction attributable to the exposure i.e., PAF. The method can be used to calculate PAFs for single or multiple/combined exposure variables, in a model with covariates and interaction terms.

PAFs were assessed in Chapter 4 to estimate the burden of stroke attributable to sub-optimal levels of CVH.

3.8.6 External Validation of Risk Assessment Tools

External validation is defined as ‘assessing the performance of a (risk prediction) model already developed, when applied to an independent dataset’ (428) for example, data from a population that belongs to a different historical period or geographic location than the development cohort (286).

The risk tools evaluated in this thesis in Chapter 5 are all based on Cox models, and use the following equation to estimate 10-year predicted risks:

$$P = 1 - S_0(10)^{\exp(\text{Centred Prognostic Index})}$$

For external validation, the same equation was used for calculating BRHS specific predicted risks where,

- $S_0(10)$ was the published 10y baseline survival function of the relevant risk tool.
- Prognostic Index was the linear predictor of the form $\beta_1 X_1 + \beta_2 X_2 + \dots \beta_n X_n$, calculated for each individual using published predictor beta coefficients multiplied by BRHS values of predictor variables.
- Centred Prognostic Index was the prognostic index centred using published means.

For composite-CVD tools, predicted probabilities were multiplied by the proportion of all events that represented stroke events obtained from authors/publications.

The two main indicators of model performance - discrimination and calibration are based on components of this equation.

3.8.6.1 Discrimination

This refers to the ability of a model to discriminate or distinguish those that experience an event from those that do not. In survival data, a risk prediction model is said to

discriminate well when it consistently assigns a lower/higher prognostic index or risk score to individuals with longer/shorter time-to event respectively. This is most commonly measured using Harrell's C-index (also called concordance index) (429) which is the fraction of all pairs of participants who can be ordered such that the one with the higher predicted survival (lower risk) is the one who survived longer (286) i.e. for which the predictions are concordant. Due to censoring, ordering is only possible for pairs in which both participants have had an event, or if one has a censored follow-up the other has had an event at an earlier point in the follow-up.

$$C_{index} = \frac{No. of concordant pairs}{No. of concordant pairs + No. of discordant pairs}$$

The C-index can range from 0.5 (as good as chance) to 1 (perfect discrimination). A value <0.7 is considered suboptimal (291).

The C-index most commonly obtained using a post-estimation command following a Cox regression, along with its 95% CIs, was used in this thesis to compare discrimination of stroke-specific or composite-CVD risk prediction tools. Additionally, visual inspection of separation of KM survival curves of 4 risk groups according to 16th 50th and 84th centiles of the prognostic index was also conducted (428).

3.8.6.2 Calibration

This refers to the agreement between predicted and observed risk. A well calibrated prediction model assigns the correct probability of event across the range of predicted risk (428). As described by Van Calster et al (430) and summarised by Steyerberg (286), sequentially stronger levels of calibration can be assessed.

- **mean calibration (calibration in the large)** is assessed as the ratio of global mean predicted risk to observed risk, where a ratio greater/less than 1 indicates global over/under-estimation.
- **calibration slope** is assessed using the beta coefficient of the centred prognostic index as a single predictor in a Cox model, indicating overfitting where the slope is < 1 and underfitting where the slope is > 1. Together with calibration in the large, this comprises **weak calibration** and is used to judge systematic over/underestimation of risks.
- **moderate calibration** is assessed by comparing observed risk at specified follow-up with mean predicted risk in deciles of predicted risk. This is often done

graphically as a calibration plot of observed risk against predicted risk alongside a 45-degree line of identity (perfect predictions).

- **strong calibration** implies that the predicted risks are equal to the observed event for each and every covariate pattern or specified subgroups.

A formal test of calibration (such as the Hosmer-Lemeshow test) for observed vs expected numbers of events in groups of participants has been suggested but this is limited in the information it provides (not much more than a p-value). It is also influenced by the flexible grouping, lacks power to detect systematic miscalibration or overfitting in small data sets and is very sensitive to large samples (286).

Hence calibration in this thesis was examined using a combination of calibration slope, calibration in the large and calibration plots produced using the pmcalplot Stata package (431). To my knowledge there is no consensus on the definition of a poor calibration slope, but arbitrary thresholds of < 0.7 (general tendency to overestimate) or > 1.3 (general tendency to underestimate) have been used (291). Assessment of calibration plots is also widely based on visual judgement (432-434)

3.8.6.3 External Validation While Adjusting for Competing Mortality

Performance of stroke-specific and composite-CVD risk tools was also examined while accounting for competing non-stroke mortality. A C-index of discrimination was obtained by adjusting the survival time of men experiencing non-stroke death to greater than the prediction time horizon ($>10y$) as suggested by Wolbers et al (435).

Calibration slope was estimated using the Fine and Gray (436) method fitted by the `stcrreg` Stata command to get the slope of the centred prognostic index, and the Wald test was used to test if this was different from 1. Mean and moderate calibration was assessed by comparing predicted risk with overall/group based cumulative incidence function obtained with the user written `stcompet` Stata package (437). Calibration plots were produced separately in Microsoft Excel.

3.8.7 Incremental Value of Biomarkers

For Chapter 7, the added value of a biomarker was first established by confirming an independent association with the outcome when added to a base model containing known established predictors. For a fair assessment, the risk equations were calibrated to BRHS data while for SABRE the base model was fitted directly to the

data for obtaining SABRE-specific predictor coefficients. Improvement in such nested models was tested formally using a likelihood ratio test (71, 286).

Additional measures for quantifying the added value of the biomarker included

- The **fraction of new information provided by the biomarker** (438) estimated using the formula

$$1 - Adequacy Index$$

Where,

$$Adequacy Index = \frac{Likelihood Ratio Chi^2 of the base model}{Likelihood Ratio Chi^2 of the base + biomarker model}$$

- Improvement in discrimination assessed by comparing the **C-index** of the base and base plus biomarker models. However, this is a rank measure which does not adequately reflect the magnitude of change in predictions, and changes in the C-index can be minimal especially if the base model already has reasonable discrimination.
- **Net Reclassification Improvement** (NRI) i.e., the difference in ability of the base and base plus biomarker models to correctly assign individuals to pre-defined risk categories, in the case of stroke events (NR_{Ie}) and non-events (NR_{Ine}). This is based on the expectation that the new biomarker would increase predicted risks for events and hence move them up the risk categories, and lower predicted risks for non-events and move them down the risk categories (439). Risk classification tables showing categorization of participants have been detailed in Chapter 7.

$$NR_{Ie} = \frac{Number of events moving up - Number of events moving down}{Number of events}$$

$$NR_{Ine} = \frac{Number of nonevents moving down - Number of nonevents moving up}{Number of nonevents}$$

- **Integrated Discrimination Improvement** or IDI, measures discrimination as the 'separation in predicted probabilities between events and non-events' using models with and without the biomarker (440). The advantage of IDI is that it

does not require pre-specified categories and takes into consideration all levels of risk improvement without losing information due to categorization (71).

$$IDI = (P_{biom} \text{ among events} - P_{biom} \text{ among nonevents}) - \\ (P_{base} \text{ among events} - P_{base} \text{ among nonevents})$$

Where, P_{biom} is the mean predicted probability estimated using the model containing the biomarker, and P_{base} the mean probability estimated using the base model.

3.8.8 Examination of Missing Data

Estimates of missing data, and characteristics of participants with and without complete data on model variables compared using appropriate statistical tests, are described in the relevant chapter sections. Predictors of missingness were explored based on data and contextual knowledge, and statistically confirmed using logistic regression models. In cases where data cannot be assumed to be missing completely at random, complete case analysis (although less precise because of loss of data from incomplete cases) is unbiased if given these predictors, missingness is independent of the outcome (441-443). This was further confirmed using logistic regression models comprising the stroke outcome and identified predictors of missingness as model variables, with missingness as dependent variable.

Table 3.1 Towns included in the British Regional Heart Study

Town	Standardised Mortality Ratios for Cardiovascular Disease in Men 35-65y, 1969-73	Number of Men Examined	Percent Response Rate
Ayr	140	301	70
Bedford	80	303	73
Burnley	114	286	80
Carlisle	121	389	85
Darlington	109	382	82
Dewsbury	142	326	79
Dunfermline	118	350	80
Exeter	90	332	84
Falkirk	98	308	75
Gloucester	84	309	73
Grimbsy	96	318	71
Guildford	78	335	82
Harrogate	82	280	77
Hartlepool	101	334	70
Ipswich	92	362	85
Lowestoft	85	324	83
Maidstone	99	319	72
Mansfield	95	321	80
Merthyr Tydfil	135	282	76
Newcastle-upon-Lyme	115	293	77
Scunthorpe	109	313	76
Shrewsbury	95	310	83
Southport	114	322	80
Wigan	134	337	77

Table adapted from Shaper et al, '*British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns*', Br Med J (Clin Res Ed), 283: 179-86. (390)

Table 3.2 Type and duration/frequency of physical activity with assigned scores

Activity	Score
Regular walking	
None	0
≤ 20 min/day	1
21-40	2
41-60	3
61-90	4
>90	5
Cycling	
None	0
≤ 15 min/day	2
16-30	4
31-45	6
46-60	8
>60	10
Recreational activity	
Very inactive	0
Fairly inactive	1
Average	3
Fairly active	5
Very active	7
Sporting activity	
None	0
Occasionally (< 1 month)	2
1-3 times/month	4
4-7	8
8-11	12
12-15	16
16-19	20
≥ 20	24

Scores for low intensity sports such as fishing and bowls were capped at 4.

Table courtesy of *Physical activity and ischaemic heart disease in middle-aged British men* (400)

Figure 3.1 Map of 24 British Regional Heart Study towns in Great Britain



Figure courtesy of *COHORT PROFILE The British Regional Heart Study 1975–2004*
(86)

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Figure 3.2 The British Regional Heart Study Timeline

Overview of British Regional Heart study (BRHS) cohort follow-up

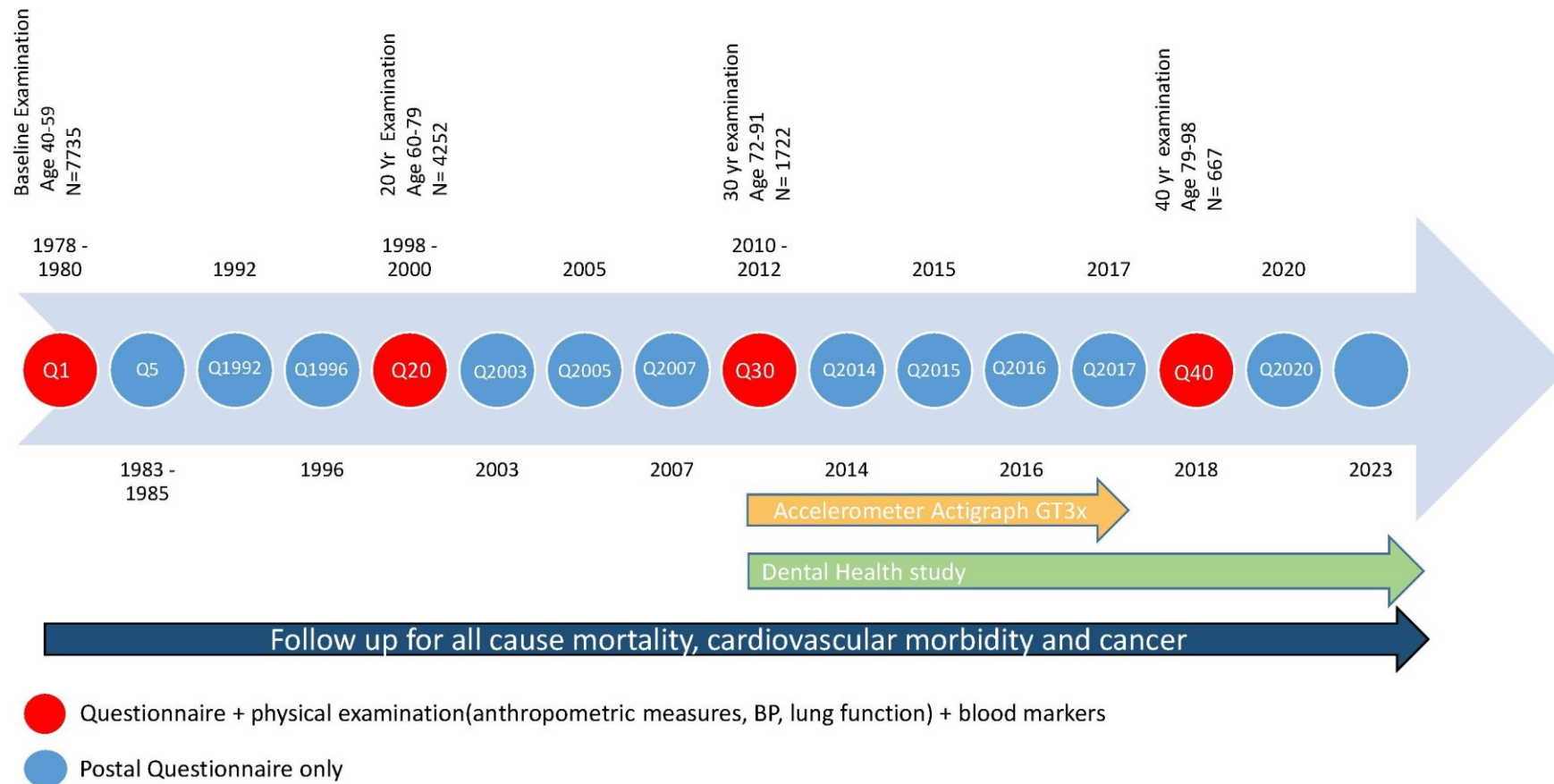


Figure provided by Lucy Lennon, Study Manager BRHS (444)

Figure 3.3 BRHS participant numbers at successive data collection points

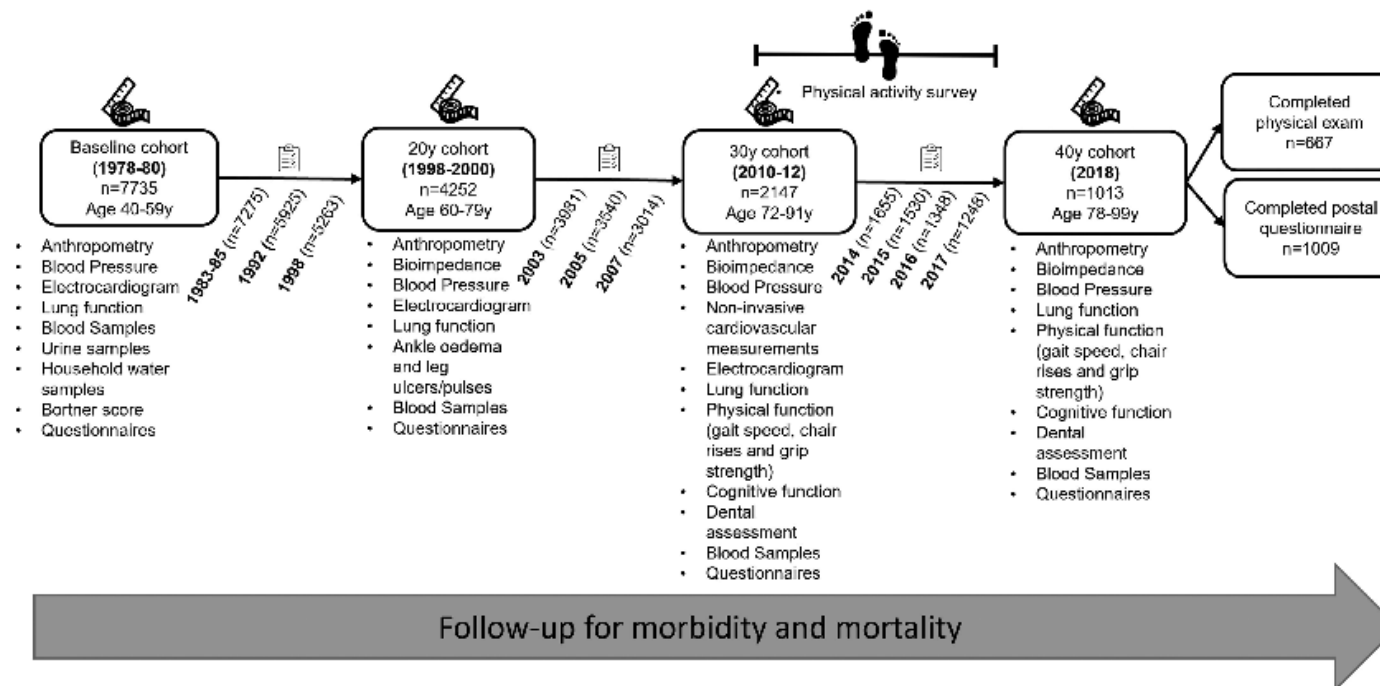
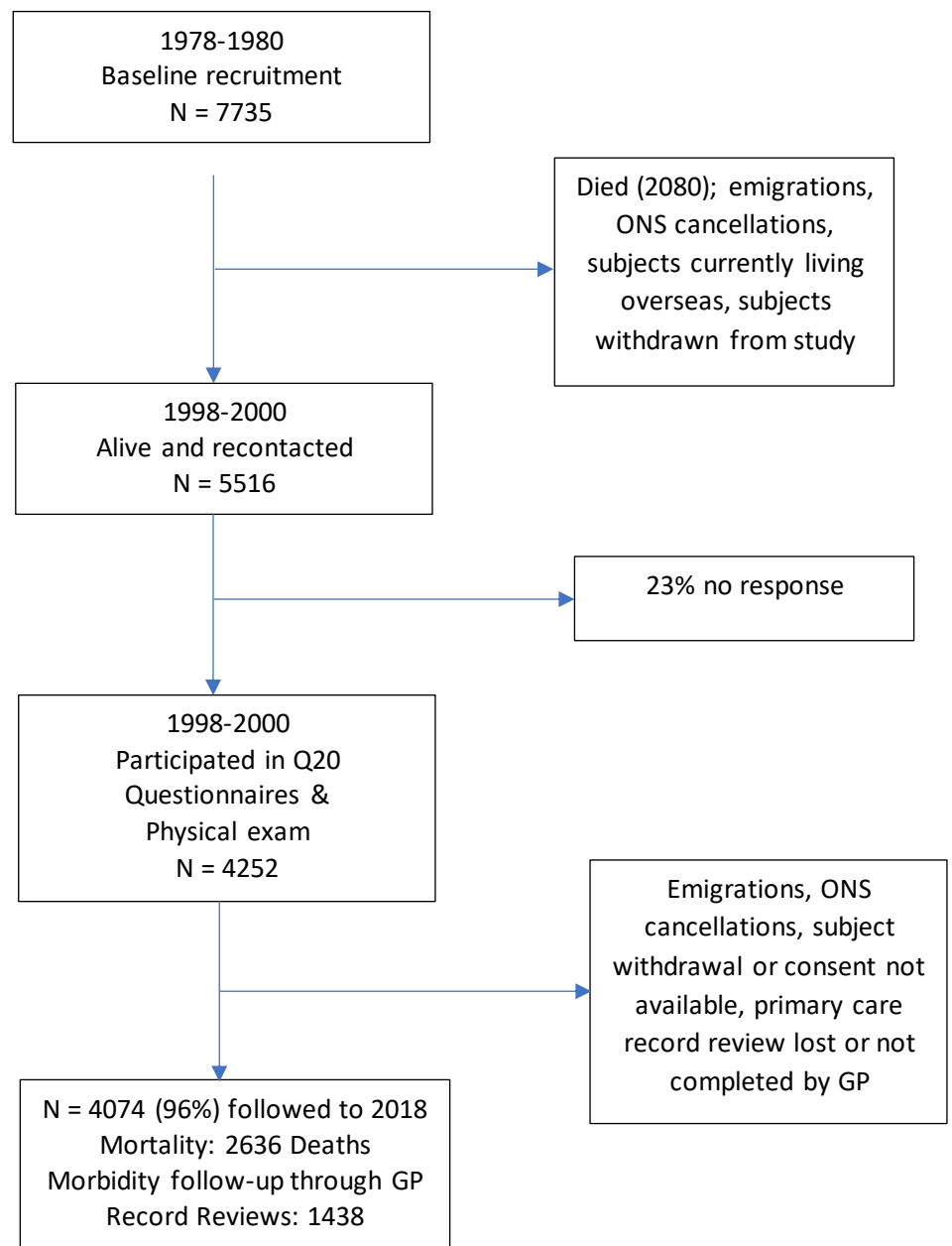


Figure courtesy of *Cohort Profile Update: The British Regional Heart Study 1978–2018: 40 years of follow-up of older British men* (392)

Figure 3.4 BRHS Participant numbers and attrition from baseline 1978-80 to end of follow-up in June 2018



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Figure 3.5 Follow-up and participant numbers from baseline V1 1988-91 to re-examination V2 2008-2011 of the SABRE study.

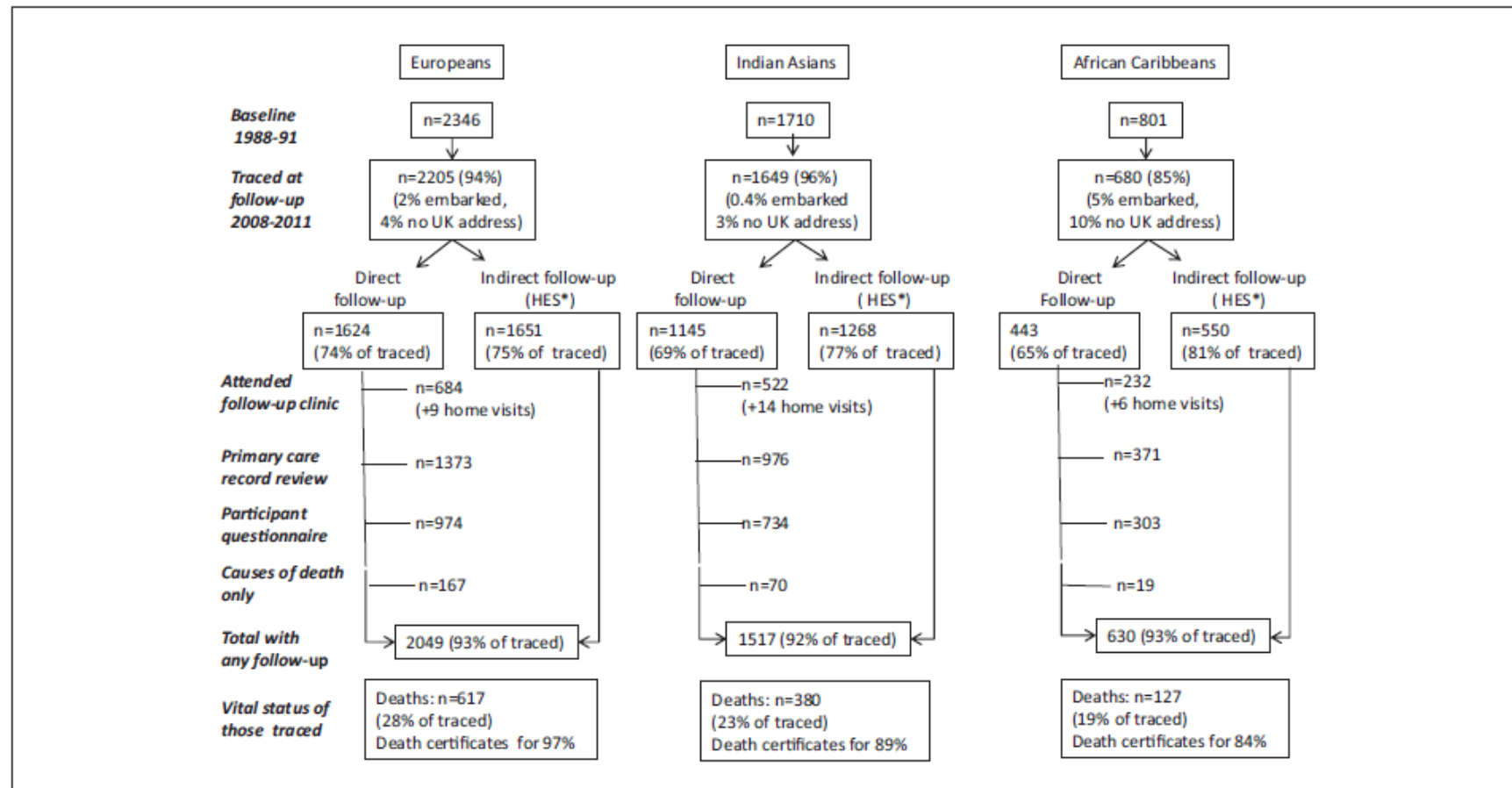


Figure courtesy of *The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited) -- a prospective population-based study* (51)

Chapter 4. Cardiovascular Health and Stroke: Prospective Associations and Impact

4.1 Summary

Better CVH has been associated with reduced risk of CVD. Most of this evidence, however, comes from research among middle-aged adults of European ancestry that evaluates stroke as one of multiple composite-CVD endpoints. Older adults and SAs are vulnerable to higher burdens of stroke. But how useful is CVH as a stroke-specific primary prevention strategy in these groups is less clear. This chapter examined the long-term (over 20 years) impact of CVH on stroke in (1) older age using data from BRHS men from middle-age onwards, and (2) middle aged SAs using data from the SABRE study. CVH was measured as an aggregate of component LS7 metrics. The association of CVH with stroke was estimated using Cox models in each cohort, and its impact estimated from population attributable fractions of stroke i.e., proportion of stroke events attributable to sub-optimal levels of CVH. In BRHS men, the associations of CVH with, and its impact on stroke decreased considerably from middle to old age. Among component LS7 metrics, BP retained the main albeit reduced impact. In SABRE SAs, better CVH was associated with decreased stroke risk, such that improving CVH to optimal levels could potentially avert more than a third of the stroke burden, with BP and FPG having the greatest impact on stroke. Findings suggest that for older adults, prevention strategies should increase focus beyond CVH to detection and management of wider age related causes of stroke. Among SAs, all components of CVH require attention, but this analysis emphasizes that interventions for some metrics may need to be prioritised.

Findings from this chapter relating to older men have been published as a peer-reviewed article (97); Cardiovascular Health and Stroke in Older British Men: Prospective Findings From the British Regional Heart Study. *Stroke*, STROKEAHA120030546. <https://doi.org/10.1161/STROKEAHA.120.030546>.

Findings comparing impact of CVH on stroke between South Asians and Europeans have been shared as an oral presentation at the Society of Social Medicine and

Population Health, Annual Scientific Meeting, Sept 2022; Prospective Associations of Cardiovascular Health with Stroke and Coronary Heart Disease in Europeans and South Asians https://jech.bmj.com/content/76/Suppl_1/A24.2 (98).

4.2 Introduction

As elaborated in section 2.3, the CVH model was devised by the AHA for advancing prevention of CVD (52). The original model consists of a collection of 7 traditional biological and behavioural cardiovascular risk factors – the LS7 metrics (BP, cholesterol, FPG, smoking, PA, diet and BMI) each categorised into ideal, intermediate and poor levels, which are then scored together to measure overall CVH. According to the model, ideal CVH corresponds to having ideal levels of all LS7 metrics (see Table 2.4 for criteria for each metric) in the absence of drug treatment in those without prevalent CVD, thus placing emphasis on primordial prevention.

Expectedly, robust protective trends have been noted between better CVH and the risk of future composite-CVD, comprising mainly CHD, and also stroke and various other manifestations of atherosclerotic CVD (53, 256, 257). Relatedly, evidence from US adults indicates that a substantial burden (70%) of composite-CVD may be avoided by achieving high CVH (55).

However, despite overlap in risk factors, stroke aetiology remains distinct from that of CHD (section 2.2.5.3), and the role of CVH may therefore be nuanced when it comes to component CVD subtypes. This may be especially true for older adults and SAs who experience a proportionally higher burden of stroke (13, 194); and in whom stroke aetiology, distribution of traditional risk factors, and their associations with stroke are different from younger/non-SA populations (sections 2.2.4.2 and 2.2.4.3).

Yet estimates of prospective associations of CVH with stroke as a specific outcome in CVD free older adults are limited (56, 258, 259) and in CVD free SAs yet to be reported (sections 2.3.2 and 2.3.3). In particular, there is little to no evaluation (266) of the population-level benefit of improving CVH in terms of specifically decreasing stroke burden i.e., the fraction of stroke that could be averted by eliminating sub-optimal CVH in the two high-risk groups.

Additionally, the CVH model stands out because of its simplicity, allowing for easy monitoring of CVH status and separate LS7 metrics, in individuals and across populations over time. Studies examining CVH indicate that prevalence of all LS7 metrics being at an ideal level is extremely low globally; and adults >60y have worse CVH (254). But studies describing associations between change in CVH status and future events have again focused on composite-CVD (270, 271) or are limited to short follow-up times (272). Whether modifying CVH status between midlife and old age can mitigate subsequent stroke risk in later life remains unclear.

This chapter therefore aims to examine the utility of CVH as a primary prevention strategy for stroke in older adults and in SAs.

4.3 Objectives

1. To compare CVH status and prevalence of component LS7 metrics among middle-aged and older British men (BRHS); and between middle-aged Europeans and first generation British SAs (SABRE).
2. To examine long-term associations of CVH with stroke risk in middle-aged and older BRHS men; and among middle-aged European and SA participants of SABRE.
3. To estimate the burden (PAF) of stroke attributable to sub-optimal levels of CVH and nonideal levels of LS7 metrics in middle-aged and older BRHS men; and among middle-aged European and SA SABRE participants.
4. To explore if change in CVH status between middle and older age is associated with subsequent stroke incidence in later life among BRHS men.

4.4 Methods

Study design, data collection and follow-up methodology for BRHS and SABRE have been detailed in Chapter 3. Analyses described in the current chapter use data on LS7 metrics and covariates collected via questionnaires and physical exams in

- the BRHS from the recruitment phase Q1 (1978-80, age 40-59y), and the 20-year follow-up examination Q20 (1998-2000, age 60-79y).

- the SABRE study from the baseline visit V1 (1998-91, age 40-69y)

4.4.1 Assessment of CVH

In both BRHS and SABRE, LS7 metrics were measured objectively except for smoking, PA and diet (details in section 3.3 for BRHS and section 3.6 for SABRE). Each metric was categorized into poor, intermediate and ideal levels, assigned 0, 1 and 2 points respectively; using AHA criteria (52) except for smoking, PA and diet which were classified using study specific definitions (Table 4.1). Points were added together to give each participant an overall CVH score (range 0-14), with higher scores indicating better CVH. The score was further categorised into poor (0-4) average (5-9) and optimal (10-14) CVH status. Because diet was not measured in BRHS at Q1, CVH score at Q1 ranged from 0-12 (with CVH status poor = 0-4, average = 5-8, and optimal = 9-12).

In BRHS, change in CVH from Q1 to Q20 was captured using trajectories, derived from CVH scores exclusive of diet (range 0–12) from each time point. The median value of 7 was used to dichotomize CVH scores, with a score ≤ 7 classed as low and >7 as high CVH. Each participant was consequently assigned to one of 4 CVH trajectory groups: low-low, low-high, high-low, and high-high.

4.4.2 Covariates

Age, social class and alcohol intake were self-reported in questionnaires as explained in sections 3.3.1 and 3.6.1.

4.4.3 Prevalent Conditions

In **BRHS**, prevalent CVD at Q1 (stroke, angina, coronary thrombosis, and MI) was determined from self-report of physician diagnosis; and at Q20 if a stroke or MI were noted in primary care record review data before Q20. AF at Q20 was determined using a 12-lead ECG at examination and through primary care records. HF at Q20 was determined using self-report of doctor diagnosed HF and from primary care records.

In **SABRE**, CHD or stroke occurring prior to study participation was identified by self-report of doctor diagnosed disease from V1 questionnaire, along with presence of pathological Q waves on ECG for determining CHD.

4.4.4 Incident Events and Mortality

BRHS men were followed for mortality and non-fatal stroke and MI from middle-age in Q1 to Q20, and again from older age in Q20 to 1st June 2018. Deaths were ascertained via NHS Central Registers as described in section 3.2.3.2. Causes of death were coded using ICD-9 (fatal stroke 430–438 and fatal MI 410–414). Non-fatal stroke and MI were ascertained through ad hoc reports from GPs and biennial review of primary care records, and further verified as described in sections 3.2.3.3 and 3.3.5.

SABRE participants were followed for mortality and non-fatal stroke and CHD from middle-age at baseline visit V1 in 1988-91, over 20y until 2011. Deaths were ascertained through National Registers as described in section 3.5.3.1 (fatal stroke ICD-9 430-439 or ICD-10 I600 to I698; fatal CHD ICD-9 410-415 or ICD-10 I200 to I259, and included death due to angina, MI or its sequelae, or atherosclerotic heart disease). Non-fatal stroke and CHD were identified by review of primary care data, through Hospital Episode Statistics with relevant diagnostic codes; through participant report of physician-diagnosed event; or a combination of these as detailed in sections 3.5.3.2 and 3.6.5.

4.4.5 Statistical Analyses

Objectives 1-3 have been addressed in both BRHS and SABRE. Objective 4 was only explored in BRHS which has data from middle-age to late-life. All analyses excluded participants with a history of stroke and CHD/MI.

4.4.5.1 Descriptive Statistics

Sociodemographic characteristics and distribution of LS7 metrics, CVH scores and CVH status categories between participants who did/not experience a stroke event; and profiles of CVH trajectory groups in BRHS, were compared using t-tests/Mann-Whitney U tests and Chi-squared/Fisher exact tests as appropriate.

4.4.5.2 Survival Analysis and Cox Proportional Hazards Regression

Crude stroke incidence was estimated per 1000 person years (/1000PY) through survival analysis. Stroke free survival probabilities were estimated across CVH status categories and trajectories using KM survival curves and tested using the log-rank test.

Cox models estimated hazard ratios (HRs) of stroke for each LS7 metric, per unit increase in CVH score, across CVH status categories and trajectory groups. Time to

event was calculated from date of participation (Q1 and Q20 in BRHS, V1 in SABRE) to a fatal or non-fatal stroke event or death, or end of follow-up (i.e., in BRHS, date of participation in Q20 for Q1 analysis and June 2018 for Q20 analysis; in SABRE the year 2011) whichever came first. Adjustments were made for social class at recruitment, and age and alcohol intake at the respective time point. Analyses in SABRE were conducted separately for each ethnic group a priori, and also adjusted for sex.

Proportional hazards assumptions examined for CVH status categories using Schoenfeld residuals were found to be valid across the follow-up period.

4.4.5.3 Population Attributable Fraction

The PAF of stroke or fraction of incident stroke events attributable to non-ideal level of LS7 metrics and to sub-optimal CVH status was estimated from adjusted models in both cohorts using the punaffcc Stata package (426), based on the method recommended by Greenland and Drescher (427) (see details in section 3.8.5). It evaluated the scenario where all participants had an ideal level of LS7 metric(s) or optimal CVH status.

4.4.5.4 Sensitivity Analyses

A number of sensitivity analyses were conducted.

1. To account for any influence of HF and AF, and associated management in older BRHS men, the association between CVH and stroke was examined after excluding those with prevalent HF and AF at Q20.
2. Associations were explored between CVH and MI (BRHS) or CHD (SABRE), and the composite-CVD outcome.
3. Lower BMI obesity thresholds have been recommended for SAs to reflect the increased cardiometabolic risk associated with their greater proportion (and central distribution) of body fat relative to muscle mass (see section 2.2.4.3). To explore the impact of these stricter BMI criteria on stroke; CVH status and its impact in SABRE SAs were additionally estimated using WHO recommended (World Health Organization Expert Consultation, 2004) BMI criteria for Asians (23kg/m² for overweight and 27.5kg/m² for obesity).
4. Main analyses described above were conducted on complete cases. However, characteristics of participants with missing data on CVH and covariates were

compared using descriptive statistics; and depending on proportion of missing data validity of complete case analysis was examined, along with robustness of associations by assigning the worst possible LS7 level (poor) to those with missing data on any LS7.

4.5 Results

4.5.1 Prevalence of LS7 Metrics and CVH Status

BRHS

Figure 4.1 illustrates the prevalence of LS7 metrics in BRHS men across middle and older age.

In BRHS, out of 7735 men recruited at Q1, 7112 (mean age 50y) were free of CVD and had complete data on LS7 metrics. Among LS7 metrics, FPG (65%) was most and BP (9%) least prevalent at ideal levels. Mean composite CVH score was 6.3 (range, 0–12), with 71% men in the average and only 12% in the optimal CVH category (Table 4.2). After a median follow-up of 19.8 years, 421 fatal and nonfatal stroke events occurred at a rate of 3.3/1000 PY [95%CI 3.01-3.65]. Only 15 men had all 6 of the LS7 metrics (diet was not measured at this examination) at an ideal level, none of whom experienced a stroke. Compared to men who remained stroke free, those who experienced a stroke were slightly older and more commonly worked in manual professions. Fewer of these men had LS7 metrics at an ideal level (except for cholesterol), and consequently, their mean CVH score was slightly lower (5.6 vs 6.3), with only 6% having optimal CVH status. Figure 4.2 demonstrates their worsening stroke free survival with deteriorating CVH status.

Among 4252 older BRHS men who participated at Q20, 3177 (mean age 68y) were free of stroke and MI with complete data on LS7 metrics. Smoking status (84%) was most and BP (6%) least prevalent at ideal levels. Mean composite CVH score was 7.7 (range 0–14, and mean 6.8 range 0-12 if excluding diet), with 76% men in the average (74% if diet excluded) and 18% in the optimal (16% if diet excluded) CVH status category (Table 4.2). After a median follow-up of 16.3 years, 363 fatal and nonfatal stroke events occurred at a rate of 8.2/1000 PY [7.44-9.14]. Fewer than 5 men had all 7 LS7 metrics at an ideal level, none of whom experienced a stroke. Compared to men who remained stroke free, those who experienced a stroke were slightly older and had

higher SBP and DBP, with a smaller proportion having the BP metric at ideal level. There were no statistically significant differences in the distribution of other LS7 metrics, CVH scores and overall CVH status. Figure 4.3 demonstrates the similar/overlapping stroke free survival across CVH status categories.

SABRE

Among middle-aged participants of the SABRE study free of stroke and CHD; SAs (n=1352, mean age 51y) were slightly younger than Europeans (n=1860, 53y), more commonly in manual occupations, and more frequently reported nil/low alcohol intake (Table 4.3). Less than 1% of both ethnic groups had 7 metrics at ideal level and 3% had poor overall CVH (score 0-4), however, more SAs had optimal CVH (score $\geq$ 10, 38% vs 33% in Europeans) (Appendix 4.1 and Table 4.3). This was mainly related to SAs having a markedly higher prevalence of non-smokers (79% vs 32% Europeans) and slightly better prevalence of ideal FFV intake (61% vs 55%), despite a lower prevalence of ideal FPG (55% vs 64%), BP (32% vs 40%) and PA (18% vs 29%) (Figure 4.4).

After a median follow-up of 20y, SAs experienced 131 and Europeans 146 stroke events at a rate of 5.1/1000PY [4.3-6.0] and 4.2/1000PY [3.6-5.0] respectively. This equates to an age and sex adjusted relative risk of 1.40 [1.09-1.77] among SAs compared to Europeans. Figure 4.5 displays worsening stroke free survival according to CVH status in both ethnic groups. In both ethnic groups, participants who went on to have a stroke were ~4y older and had worse CVH, particularly higher prevalence of poor BP and FPG, while European participants also had higher prevalence of smoking and non-ideal cholesterol (Table 4.3).

4.5.2 Long-term Risk of Stroke Associated with CVH

BRHS

In models adjusted for age, social class and alcohol intake (Table 4.4), a unit increase in CVH score was associated with 16% reduced risk of stroke (HR 0.84 [0.79–0.89]) in middle-aged BRHS men, and with 5% reduced risk (HR, 0.95 [0.90–1.01]) in older BRHS men. The protective trend associated with better CVH status i.e., average, or optimal compared to poor also attenuated (Figure 4.6) from middle-age (HR 0.59 [0.47-0.73] for average CVH and 0.39 [0.25-0.61] for optimal CVH, p for trend <0.001)

to older age (0.73 [0.46, 1.15] for average and 0.68 [0.41, 1.13] for optimal CVH, *p* for trend 0.14).

Appendix 4.2 shows associations with stroke of ideal and intermediate levels of individual LS7 metrics relative to poor. Although some trends did not reach statistical significance, healthier levels of all 6 measured metrics were associated with reduced risk of stroke in middle-aged BRHS men. Among older men however, BP remained the only metric showing a statistically significant protective trend, which was weaker in magnitude than for middle-aged men. FPG and PA showed non-significant associations in the expected direction. Diet was not associated with stroke; and associations with cholesterol and BMI appeared to reverse (i.e., higher risk with ideal levels) although these were also not statistically significant.

SABRE

Among middle-aged SABRE participants, a unit increase in CVH score was associated with similarly reduced risk of stroke in SAs HR 0.84 [0.77-0.92] and Europeans HR 0.91 [0.83-0.99] (Table 4.5). Likewise, better CVH status was associated with similar protective trends in both ethnic groups, although the trends fell just short of conventional (*p*<0.05) statistical significance. HR for average and optimal CVH in SAs 0.75 [0.30-1.87] and 0.41 [0.15-1.07]; and in Europeans 0.65 [0.30-1.41] and 0.49 [0.21-1.11] in EUs, respectively (Figure 4.7).

Appendix 4.3 shows risk of stroke across levels of LS7 metrics in each ethnic group. Among SAs, BP and FPG showed statistically significant strong protective trends, while BMI and cholesterol showed non-significant associations in expected directions, and smoking was not associated with stroke. In comparison, among Europeans FPG and smoking showed significant protective trends while BP, diet and ideal levels of cholesterol showed non-significant associations in expected directions.

4.5.3 PAF of Stroke Attributable to Sub-Optimal CVH

BRHS

Estimation of PAF showed that among middle-aged BRHS men, 39% [95%CI 9.98-58.1] of the stroke burden over the subsequent 20y period was attributable to sub-optimal i.e., poor, or average CVH status (Table 4.6). For older men, 6% [-16.8-25.0] of the stroke burden over a median follow-up of 16y (and 10% [12.8-28.4] based on a score that excluded diet) was attributable to sub-optimal CVH (Figure 4.8). The PAFs

of stroke linked to individual LS7 metrics also decreased with age, particularly for smoking. While the PAF of stroke remained greatest for non-ideal BP among all metrics, this was also reduced from middle age to older age by nearly a third.

SABRE

Among middle-aged SABRE participants, 36% [11.3-53.4] of strokes occurring over the subsequent two decades in SAs and 21% [-7.03-41.4] in Europeans were attributable to sub-optimal CVH (Table 4.6 and Figure 4.9). Among individual metrics in SAs, the largest fraction of stroke was attributable to non-ideal BP and then to non-ideal glucose. For Europeans, the largest PAF was due to non-ideal cholesterol, followed by smoking.

4.5.4 Change in CVH of BRHS Men Over Time

A fifth of BRHS men maintained high CVH from Q1 to Q20 and just under a fifth improved their CVH from low to high. Half of the men had persistently low CVH over the same period and CVH of 13% of the men deteriorated from high to low (Table 4.7). Incidence rates [95% CI] of stroke/1000PY were low-low 9.8 [8.6–11.2]; low-high 6.2 [4.7–8.2]; high-low 7.3 [5.5–9.8]; and high-high 7.9 [6.3–9.8]. In comparison to low-low, all remaining groups showed reduced probabilities of stroke (Figure 4.10). Low-high in particular had a 40% statistically significant reduced stroke risk (HR, 0.60 [0.44–0.83]).

4.5.6 Sensitivity Analyses

BRHS

Of 3177 men without CVD, with complete data on LS7, n=49 (1.5%) had prevalent HF and n=130 (4%) had AF. Excluding these participants did not make material differences to CVH and stroke associations (Appendix 4.4).

In older BRHS men, inverse trends between better CVH status and MI, and the composite outcome of MI and stroke, appeared stronger than for stroke alone. Nearly 30% of the combined cases of MI and stroke were attributable to sub-optimal CVH at Q20. In analysis comparing trajectories to low-low, all groups had significantly reduced risk of MI and composite events; with the high-high group having a particularly low risk

of MI and the high-high and low-high groups having a similarly low risk of the composite outcome (Appendix 4.4).

Consideration of missing data

At Q1, less than 3% of men without a history of CVD were missing data on LS7 metrics or covariates. At Q20, 17% of men without a history of CVD were missing data on LS7 metrics or covariates. Missing data on diet was 6%, on cholesterol and glucose 4%, on PA 2% and <1% on other metrics/covariates. Compared to those with complete data (n=3135), men with missing data (n=663) were a year older with higher stroke event rate (p=0.18), but with similar mean SBP, DBP and smoking habits (Appendix 4.5). Men with missing data had slightly worse overall CVH in midlife, while their mean CVH score excluding diet at Q20 was similar.

Missingness was associated with 4 of the LS7 metrics – poorer diet and PA, cholesterol, and BMI; as well as with age and social class. Age was the only variable fully observed i.e., missingness was dependent on a combination of observed and missing data and hence was assumed missing not at random. In a model adjusted for predictors associated with missingness; missingness was independent of stroke.

Further, when robustness of associations was examined by assigning the worst possible LS7 level (poor) to those with missing data on any LS7 (worst case scenario approach), there was no marked change in associations and PAF (Appendix 4.6).

SABRE

In SAs and Europeans, inverse associations between CVH and CHD, and CVH and the composite outcome of CHD and stroke were similar; and appeared stronger than for stroke (Appendix 4.7). About a third of the burden each of stroke, CHD, composite-CVD was attributable to sub-optimal CVH in SAs. In Europeans, a greater burden of CHD (45%) and composite-CVD (36%) compared to stroke (21%) was attributable to sub-optimal CVH.

On applying Asian BMI cut-offs (23kg/m² for overweight and 27.5 kg/m² for obesity), 244/644 (~40%) SAs were reclassified from intermediate level BMI to poor, and another 292/538 (~50%) from ideal to intermediate. This reduced the proportion of with optimal CVH from 38 to 30% (Appendix 4.8). The inverse association between CVH and stroke was stronger and significant such that SAs with optimal CVH (Asian BMI cut-offs applied) had a 72% lower risk of stroke compared to those with poor status,

leading to an increase in PAF of stroke from 36 to 44% (Appendix 4.7). The magnitude of associations with, and impact on, CHD remained unchanged.

Consideration of missing data

Among SABRE participants (without a baseline history of CVD and with event follow-up) proportion with missing data on LS7 metrics or covariates was low (8% SAs and 5% Europeans), with characteristics very similar to those with complete data, and no statistically significant differences in stroke event rate within each ethnic group (Appendix 4.9).

4.6 Discussion

4.6.1 Summary of Key Findings

This chapter examined the impact of CVH on stroke in older men and SAs, and hence utility of the CVH framework for stroke prevention in these groups.

Ideal CVH (all LS7 metrics at ideal level i.e., score 14) was extremely rare (<1%). Just under a fifth of older BRHS men had optimal CVH (i.e., a score ≥ 10). Between midlife and older age, the long-term association of CVH with stroke risk became weaker. The burden of stroke attributable to sub-optimal CVH or, the fraction that could be eliminated if all participants achieved optimal CVH, also decreased; and was lower than the fraction of MI/composite-CVD attributable to sub-optimal CVH in older age. The impact of non-ideal BP also diminished but remained highest among all metrics. However, compared to having low CVH status through adult life, improvement in CVH between middle and older age was associated with reduced later life stroke risk.

Middle-aged SAs had slightly better CVH than their European counterparts, and this was driven by different combinations of underlying metrics. Optimal CVH was associated with a 60% (statistically non-significant) reduced risk of stroke. A little more than a third of the stroke burden in SAs was attributable to sub-optimal CVH compared to a fifth in Europeans. This increased further when lower Asian BMI thresholds for obesity were used to estimate CVH. Among individual LS7 metrics, the largest impact on stroke was due to non-ideal BP followed by non-ideal glucose.

4.6.2 Comparison with Studies Examining CVH in Relation to Stroke in Older Adults

CVH status among older BRHS men (nearly a fifth with optimal CVH, and 6% with 5 or more ideal metrics) was similar to that observed among older White/European participants recruited contemporaneously in the Northern Manhattan (258), REGARDS (259) and French-3C studies (56). The comparison in CVH status between middle and older age conducted by this examination of BRHS men suggested this was actually a small improvement from midlife, and linked to increased prevalence of ideal PA, cholesterol and (non) smoking despite falling prevalences of ideal BP, BMI and glucose. Ideal (non) smoking was similarly reported as the best metric across these cohorts (56, 258, 259) and ideal BP as the worst among older French adults (56).

A protective inverse association between better CVH and stroke reported in these studies of older adults (56, 258, 259) was also noted among older BRHS men, albeit smaller in magnitude possibly due to a longer follow-up. With reference to inadequate CVH, HR of optimum CVH was 0.49 [0.29-0.89] among White participants of REGARDS (259) compared to 0.68 [0.41-1.13] among BRHS men. However, BRHS analysis additionally found that this protection was clearly weaker in comparison to protection offered by CVH over a similarly long follow-up in midlife. This is likely explained by the attenuated/reversed associations of underlying LS7 metrics (section 2.2.4.2) observed across the two time points, including the weakened association of BP as the key risk factor for stroke (128). In support, a most recent age-stratified examination of the REGARDS cohort describes a significantly smaller magnitude of associations of hypertension, diabetes and smoking with ischaemic stroke events between the ages of 45y-80y (445).

Together these lead to a considerably reduced proportion of the stroke burden (only 6%) being avoidable by all men achieving *optimal* CVH (CVH score ≥ 10) in older age compared to middle age (39%). In the context of primary prevention, to my knowledge this is the first study estimating the impact of CVH specifically on stroke in older Europeans, and how this varies from midlife. Previous work among predominantly middle-aged Chinese adults (266) reported nearly 2/3rd of the stroke burden would be avoidable if everyone could attain *ideal* CVH (all LS7 metrics at an ideal level). In comparison, BRHS analyses also showed that among middle-aged men, the burden of stroke avoidable by having ideal CVH was significant at 73% (excluding diet), but

this decreased to 38% for older men (whether or not diet was considered) (Table 4.6). However, using the full range of CVH score (0–12/14) as opposed to only an aggregate of ideal LS7 metrics (0–6/7) considers intermediate levels of a metric and may be more realistic for older adults when drug therapies for diabetes mellitus, dyslipidaemia, and hypertension preclude ideal levels of these risk factors.

Relatedly, the burden of stroke which could potentially be eliminated by achieving ideal BP control also decreased from (50% to 35%) with age, and was similar to that estimated (despite using slightly different methodology) by the Rotterdam study (225) among men of a similar mean age (69y) as BRHS; and to the PAF of hypertension calculated (with a higher cut-off) among European participants of the INTERSTROKE study (27) (which also noted hypertension as a stronger risk factor in those <55 years). It is likely that even this (35%) is an overestimate, since practically, all men of older age are unlikely to attain ideal BP as defined by the AHA. Both the Rotterdam and INTERSTROKE studies also reported a similarly small PAF of stroke due to diabetes as noted for non-ideal levels of FPG in older BRHS men (27, 225).

Despite the long follow-up, BRHS analysis noted stronger and significant inverse associations of CVH with MI as a specific endpoint, and with the composite endpoint of MI and stroke among older men. This was reflected in the higher PAF of MI (40%) and the composite endpoint (27%) compared to stroke alone (6%), and alludes to the greater influence of conventional factors in old age on coronary outcomes as opposed to stroke, as has also been documented among Swedish men (64). Findings suggest that CVH based health promotion targeting conventional factors such as LS7 among older adults would be less likely to reduce the burden of stroke in contrast to MI (discussed further under implications in Chapter 8).

4.6.3 Comparison with Studies Examining Changes in CVH

Trajectory analysis looked at the potential of improving low CVH from midlife to older age. In previous work analysing associations of change in CVH status with broad CVD outcomes, Enserro et al (270) using a 5y median follow-up of the Framingham Offspring study concluded that irrespective of whether they improved or not, people starting with low CVH status had higher rates of composite-CVD compared with those maintaining high CVH through the study period. In comparison, analysis of Whitehall-II data based on a much longer follow-up indicated a small benefit for those improving

CVH from low to high, although a more precise categorization of CVH trajectories (9 groups based on low, moderate and high CVH) failed to show consistent associations with incident CVD (271).

In BRHS analysis, older BRHS men who improved CVH from low to high had reduced risk of stroke or MI combined, of a magnitude like that associated with maintaining high CVH throughout adult life, implying later life CVH can have a greater bearing on subsequent CVD. And this benefit was also apparent for stroke alone. However, it was not possible to say when between middle and older age men may have transitioned in CVH status, or indeed, if there was >1 transition. Exposure durations may hence be variable, and hazards may not accurately reflect this. Moreover, the binary CVH score cut-off was arbitrarily based on the median for both Q1 and Q20, although this is similar to how trajectory groups have been created by others (270).

4.6.4 Comparison with Studies Examining CVH in South Asians

The distribution of LS7-based CVH status in SABRE SAs is comparable to that found in other studies conducted in populations of SA ancestry (273, 278), with some variation in the prevalence of individual metrics making up CVH. In the MASALA study (278) of US-based SAs (40-84y, mean 55y), and the Indian multi-centre cross-sectional survey of middle-class urban men and women (20-75y) reported by Gupta et al (273), prevalence of all 7 metrics at ideal level was as low (<1%) as SABRE (0% in MASALA); and a similar proportion of participants had ≥ 4 metrics at ideal level (~40% vs 37% in SABRE-SAs). Both studies began almost 2 decades after SABRE yet all three describe a consistently high prevalence of ideal (non) smoking, a consistently low prevalence of ideal BP and a remarkably similar prevalence of ideal BMI (<25kg/m², 40-44%) between SABRE, MASALA and 40-69y Indian adults. Gupta et al also report ideal PA as one of the least frequent metrics as in SABRE.

In support of this similarity in BMI, all of SABRE (89, 94) and 98% of MASALA (446) participants were immigrants, majority being born in India; and having lived in the UK or US for an average of at least 2 decades, perhaps indicating a notional 'healthy migrant' effect. However main migration to the US took place later than to the UK, and included individuals who were professionals or migrating for higher education. This is reflected in nearly 90% of the MASALA cohort being educated to degree level, with majority reporting above average annual income compared to 75% of

SABRE participants belonging to a manual social class. Moreover, the prevalence of ideal diet (measured by an adapted food frequency questionnaire) was extremely low among the MASALA cohort. These differences may lead to an expectation of lower BMI levels among the earlier arriving UK migrants. But in contrast to SABRE, MASALA recruited SA participants over a wider age range, with roughly equal numbers by sex for each decade starting from 40 to 70y and excluded anyone with weight >136kg (due to its CT scan measures protocol) (446). Additionally, a third of Masala participants reported walking for exercise with a high proportion of participants meeting ideal physical activity levels (278), which may all have influenced the prevalence of ideal BMI. It would be very interesting to examine how CVH in general and BMI in particular compares between second generation migrants to the UK and US.

4.6.5 Comparing Impact of CVH between South Asians and Europeans

In comparison to European participants, the slightly higher prevalence of optimal CVH in SABRE SAs is encouraging. However, this was mainly linked to greater prevalence of a single metric i.e., non-smoking behaviour in SAs. The proportion of SAs with ideal BP and glucose – two key stroke risk factors was significantly lower. Level of ideal PA was also worse, as indicated by other comparisons (207, 447).

While previous work based on limited follow-up of SABRE has recorded a greater impact of combined health behaviours (smoking, FFV intake, physical activity and alcohol intake) on composite-CVD in SAs compared to Europeans (448), to my knowledge this thesis is the first in documenting the prospective impact of the CVH model on stroke in SAs. Associations with overall CVH score were evidently protective. Slightly over a third of the stroke burden would be avoidable if all SAs achieved optimal CVH. This impact was larger than the impact of CVH on stroke in Europeans. Although it was not possible to disaggregate stroke subtypes in SABRE, this is conceivable given the higher prevalence of cerebral small vessel disease and lacunar strokes in SAs (18, 209), with a stronger link to hypertension (50) and dysglycemia (11, 51). The individual PAFs of stroke for non-idea levels of BP (67%) and glucose (22%) were much higher than those noted for Europeans and support this observation. These estimates are also similar in magnitude to the PAFs reported for high BP (55.8%) and high FPG (24.7%) by the GBD study for the South Asia region using slightly stricter defining criteria and different methodology (2).

PAF of stroke increased slightly once BMI risk thresholds were lowered for SAs. A comprehensive meta-analysis concluded that BMI had a J-shaped dose-response relationship with (all) stroke, with Asians having an increased risk at relatively lower BMIs (27.5kg/m^2) compared to Europeans (30kg/m^2) (142). The stringent BMI thresholds placed more SAs with increased risk in a poor/average CVH status and the increased PAF of stroke agrees with this observation. The impact on CHD remained unchanged possibly due to the stronger association of (BMI linked) hyperglycaemic states with stroke as opposed to CHD in SABRE-SAs (51, 211).

4.6.6 Strengths and Limitations

General strengths and limitations of the two data sets have been presented in sections 3.4 and 3.7.

Specifically for this chapter, the BRHS analysis is novel in examining the impact of CVH on stroke as a specific outcome – using prevalence, effects and attributable burdens, during both middle and older age within the same population; with near complete follow-up, over an extended period and with reliable stroke capture (87, 88). While participants are limited to British-White men, findings are relevant to a large section of the older UK and wider European population. A measure of diet was not available at middle age and for deriving CVH trajectories, but the contribution of an overall dietary score to CVH, which also includes factors with which a healthy diet is linked, may be less consistent with respect to stroke/CVD (56, 259, 262). Other methodological limitations include survivor selection bias which is inherent to long-term prospective studies. BRHS men must have survived to a minimum age of 60y to become participants of the Q20 examination (60-79y). It is possible therefore that men with poor CVH at Q20 represented the healthiest group of such men who theoretically had a risk of stroke not vastly different from contemporaries with better CVH, resulting in an underestimate of the impact of CVH on stroke. However, while survivor bias could underlie the magnitude of the association; the noted effect size can still inform the focus of preventive measures in this or similar groups of survivors. Additionally, this should not affect internal validity of findings, and examining a group of survivors may be more relevant for translating findings to a globally ageing population.

The SABRE study data made it possible to compare the distribution of CVH/LS7 metrics between SAs and Europeans within the same cohort, and importantly to study

the prospective impact of CVH in SAs. Although SABRE has a reasonably large cohort of SAs and Europeans, the number of stroke events is modest, and could not be classified into subtypes. SABRE participants are predominantly male, while some metrics like BMI may have sex-specific effects. Although no significant interactions were noted between CVH and sex, the analysis may have been limited in detecting such a difference. SABRE-SAs are first generation migrants of Indian descent and so findings may not be fully generalizable to later generations or to SA groups living in non-urban settings elsewhere (274). It should also be mentioned that although a large proportion of SAs were categorised to be ideal with respect to non-smoking behaviour; this metric does not include a measure of forms of smokeless tobacco the consumption of which is prevalent among some sections of the SA population (449, 450). Evidence of a harmful (albeit weak) association between chewing tobacco and stroke has been noted based on studies from India and Bangladesh (451). It remains to be established how incorporating the various forms of smokeless tobacco within the CVH metric would affect its impact on the burden of stroke between ethnic groups.

Importantly, in both cohorts, definitions of PA and diet differ from that prescribed by the AHA, however they have been applied similarly to the Q1/Q20 analyses in BRHS, and to both ethnic groups in SABRE and should have internal validity. Both PA and diet were also self-reported and may suffer from misclassification. In SABRE especially, estimates of PA levels are generally in the higher range, possibly due to social reporting bias. Additionally, measuring diet as FFV intake captures only one quantitative component of a wider healthy diet. FFV intake was noted to have high prevalence in SABRE, but this could not account for the qualitative characteristics of this intake. The analysis may hence be underestimating the true effect of PA and diet on stroke.

4.7 Conclusion

The stroke-specific impact of CVH reduces from midlife to old age, with only 6% of the stroke burden attributable to sub-optimal CVH in older men. This supports the argument that prevention efforts targeting traditional risk factors and behaviours should begin early such that optimal CVH is achieved well before old age sets in. Among middle aged SAs, just over a third of the stroke burden was due to sub-optimal

CVH, with main contributions from BP, glucose and potentially BMI. The public health and research implications of these findings for primary prevention of stroke in both groups are discussed at length in Chapter 8.

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Table 4.1 Classification of LS7 metrics (points) in BRHS and SABRE participants.

	BRHS Q1 (1978-80) and Q20 (1998-2000)			SABRE 1988-91		
	Ideal (2)	Intermediate (1)	Poor (0)	Ideal (2)	Intermediate (1)	Poor (0)
Body Mass Index* (kg/m ²)	<25	25 to <30	≥30	<25	25 to <30	≥30
Blood pressure* (mmHg)	<120/80 and untreated	SBP ≥120 - <140, or DBP ≥80 - <90 or treated to goal	SBP ≥140 or DBP ≥90	<120/80 and untreated	SBP ≥120 - <140, or DBP ≥80 - <90 or treated to goal	SBP ≥140 or DBP ≥90
Blood Glucose* (mmol/l)	<5.6 and untreated	5.6 to <7.0 or treated to goal	≥7.0	<5.6 and untreated	5.6 to <7.0 or treated to goal	≥7.0
Total Cholesterol* (mmol/l)	<5.2 and untreated	5.2 to <6.2 or treated to goal	≥6.2	<5.2 and untreated	5.2 to <6.2 or treated to goal	≥6.2
Smoking	Q1 Never smoked. Q20 Never smoked or gave up > 5y ago	Q1 Ex-smoker. Q20 Gave up smoking up to 5y ago	Q1 & Q20 Smoking currently	Never smoked	Ex-smoker	Smoking currently
Physical Activity	Physical activity index of ≥9 corresponding to Moderate, Moderately Vigorous, and Vigorous PA	Physical activity index of 3-8 corresponding to Occasional to Light PA	Physical activity index of 0-2 i.e., Inactive	Upper quartile of MJ/week energy expended in sports, walking, cycling and daily activities	Middle quartiles MJ/week	Lowest quartile MJ/week
Diet	Only at Q20 Top tertile of EDI 27-35	Only at Q20 Middle tertile of EDI 24-26	Only at Q20 Bottom tertile of EDI 12-23	Both FFV on most days or either one on most, and the other 2-3 days/week	Both FFV on 2-3 days/week or either one never or once/week	Both FFV never or once per week

*AHA criteria. DBP: diastolic blood pressure, EDI: Elderly Diet Index, FFV: fresh fruit and vegetables, PA: physical activity, SBP: systolic blood pressure

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Table 4.2 Sociodemographic and CVH characteristics of middle-aged (Q1) and older (Q20) BRHS men free of prevalent stroke and heart disease.

	Q1 1978-1980			P value	Q20 1998-2000			P value
	Total Cohort (N=7112)	Men without incident stroke (N=6691)	Men with incident stroke ¹ (N=421)		Total Cohort (N=3177)	Men without incident stroke (N=2814)	Men with incident stroke ² (N=363)	
Age (yrs)	50 (5.8)	50 (5.8)	53 (5.4)	<0.001	68 (5.4)	68 (5.4)	70 (5.4)	<0.001
Social class								
Non-Manual	40	41	33	0.01	48	48	48	0.79
Manual	57	57	62		49	49	50	
Armed Forces	3	3	4		3	3	2	
Alcohol intake								
None	6	5	8	0.05	9	9	10	0.51
Occasional	24	24	20		26	26	30	
Light	33	33	31		45	45	41	
Moderate	27	27	28		16	16	15	
Heavy	11	11	13		3	3	3	
BMI (kg/m²)	25 (3)	25 (3)	26 (3)	0.03	27 (3.6)	27 (3.6)	27 (3.5)	0.98
Poor	8	8	10	0.07	16	16	13	0.20
Intermediate	46	46	48		53	53	56	
Ideal	46	47	42		32	32	32	
SBP (mmHg)	145 (21)	144 (20)	155 (25)	<0.001	150 (24)	150 (24)	155 (25)	<0.001
DBP (mmHg)	82 (13)	82 (13)	86 (16)	<0.001	86 (11)	86 (11)	87 (12)	0.01
Blood Pressure								
Poor	58	57	72	<0.001	67	67	73	0.045
Intermediate	33	34	24		26	27	23	
Ideal	9	9	4		6	7	4	

4 Impact of CVH on Stroke

	Q1 1978-1980			P value	Q20 1998-2000			P value
	Total Cohort (N=7112)	Men without incident stroke (N=6691)	Men with incident stroke ¹ (N=421)		Total Cohort (N=3177)	Men without incident stroke (N=2814)	Men with incident stroke ² (N=363)	
Glucose (mmol/l)	5.6 (1.4)	5.6 (1.4)	5.9 (1.9)	<0.001	6 (1.7)	6 (1.7)	6 (1.7)	0.83
Poor	8	8	11		9	9	10	
Intermediate	27	27	30	0.02	43	43	45	0.56
Ideal	65	65	59		48	48	45	
Cholesterol (mmol/l)	6.3 (1.0)	6.3 (1.0)	6.3 (1.0)	0.43	6 (1.1)	6 (1.1)	6 (1.1)	0.73
Poor	49	49	49	0.49	40	40	40	
Intermediate	36	36	38		39	40	37	0.62
Ideal	15	15	13		21	20	22	
Physical Activity								
Poor	8	8	11		10	10	9	
Intermediate	53	53	58	0.002	42	41	45	0.25
Ideal	38	39	31		48	49	46	
Smoking								
Poor	41	40	50		13	13	12	
Intermediate	35	35	34	<0.001	3	3	2	0.28
Ideal	24	25	16		84	84	87	
Elderly Diet Index	...	...	...		24 (3)	24 (3)	24 (3)	0.94
Poor	...	...	...		38	38	36	
Intermediate	...	...	...		37	37	39	0.74
Ideal	...	...	...		24	24	25	
CVH Score	6.3 [†] (1.9)	6.3 [†] (1.9)	5.6 [†] (1.8)	<0.001	7.7 [‡] (2)	7.7 [‡] (2)	7.7 [‡] (2)	0.95
					6.8 [†] (1.7)	6.8 [†] (1.7)	6.8 [†] (1.7)	0.71

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	Q1 1978-1980			P value	Q20 1998-2000			P value
	Total Cohort (N=7112)	Men without incident stroke (N=6691)	Men with incident stroke ¹ (N=421)		Total Cohort (N=3177)	Men without incident stroke (N=2814)	Men with incident stroke ² (N=363)	
CVH Status[§]								
Poor	17	17	28	<0.001	6	6	6	0.99
Average	71	71	67		76	76	77	
Optimal	12	12	6		18	18	18	
CVH Trajectories					N=3369	N=2980	N=389	
Low-Low	...	...	...		52	51	56	0.07
Low-High	...	...	...		17	17	12	
High-Low	...	...	...		13	13	12	
High-High	...	...	...		19	19	20	

Numbers are % or mean (SD).

N varies for alcohol and social class due to missing data.

At Q1 for alcohol total n=7109, men without stroke n=6688; social class total n=7100, men without stroke n=6679.

At Q20 for alcohol total n=3142, men without stroke n=2784 and men with stroke n=358; social class total n=3170, men without stroke n=2807.

P values compare characteristics between participants who do/do not experience incident stroke.

Abbreviations: BMI, Body Mass Index; CVH, Cardiovascular Health; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure.

¹Between baseline and Q20. ²Between Q20 and June 2018. †range 0-12 excluding diet; ‡0-14 with diet;

§Poor: 0-4 Q1 and Q20, Average: 5-8 Q1 and 5-9 Q20, Optimal: 9-12 Q1 and 10-14 Q20.

4 Impact of CVH on Stroke

Table 4.3 Sociodemographic and CVH characteristics of middle-aged European and South Asian SABRE participants free of prevalent stroke and CHD.

	Total Cohort			Europeans			South Asians		
	Europeans (N=1860)	South Asians (N=1352)	P value	Without incident stroke (N=1714)	With incident stroke ¹ (N=146)	P value	Without incident stroke (N=1221)	With incident stroke ² (N=131)	P value
Age (yrs)	53 (7)	51 (7)	<0.001	52 (7)	56 (6)	<0.001	50 (7)	54 (7)	<0.001
Men/Women	76/24	82/18	<0.001	76/24	79/21	0.39	82/18	84/16	0.62
Social class`									
Non-Manual	40	25	<0.001	41	30	0.01	25	20	0.18
Manual	60	75		59	70		75	80	
Alcohol intake^	8 [1,20]	1 [0, 11]	<0.001	8 [1, 20]	8 [0, 26]	0.78	1 [0, 10]	3 [0, 16]	0.24
BMI (kg/m²)	26 (4)	26 (4)	0.81	26 (4)	26 (4)	1.00	26 (4)	26 (4)	0.55
Poor	14	13		14	14		12	14	
Intermediate	43	48	0.04	43	42	0.98	47	50	0.73
Ideal	42	40		42	43		40	37	
SBP (mmHg)	122 (17)	125 (18)	<0.001	122 (16)	128 (21)	<0.001	124 (17)	134 (17)	<0.001
DBP (mmHg)	77 (11)	80 (10)	<0.001	77 (11)	78 (12)	0.43	80 (10)	84 (11)	<0.001
Blood Pressure									
Poor	19	26		18	26		25	41	<0.001
Intermediate	42	41	<0.001	42	42	0.03	41	49	
Ideal	40	32		40	32		35	10	
Glucose (mmol/l)	5 [5, 6]	6 [5, 6]	<0.001	5 [5, 6]	6 [5, 6]	0.05	5 [5, 6]	6 [5, 8]	<0.001
Poor	5	15		4	9		14	30	<0.001
Intermediate	31	30	<0.001	31	35	0.02	30	27	
Ideal	64	55		65	56		56	44	
Cholesterol (mmol/l)	6.1 (1.2)	5.9 (1.1)	<0.001	6.1 (1.2)	6.2 (1.1)	0.09	5.9 (1.1)	6.1 (1.2)	0.01
Poor	42	36		42	45		36	43	
Intermediate	35	38	0.01	35	43	0.01	38	36	0.25
Ideal	23	26		23	13		26	21	

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	Total Cohort			Europeans			South Asians		
	Europeans (N=1860)	South Asians (N=1352)	P value	Without incident stroke (N=1714)	With incident stroke ¹ (N=146)	P value	Without incident stroke (N=1221)	With incident stroke ² (N=131)	P value
Physical Activity (MJ/wk)	10 [7, 15]	9 [4, 13]	<0.001	10 [6, 15]	11 [7, 16]	0.48	9 [4, 13]	9 [4, 13]	0.87
Poor	20	30		20	16		30	34	
Intermediate	51	52	<0.001	51	53	0.54	52	47	0.56
Ideal	29	18		29	31		18	19	
Smoking									
Poor	33	13		32	41		13	!	
Intermediate	35	8	<0.001	36	34	0.04	8	!	0.93
Ideal	32	79		33	25		79	79	
FFV Intake									
Poor	7	5		7	12		5	!	
Intermediate	37	35	<0.001	37	40	0.06	34	!	0.32
Ideal	55	61		56	48		61	60	
CVH Score	8.5 (2.1)	8.7 (2.1)	<0.001	8.5 (2.1)	7.8 (2.0)	<0.001	8.8 (2.1)	7.9 (1.9)	<0.001
CVH Status[§]									
Poor	3	3		3	!		3	!	
Average	64	60	0.014	64	!	0.02	58	!	0.001
Optimal	33	38		33	23		39	23	

Numbers are % or mean (SD) or median [25th centile, 75th centile].

N varies for alcohol and social class due to missing data: 'European 1843, South Asian 1317. ^European 1800, South Asian 1304.

P values compare characteristics between European and SA and within ethnic groups between participants who do/do not experience incident stroke. § Poor=0-4, Average=5-9, Optimal=10-14.

! small numbers not disclosed.

Abbreviations: BMI, Body Mass Index; CHD: Coronary Heart Disease; CVH, Cardiovascular Health; DBP, Diastolic Blood Pressure; FFV: Fresh Fruit & Vegetable; SBP, Systolic Blood Pressure.

4 Impact of CVH on Stroke

Table 4.4 Risk of stroke in middle-aged (Q1) and older (Q20) BRHS men free of prevalent stroke and heart disease.

		Q1 1978-1980 ¹			Q20 1998-2000 ²			
		Events/N	Rate/1000PY [95% CI]	HR [95% CI]	Events/N	Rate/1000PY [95% CI]	HR [95% CI]	
				Model 1 N=7112			Model 1 N=3177	Model 2 N=3135
CVH Score				0.83 [0.78-0.87]			0.95 [0.90-1.00]	0.95 [0.90-1.01]
CVH Status [§]								
Poor	116/1229	5.72 [4.76-6.86]	1	1	21/183	10.2 [6.63-15.6]	1	1
Average	280/5050	3.08 [2.74-3.47]	0.56 [0.45-0.70]	0.59 [0.47-0.73]	278/2426	8.35 [7.42-9.39]	0.71 [0.45-1.10]	0.73 [0.46-1.15]
Optimal	25/833	1.58 [1.07-2.34]	0.35 [0.23-0.54]	0.39 [0.25-0.61]	64/568	7.38 [5.77-9.42]	0.65 [0.40-1.07]	0.68 [0.41-1.13]
P for trend			<0.001	<0.001			0.09	0.14

Model 1 adjusted for age. Model 2 adjusted additionally for social class and alcohol intake at Q1/Q20.

¹Followed from Q1 to Q20; ²Followed from Q20 to June 2018; [§]Poor: 0-4 Q1 and Q20, Average: 5-8 Q1/5-9 Q20, Optimal: 9-12 Q1/10-14 Q20. CVH: cardiovascular health.

4 Impact of CVH on Stroke

Table 4.5 Risk of stroke in middle-aged European and South Asian SABRE participants free of prevalent stroke and CHD.

Europeans					South Asians			
	Events/N	Rate/1000PY [95% CI]	HR [95% CI]		Events/N	Rate/1000P Y [95% CI]	HR [95% CI]	
			Model 1 N=1860	Model 2 N=1785			Model 1 N=1352	Model 2 N=1269
CVH Score			0.88 [0.81-0.96]	0.91 [0.83-0.99]			0.84 [0.77-0.91]	0.84 [0.77-0.92]
CVH Status[§]								
Poor	!	7.36 [3.51-15.4]	1	1	!	8.28 [3.45-19.9]	1	1
Average	!	4.87 [4.02-5.89]	0.64 [0.30-1.38]	0.65 [0.30-1.41]	!	6.38 [5.22-7.79]	0.75 [0.31-1.86]	0.75 [0.30-1.87]
Optimal	33/606	2.80 [1.99-3.94]	0.44 [0.19-0.99]	0.49 [0.21-1.11]	30/507	2.99 [2.09-4.27]	0.39 [0.15-1.02]	0.41 [0.15-1.07]
P for trend			0.048	0.09			0.054	0.07

Model 1 adjusted for age and sex. Model 2 adjusted additionally for social class and alcohol intake. Median follow-up 20y.

[§]Poor: 0-4, Average: 5-9, Optimal: 10-14.

! small numbers not disclosed. CVH: cardiovascular health.

Table 4.6 PAFs % [95% CI] of stroke in middle-aged (Q1) and older (Q20) BRHS men; and middle-aged SABRE participants, free of prevalent stroke and heart disease

	BRHS	
	Q1 1978-1980	Q20 1998-2000
CVH Status	-	6.4 [-16.8-25.0]
CVH Status excluding diet	38.6 [9.98-58.1]	10.1[-12.8-28.4]
Body Mass Index	5.64 [-5.73-15.8]	-0.05 [-16.3-13.9]
Blood Pressure	50.3 [20.9-68.8]	35.2 [-3.32-59.4]
Glucose	7.63 [-0.03-14.7]	7.49 [-3.76-17.5]
Cholesterol	13.1 [-11.1-32.0]	-14.0 [-38.5-6.11]
Physical Activity	15.1 [1.77-26.6]	8.34 [-2.42-18.0]
Smoking	26.7 [8.53-41.3]	1.34 [-2.73-5.25]
Diet	-	2.66 [-16.7-18.8]
All LS7 metrics	-	37.8 [-9.40-64.7]
All LS7 excluding diet	72.8 [51.1-84.8]	38.5 [-2.87-63.3]
	SABRE	
	Europeans	South Asians
CVH Status	20.8 [-7.03-41.4]	35.7 [11.3-53.4]
Body Mass Index	-4.54 [-26.9-13.9]	11.1 [-13.0-30.1]
Blood Pressure	6.93 [-18.2-26.7]	66.6 [43.1-80.4]
Glucose	9.60 [-4.88-22.1]	21.5 [3.52-36.1]
Cholesterol	31.5 [-4.66-55.2]	8.15 [-28.1-34.1]
Physical Activity	-17.0 [-49.0-8.15]	-16.8 [-63.3-20.7]
Smoking	20.2 [-7.02-40.5]	-0.69 [-10.5-8.23]
Diet	15.5 [-0.59-29.0]	5.30 [-10.2-18.7]
All metrics	53.1 [5.50-76.7]	68.0 [29.2-85.6]

Population attributable fraction (PAF) calculated using the punafcc package for Stata, evaluating the scenario where all participants had the metric(s) ideal level, or optimal CVH. Adjusting for age, social class and alcohol intake (+ sex in SABRE). Negative values of PAF correspond to respective HRs or 95% CI having value above 1.

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Table 4.7 Profiles of CVH trajectories in BRHS men

	CVH Trajectories over 20 years ¹			
	Low-Low (N=1740)	Low-High (N=563)	High-Low (N=425)	High-High (N=641)
Age (yrs)*	69 (5.4)	69 (5.5)	67 (5.2)	67 (5.4)
Social class				
Non-Manual	41	46	56	59
Manual	56	51	42	39
Armed Forces	3	3	2	2
BMI (kg/m ²)*	27.9 (3.8)	25.6 (3.1)	26.7 (3.0)	2.6
Poor	25	4	13	2
Intermediate	56	50	63	39
Ideal	19	46	23	58
BP (mmHg)				
Systolic*	156 (23)	144 (23)	152 (21)	138 (24)
Diastolic*	87 (11)	83 (10)	88 (10)	83 (11)
Poor	79	51	77	44
Intermediate	19	37	21	39
Ideal	2	12	2	17
Glucose (mmol/l)*	6.4 (2.2)	5.5 (0.9)	5.9 (1.0)	5.5 (0.7)
Poor	16	1	6	1
Intermediate	49	30	55	31
Ideal	36	69	40	68
Cholesterol (mmol/l)*	6.3 (1.1)	5.6 (0.9)	6.2 (1.0)	5.5 (0.9)
Poor	52	15	53	17
Intermediate	36	50	36	43
Ideal	12	35	11	40
Physical Activity				
Poor	15	2	11	3
Intermediate	50	28	49	28
Ideal	35	70	40	70
Smoking				
Poor	20	4	10	3
Intermediate	5	1	1	1
Ideal	75	95	88	97
CVH score*†	5.7 (1.2)	8.5 (0.7)	6.3 (0.9)	8.8 (0.9)
Number of Strokes	217	48	46	78
Rate/1000PY [95% CI]	9.79 [8.57-11.2]	6.17 [4.65-8.19]	7.33 [5.49-9.79]	7.85 [6.29-9.81]
Hazard Ratio [95% CI]‡	1	0.60 [0.44-0.83]	0.83 [0.60-1.15]	0.86 [0.66-1.12]

Profiles are as at Q20. P<0.001 for all comparisons.

¹N=3369, stroke events=389 for men followed from 1998/2000 to June 2018

Numbers are % except as stated. *mean (sd)

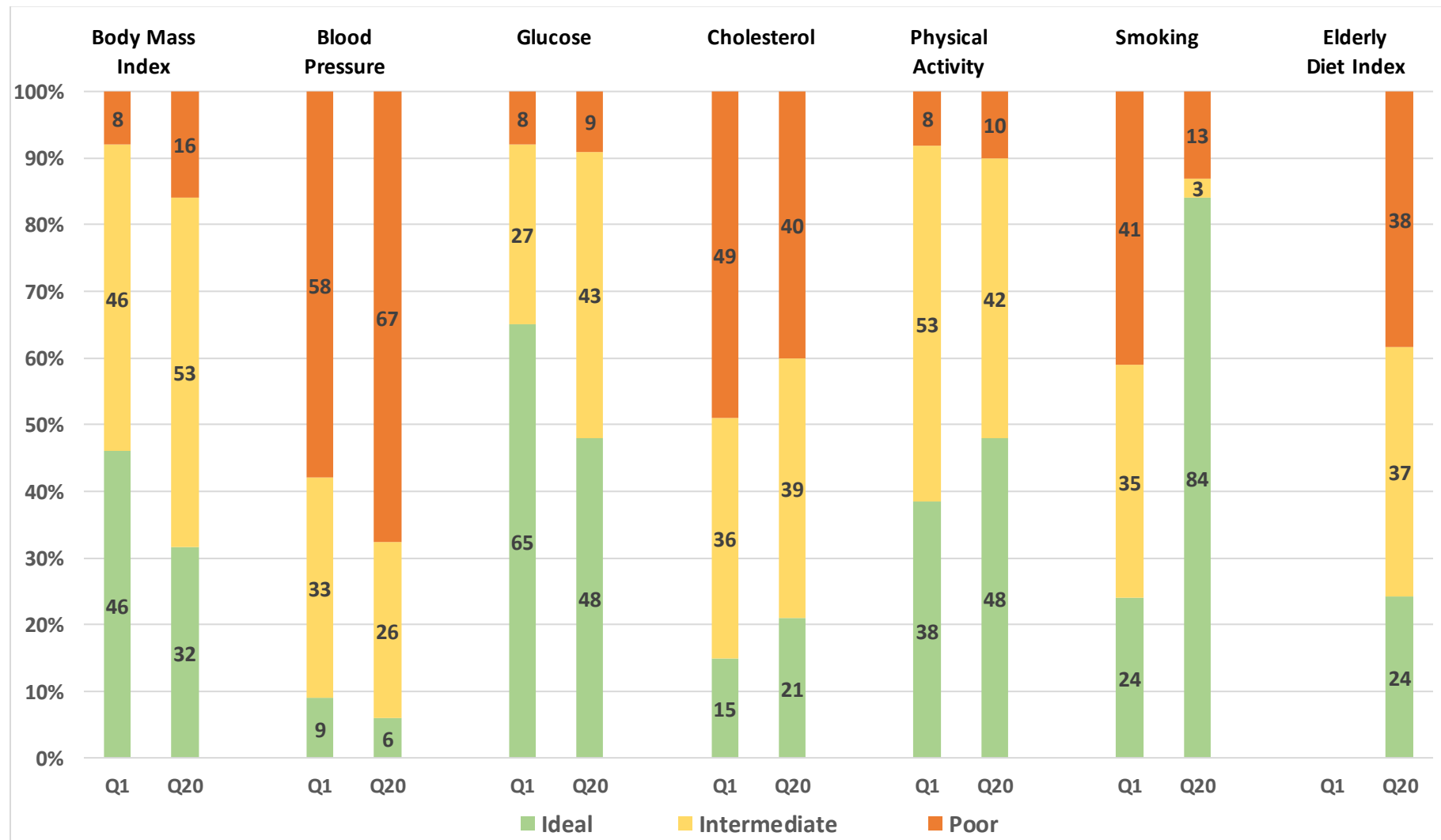
†range 0-12 excluding diet

‡adjusted for social class at baseline, age and alcohol intake at Q20, with events/N = 384/3323.

BMI, Body Mass Index; BP, Blood Pressure; CVH, Cardiovascular Health

4 Impact of CVH on Stroke

Figure 4.1 Prevalence of LS7 metrics in BRHS men free of CVD across middle (40-59y, Q1) and older age (60-79y, Q20).



Diet was not measured at Q1

Figure 4.2 KM survival curves representing stroke free survival in CVD free BRHS men followed from Q1 (1978-80) to Q20 (1998-2000)

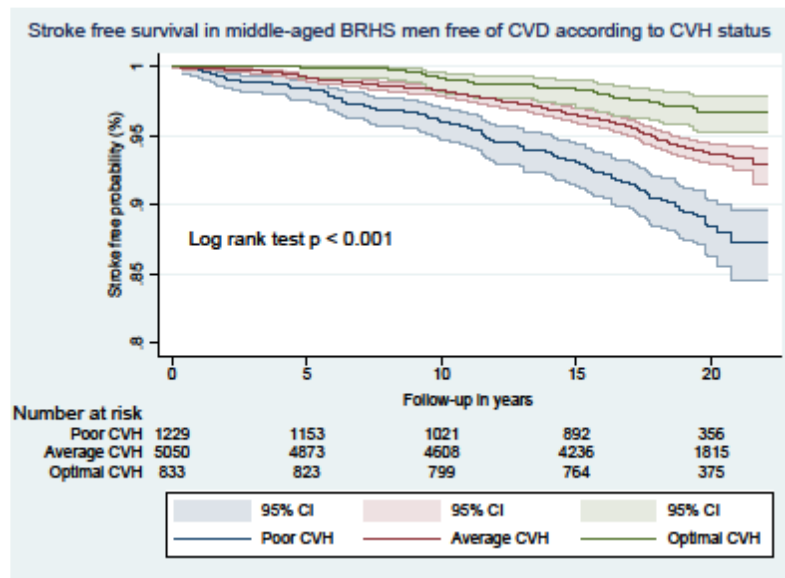
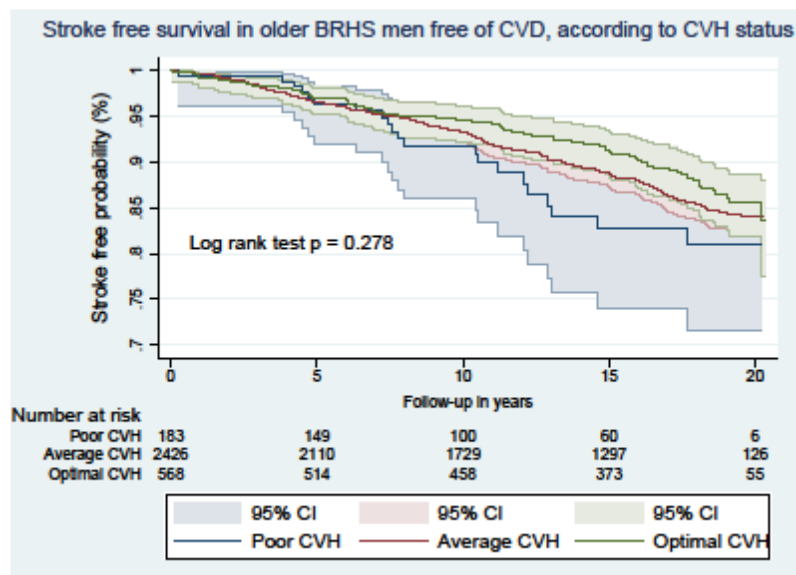


Figure 4.3: KM survival curves representing stroke free survival in CVD free BRHS men followed from Q20 (1998-2000) to June 2018



4 Impact of CVH on Stroke

Figure 4.4 Prevalence of Life's Simple 7 metrics in SABRE participants free of prevalent cardiovascular disease.

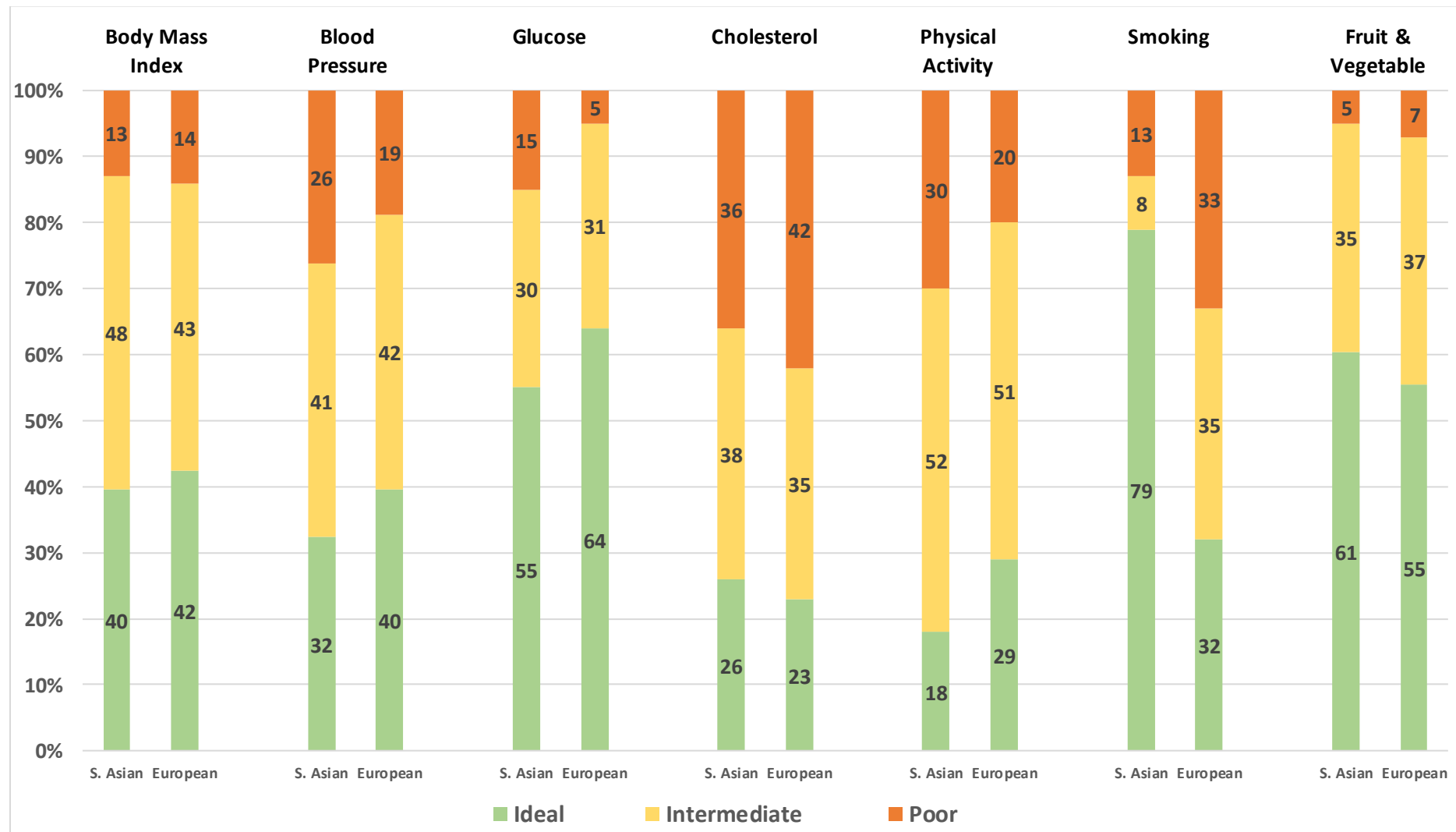
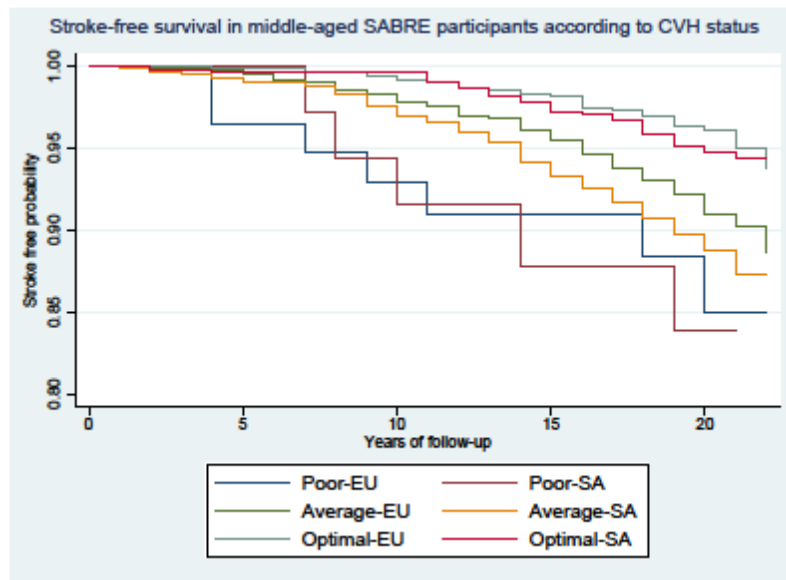


Figure 4.5 KM survival curves representing stroke free survival in CVD free SABRE participants followed from 1988-91 to 2011.



P values for log rank test for survival across CVH within each ethnic group are Europeans (EU) 0.003 and SAs 0.0002.

Figure 4.6 Hazard ratios of stroke across CVH status categories in middle-aged (Q1) and older (Q20) BRHS men free of stroke and MI.

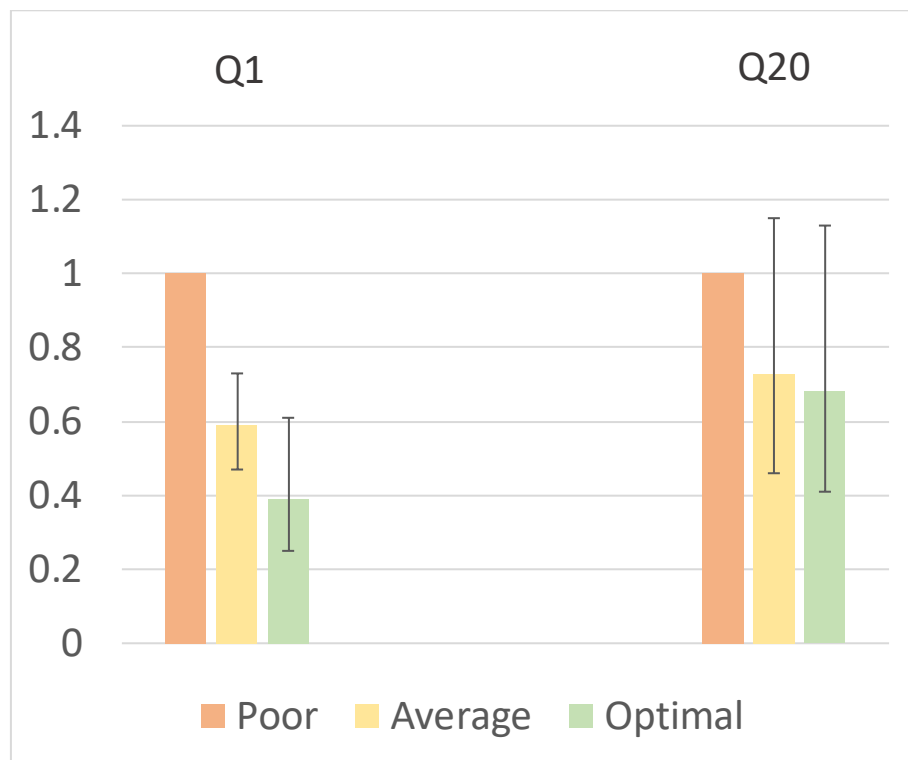


Figure 4.7 Hazard ratios of stroke across CVH status categories in middle-aged South Asian and European participants of SABRE free of stroke and CHD

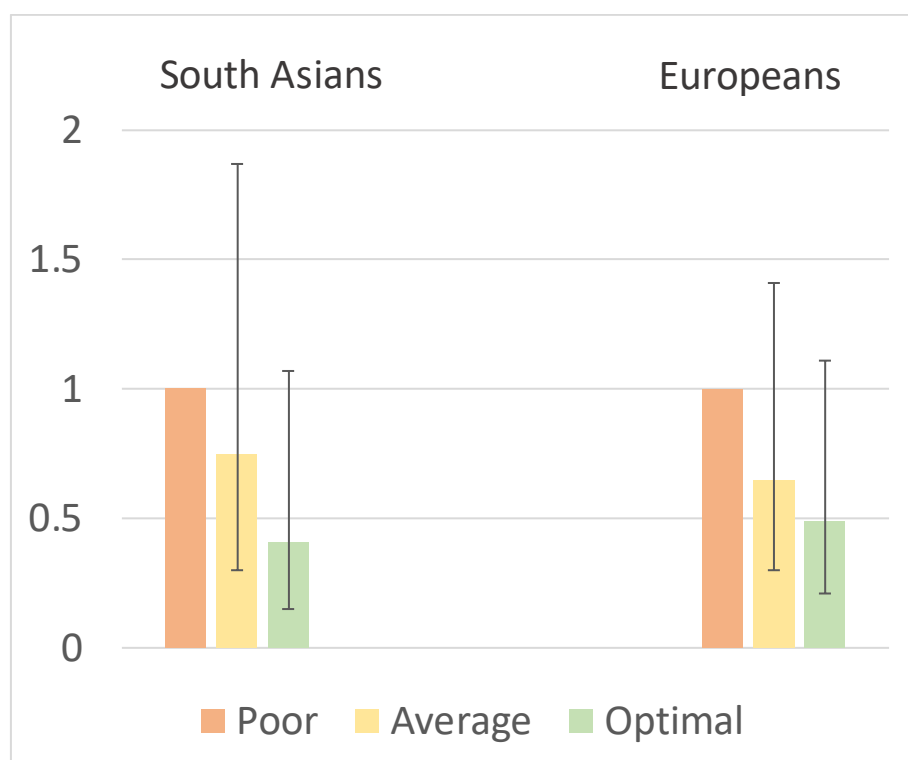


Figure 4.8 Population attributable fraction of stroke due to sub-optimal CVH in middle-aged (Q1) and older (Q20) BRHS men free of stroke and MI.

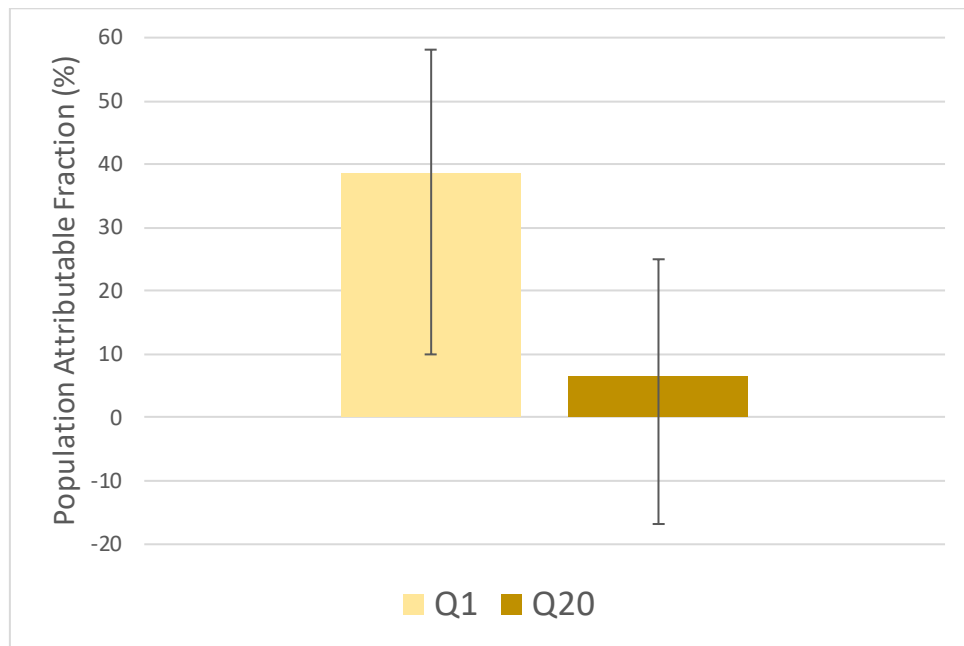


Figure 4.9 Population attributable fraction of stroke due to sub-optimal CVH in middle-aged South Asian and European participants of SABRE free of stroke and CHD.

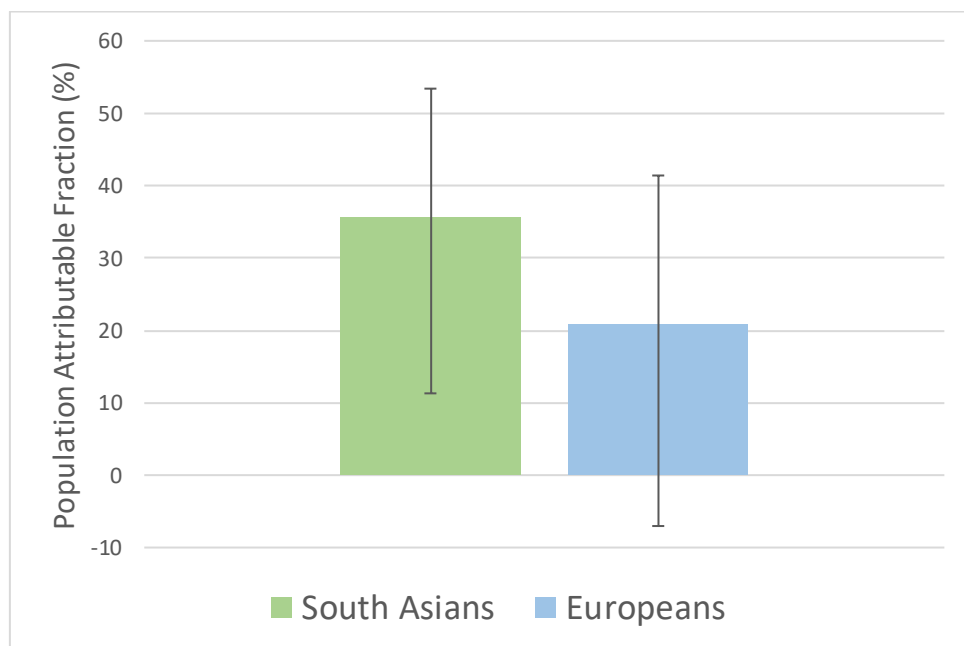
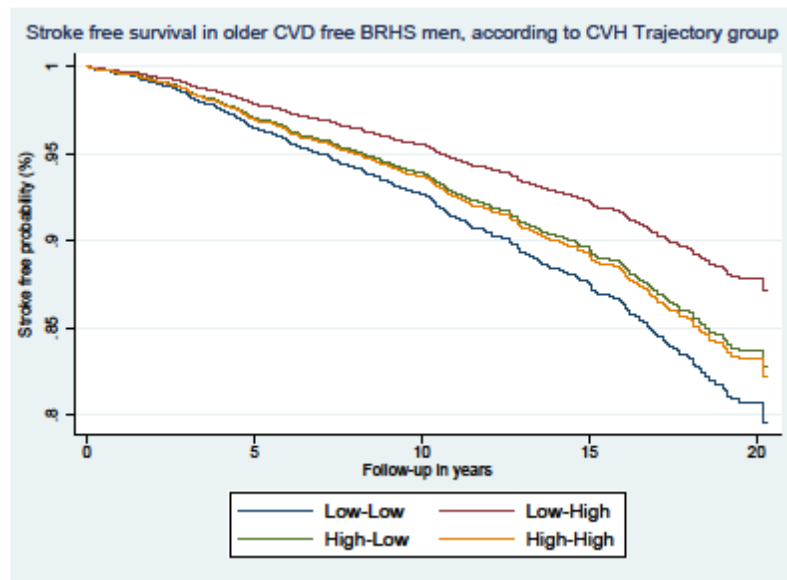


Figure 4.10 Stroke free probability curves in CVH trajectory groups among BRHS men free of prevalent CVD at Q20; adjusted for age, social class, and alcohol intake.



Chapter 5. Prediction of Stroke Risk in Older Adults: Performance of Stroke-Specific and Composite-CVD Risk Prediction Tools

5.1 Summary

Correctly estimating the absolute risk of stroke is critical for informing primary prevention in older adults in whom benefits vs harms of preventive interventions are less certain. It is unclear whether currently used composite-CVD prediction tools perform better or worse than stroke-specific tools for capturing the true risk of stroke events in older adults. This chapter describes external validation of 2 stroke-specific (FSRP and QSTROKE) and 2 composite-CVD risk tools (QRISK3 and PCE), for predicting 10y risk of stroke events in older (60-79y) men from the BRHS. Results indicated that performance of all tools was broadly comparable. Stroke risk discrimination was weak (C-indices 0.63–0.66). FSRP and QStroke overestimated the probability of having a stroke among older men at higher risk, while QRISK3 and PCE showed better calibration overall with minor mis-estimations across the risk range. Non-stroke deaths worsened discriminative and predictive accuracy of all tools. However, in those without a history of CVD or statin use, QRISK3 remained relatively well calibrated for stroke events, including among oldest men. All tools displayed similar sensitivity (63-73%) and specificity (52-56%) for stroke events using KM-observed risks as cut-offs. But when QRISK3 and PCE were evaluated using conventional thresholds for CVD prevention, sensitivity for stroke events was 99%, with false positive rate 97%. Findings suggest that stroke risk discrimination in older age needs improvement and the setting of intervention thresholds and hence allocation of interventions should be contextualized for the age-related burden of stroke.

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5.2 Introduction

The previous chapter discussed CVH as a model for primary prevention of stroke at the population-level. A complementary arm of primary prevention is the 'high-risk approach', based on identifying individuals at high risk, and offering them individual preventive interventions if they cross a predefined threshold (222). This involves risk assessment through prediction tools which estimate an individual-specific probability of having an event over a period of usually 10y, using individual-specific risk factor levels. Tools need to be externally validated i.e., assessed on how well they can discriminate between low and high risk and how accurate the predicted risks are, for a target population in which they will be used (section 2.4.1).

Stroke risk is assessed in clinical practice as part of the composite risk of CVD (57, 58, 452) as opposed to being estimated separately. There are advantages and disadvantages of this approach. For a set of predictors to reliably estimate the risk of a composite outcome, its component events must be associated with the predictors in a similar direction. The comparable atherosclerotic aetiology and overlapping risk factors of CHD and IS suggest that combining them together as the composite outcome of a single model is therefore a statistically and clinically efficient way to estimate as well as communicate risk and thus a feasible public health strategy. Specifically, because a composite model predicts the risk of *any* of the CVD events, a low absolute risk estimate means the patient is less likely to experience *any* of the composite events in the designated time horizon – which is easy enough to understand. A single risk model can consequently also be used to estimate net benefit and cost-effectiveness of interventions that modify the shared risk factors (453). But, there are concerns with using this approach in older adults (see section 2.4.2.1).

Briefly, ageing is accompanied by attenuation (46, 47, 177) and/or reversal (44) in risk factor-CVD associations. However, CVD risk tools used widely, in the UK (58) and US (57), have been developed from predominantly middle-aged cohorts, and composite-CVD risk prediction itself becomes less reliable in older adults (291, 308). Secondly, the role and predictive power of major risk factors like BP, smoking and diabetes likely differs between CVD subtypes (64) and contemporary authors suggest disaggregating CVD risk by component events (60-63). Thirdly, estimating a composite risk is based on the assumption that component events are of equal importance and relevance to

patients, which is not a given (454), especially for older adults who are more apprehensive about the risk of a life-changing illness like stroke than of less disabling events or even death (68, 305). A single risk estimate does not provide this information, and for a particular patient gives no indication about which of the component CVD events it applies to or if it applies to all of them similarly. Moreover, composite risk is estimated using time to the first of any of the component events and cannot capture the overall burden of each event. For clinicians, knowledge of which specific event type is driving a patient's cardiovascular risk can be valuable for suggesting relevant management.

The risk of stroke can be obtained by scaling predicted composite-CVD risk by the proportion of all events that were constituted by stroke. But stroke forms a greater proportion of CVD compared to heart disease with ageing (13, 67, 171) and using scaling factors from middle-aged developmental cohorts may be inaccurate for older populations. The limited evidence on using PCE for predicting stroke risk (294, 311) suggests over-prediction in older US adults. And whether QRISK3, recommended by NICE for estimating CVD risk in British adults (32) captures the true risk of stroke in an older British population has not yet been examined.

Of the stroke-specific risk tools, the Framingham Stroke Risk Profile (FSRP) (69), although derived from an older age cohort, overpredicted stroke risk when validated in European and US older adults, with just average discrimination particularly among men (294-297). Validation studies using prospective data from an older UK population are lacking, even for QStroke developed more recently using UK primary care data (20). Additionally, the performance of both tools has not been independently assessed in older British adults free not just of stroke but also of broader cardiovascular disease conditions i.e., a strictly primary prevention sub-population in whom accurately assessing the absolute risk of stroke may critically inform risk-benefit discussions regarding uptake of prevention interventions.

This chapter aims to compare the performance of 2 stroke-specific (FSRP and QSTROKE) and 2 composite-CVD risk tools (QRISK3 and PCE), selected for validation based on derivation cohorts and use within the UK (QRISK3 and QStroke) and US (PCE and FSRP), in predicting stroke risk among older adults.

5.3 Objectives

1. To externally validate FSRP and QStroke; and QRISK3 and PCE among older men from the BRHS.
2. To evaluate how the tools classify men with respect to stroke risk according to cut-offs based on observed risk, and for composite-CVD tools using high risk thresholds recommended clinically.
3. To assess performance of FSRP, QStroke and QRISK3 head-to-head in a common subsample of older men free of a wide range of CVD conditions and not under specific CVD prevention treatments. (See 5.4.3 below for justification of why PCE is not included in this objective.)

5.4 Methods

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis - TRIPOD guidelines (293) have been used to report the validation analyses (Appendix 5.1).

5.4.1 Summary of Development Cohorts

FSRP for men

Male participants (n=2372) of the Framingham Heart Study 55-84y (mean 65y), free of stroke, from examination cycles 9 (1964) and 14 (1975), with 10 years of follow-up (69, 287). Primary outcome included strokes (IS and HS) and TIAs.

QStroke for men

Male patients (n=1,748,108) 25-84y (mean 45y) registered on the QResearch primary care database over 1st Jan 1998 – 1st Aug 2012; and without a history of stroke/TIA and anticoagulant use (20). Primary outcome was the first recorded diagnosis of stroke or TIA, excluding HS.

QRISK3 for men

Men (n=3,869,847) 25-84y (mean 43y), registered on the QResearch database over 1st Jan 1998 – 31st Dec 2015, without history of CVD and statin use. Primary outcome was a composite of fatal or non-fatal CHD, IS, and TIA (58).

PCE for men

White men (n=9,098) 40-79y (mean 56y), from 4 large US community-based cohorts, free of previous MI (recognized or unrecognized), stroke, congestive HF, percutaneous coronary intervention, coronary bypass surgery, or AF with ≥ 12y follow-up (57). Primary outcome was a composite of CHD death, non-fatal MI, fatal and non-fatal stroke.

5.4.2 BRHS Validation Sample

The study design, data collection and follow-up methodology for BRHS have been detailed in Chapter 3. Analyses described in the current chapter use data from questionnaires and physical examination conducted at the 20-year follow-up of BRHS Q20 (1998-2000, age 60-79y). For external validations, men were followed from Q20 to the first of stroke/TIA event or death (see section 3.2.3.2-3 and 3.3.5 for details on event ascertainment); or a maximum of 10y to match the time horizon of the four risk tools.

Definitions of endpoints, predictors, and eligibility of all risk tools with corresponding BRHS measures are detailed in Table 5.1 and Table 5.2.

5.4.3 Statistical Analysis

External validation has been informed by guidelines from Royston and Altman (428) and Steyerberg (286).

Each tool was first validated for its respective stroke outcome using sub-samples of men selected per its eligibility criteria (Objective 1). Subsequently the performance of FSRP, QStroke and QRISK3, which share IS and TIAs as common outcomes, was examined head-to-head in a further common subsample of men without a history of stroke, TIA, CHD (MI, angina, percutaneous transthoracic coronary angioplasty and, coronary artery bypass grafting), HF, AF, intermittent claudication (IC) and statin or anticoagulant use (Objective 3). PCE was excluded from this comparison because TIAs are not part of its original outcome, which would lead to inherent miscalibration.

Number of events in BRHS validation samples was well above the minimum of 100 events recommended as criteria for sample size for external validation (455).

The 4 risk tools model their predictors using Cox models. 10y predicted probabilities (P) of the outcome were calculated using

$$P = 1 - S_0(10)^{\exp(\text{Centred Prognostic Index})}$$

Where,

- $S_0(10)$ was the published 10y baseline survival function of the relevant risk tool.
- Prognostic Index was the linear predictor of the form $\beta_1X_1 + \beta_2X_2 + \dots \beta_nX_n$, calculated for each individual participant using published predictor beta coefficients multiplied by BRHS values of predictor variables.
- Centred Prognostic Index was calculated for the risk tools in two different ways, as described in their published algorithms. For FSRP and PCE, the prognostic index was centred using the published mean prognostic index. For QStroke and QRISK3, continuous variables were centred using published variable means before calculating the prognostic index.

Proportional hazards assumption using centred prognostic index in the Cox model was tested using the Stata post-estimation command `estat phtest`, and visually by plots of Schoenfeld residuals against time. The assumption appeared to be valid for all 4 tools.

For composite-CVD tools, predicted probabilities were multiplied by the proportion of all events that represented stroke events as described by D'Agostino et al (306). This was a scaling factor of 0.366 for the proportion of stroke/TIA for QRISK3 calculated from published data (58), and 0.289 for the proportion of hard strokes for the PCE for White men requested from authors (personal communication with Sean Coady at National Institute of Health, USA).

Two main indicators of external validation were assessed for each risk tool - discrimination and calibration.

5.4.3.1 Discrimination

The ability of the risk prediction tool to separate participants who go on to have an event from those that don't (section 3.8.6.1) was assessed by using the centred prognostic index in a Cox model and estimating Harrell's C-index [95% CIs] using `somersd` Stata package (456), see section 3.8.6.1 for details. The C-index ranges from 0.5 (as good as chance) to 1 (perfect discrimination), with a value <0.7 considered suboptimal (291). This was supplemented with visual inspection of separation of KM survival curves of 4 risk groups according to 16th, 50th and 84th centiles of the centred prognostic index (428).

5.4.3.2 Calibration

As detailed in section 3.8.6.2, the beta coefficient [95%CI] of the centred prognostic index as a single predictor in a Cox model represented the calibration slope; indicating overfitting if the slope was <1 and underfitting when >1 (430). Miscalibration was further tested using a Likelihood-Ratio test for beta of the centred prognostic index = 1. Mean calibration or calibration in the large was estimated as the ratio of global mean predicted risk to observed risk (KM method), where a ratio greater/less than 1 indicated global over/under-estimation. Moderate calibration (430) was assessed by comparing KM observed risk at 10y with mean predicted risk in deciles of predicted risk (pmcalplot Stata package (431) and MS Excel), and additionally across 4 age-groups (≤ 65 , $>65\text{--}\leq 70$, $>70\text{--}\leq 75$ and >75 years) in the common subsample.

5.4.3.3 Classification of Stroke Risk

To determine how well predicted probabilities classified men as being at high or low stroke risk (Objective 2), sensitivity/specificity (Sn/Sp%) of tools was measured at predefined thresholds corresponding to the overall KM-observed risk of the validation samples. This was estimated using the stroccurve package to account for censoring (457). Sn/Sp of the conventional composite-CVD risk thresholds i.e. 10 % for QRISK3 (32) and 7.5 % for PCE (30, 57) in classifying men with respect to stroke was also examined.

5.4.3.4 Sensitivity Analyses for Effect of Competing Mortality

As elaborated in section 2.4.3, the modelling of most risk prediction tools does not account for non-stroke deaths as a competing event. These occur with increasing frequency as the population ages, and ignoring their probability can inflate the real risk of experiencing a stroke (124). The few studies examining the effect of competing deaths have been limited to composite-CVD risk prediction (312-314). Sensitivity analyses accounting for non-stroke mortality were run to assess the effect of competing deaths on stroke risk prediction across all 4 tools. I used the Fine and Gray (436) (stcrreg) method to get the slope of the centred prognostic index and this was tested for difference from 1 using Wald test. I used methods by Wolber's et al (435) for calculating the C-index for discrimination by adjusting the survival time of men experiencing non-stroke death to greater than the prediction time horizon ($>10y$). I used the stcomp package (437) to obtain overall and group based cumulative

incidence function to assess mean and moderate calibration. Sn/Sp while accounting for competing risks were estimated using strocure with adjusted survival time.

5.4.3.5 Consideration of Missing Data

Missing data in validation samples was low and ranged from 6% in FSRP to 10% in PCE and 12% in QStroke and QRISK3. Main variables with missing data were CKD and measures of cholesterol (5%) and diabetes (3%). There were minimal differences in characteristics of men with/without complete information, especially with respect to outcome events (Appendix 5.2A-E). For each validation sample, regression models adjusting for relevant predictors and social class with which missingness was associated confirmed that missingness was independent of stroke. Analyses were hence limited to complete cases.

5.5 Results

For Objective 1, Appendix 5.3-6 provide detailed comparisons of baseline and performance characteristics between the BRHS validation sample and development sample of each tool. Table 5.3 provides main external validation, and sensitivity/specificity measures for all tools.

Overall BRHS men had a mean age of 68y, and a median follow-up of 10y. Information on Townsend scores and valvular heart disease was not available in BRHS, and these predictors were excluded from analysis of the respective Q models. However, social class measured in BRHS using the Registrar General's Classification (397) and by the index of multiple deprivation (IMD) were both not associated with strokes/TIAs in the sample. Some valvular heart disease was captured by proxy use of anticoagulants, but data from these participants were eventually omitted due to exclusion criteria of QStroke (Table 5.1).

5.5.1 FSRP Validation

There were 366 stroke and TIA events in 3762 BRHS men free of stroke and TIA (incidence 11.7 [10.5-12.9] per 1000PY). Men were similar to the FSRP derivation sample in terms of age, mean SBP and diabetes prevalence. However, twice as many BRHS men were using BP medication (32% vs 16%) while the prevalence of smoking and definite LVH was lower. Mean prognostic index of both cohorts were very similar (BRHS 5.85 vs FSRP 5.68) (Appendix 5.3).

Discrimination by C-index [95%CI] was 0.6346 [0.6068-0.6624] (Table 5.3). KM curves were separated but slightly less so for low/intermediate and high/very high-risk groups (Appendix 5.7A).

Calibration slope [95%CI] was 0.66 [0.52-0.80], and mean calibration 1.24 (Table 5.3). FSRP over-estimated risk in the top 3 deciles (Figure 5.1a), beyond risk of 15% and above the KM estimate of failure i.e., 10.97%.

5.5.2 QStroke Validation

There were 307 incident IS and TIAs in 3376 BRHS men free of stroke, TIA and without a history of anticoagulant use (10.8 [9.7-12.1] per 1000PY). Around 40 men who went on to have HS were excluded from this analysis. Given QStroke baseline characteristics have been provided for a combined sample of men and women (20); BRHS men were older (mean age 68y vs 45y), had higher mean systolic BP (141 vs 130mmHg) and higher prevalence of antihypertensive use, AF, diabetes, CKD, CHD, HF (Appendix 5.4). A smaller proportion of BRHS men were smokers or had a family history of premature CHD.

C-index in BRHS 0.6431 [0.6136-0.6726] (Table 5.3) was less than that reported by QStroke authors (0.87) in data comprising of participants of a wider age range (20, 300). However, KM curves for the four risk groups were spaced out (Appendix 5.7B).

Calibration slope was 0.88 [0.69-1.08]; mean calibration 1.16 (Table 5.3). Decile-based calibration was good (Figure 5.1b) except for over-estimation in the top decile (above predicted risk 21%).

5.5.3 QRISK3 Validation

There were 232 incident IS and TIAs (10.2 [9.0-11.6] per 1000PY) in 2669 BRHS men free of stroke, TIA, CHD and without a history of statin use. Thirty-one men with incident HS were excluded. BRHS men were older (mean age 68y vs 43y), had higher mean SBP (142 vs 129mmHg) and prevalence of antihypertensive use, AF, diabetes and CKD compared to the QRISK3 derivation sample (Appendix 5.5). Comparatively fewer BRHS men were smokers; had a family history of premature CHD; or reported use of corticosteroids. Migraine, rheumatoid arthritis and erectile dysfunction were determined for very few men. The prevalence of SLE and severe mental illness, determined by limited inquiry came to be nil.

C-index 0.6317 [0.5970-0.6664] (Table 5.3) was lower than that reported when QRISK3 was validated for composite-CVD (<0.65) in primary care data for adults >65y (312). There was some separation between KM curves (Appendix 5.7C).

Calibration slope was 0.82 [0.58-1.06]; mean calibration 1.03 (Table 5.3). Decile-based plots showed minor disagreements between observed and predicted risks across the probability range (Figure 5.1c).

5.5.4 PCE Validation

PCE predicts hard strokes only, of which there were 184 in 3047 BRHS men free of stroke, MI, coronary intervention procedures, congestive HF and AF (6.94 [6-8] per 1000PY). BRHS men were older (mean age 68y vs 56), had higher mean SBP, mean cholesterol and HDL-cholesterol as well as higher prevalence of antihypertensive use and diabetes, but a smaller proportion of smokers. Mean prognostic index was 62.2 in BRHS vs 61.2 in the PCE derivation sample (Appendix 5.6).

C-index was 0.6606 [0.6215-0.6997] (Table 5.3), with overlapping KM curves for low and intermediate risk groups (Appendix 5.7D).

Calibration slope was 0.92 [0.68-1.16]; mean calibration 1.12 (Table 5.3). Predicted probabilities followed the KM failure function closely with slight over estimation in intermediate deciles (Figure 5.1d).

5.5.5 Classifying participants as High or Low Stroke Risk

Using the respective KM-observed risk as a threshold for classifying men as at high risk of events, the 4 tools had similar Sn/Sp: FSRP 67/54%, QStroke 71/52%, QRISK3 calibrated for stroke 63/56% and PCE 73/52% (Table 5.3).

Using risk thresholds for CVD prevention by statin initiation, recommended by NICE-10% (32) and the American College of Cardiology/American Heart Association-7.5% (30, 57), to respectively categorise men as high risk based on QRISK3 and PCE composite-CVD probabilities (prior to correction for stroke outcomes), resulted in 99% sensitivity for respective stroke events, and a specificity of 2-3% for both tools, indicating a very high false positive rate. Examining higher cut-offs (Appendix 5.8) improved specificity and positive predictive values with some loss of sensitivity but negative predictive values remained high.

5.5.6 Sensitivity Analyses Adjusting for Competing Risks For External Validation of FSRP, QStroke, QRISK3 and PCE

Cumulative incidence function (CIF) of stroke events was lower than the KM-observed risk for each tool, as expected. Adjustment for non-stroke deaths generally worsened discrimination and calibration of all tools (Appendix 5.3-6). Calibration slope deviated further below 1, and when examined with respect to CIF, mean calibration showed slightly increased global over-prediction. In decile-based plots overestimation became exaggerated (Figure 5.1a-d, grey diamonds and dashed line graphs).

5.5.7 Performance of FSRP, QStroke and QRISK3 on a Common CVD-free Sample

There were 2441 men (mean age 68y) without a history of stroke, TIA, CHD, HF, IC, AF, statin and/or anticoagulant use, who experienced 113 ischaemic strokes and 83 TIA events over 10y (Appendix 5.9).

QStroke had a higher C-index 0.6584 [0.6220-0.6949] than FSRP and QRISK3 however confidence intervals for all tools overlapped (Table 5.4), and KM survival curves indicated similar discrimination by the 3 tools with FSRP and QStroke discriminating less between low- and intermediate- risk groups (Appendix 5.10).

QRISK3 showed better mean (Table 5.4) and decile-based calibration (Figure 5.2a-c). Relative overestimation by FSRP and QStroke was more evident in higher deciles particularly with respect to CIF. The tools showed similar Sn/Sp when examined using KM risk and CIF cut-offs. On comparing predicted risks of the three tools according to deciles of their averaged risk, agreement was evident for nearly all except the highest deciles (Figure 5.3).

In analysis by age-groups, the gap between CIF and KM risk progressively widened with age (Table 5.5, Figure 5.4); for men >75y, the CIF was 4% lower than KM risk. Both FSRP and QStroke overestimated risks up to 75y. For men >75y, mean risk predicted by FSRP was slightly lower than the KM-estimate but higher than the CIF, while that predicted by QStroke was similar to KM-risk and 3% higher than CIF. QRISK3 predictions were also higher relative to KM and CIF risks, but the difference became smaller with age. In men >75y, QRISK3 underestimated risk in comparison to the KM estimate, but mean prediction was more aligned with CIF.

5.6 Discussion

5.6.1 Summary of Key Findings

This chapter investigated how well stroke-specific (FSRP and QStroke) and composite-CVD (QRISK3 and PCE) risk prediction tools estimate the true risk of stroke events in older men. While acknowledging the slightly different stroke outcomes of these tools, three main findings emerge.

Firstly, all tools discriminated only modestly, with discrimination falling further on adjustment for competing risks. Secondly, FSRP and QStroke tended to overestimate risk at higher predicted probabilities while composite-CVD tools QRISK3 and PCE showed better global calibration with minor mis-estimations across the range of risk. Calibration generally worsened when non-stroke deaths were accounted for. However, in men without a broad range of cardio/cerebro/vascular conditions, QRISK3 showed better calibration despite adjustment for competing deaths.

Finally, all tools displayed similar sensitivity (63-73%) and specificity (52-54%) using validation sample-based KM-observed risk as cut-offs. However, when QRISK3 and PCE were evaluated using risk thresholds recommended for statin initiation as primary prevention of CVD, both falsely categorised a large proportion of men as being at high risk for stroke events.

5.6.2 Comparison of Discrimination Indices with External Validation Studies in Older Adults

A risk prediction tool with a C-index of 0.7 and above is considered to have good discrimination (291). None of the tools examined here reached this level. Discrimination by FSRP and PCE was worse than that noted among contemporary Dutch, French and US older adults (294, 296, 297). Interestingly, most recent work done by Hong et al (311) among more than 62,000 individuals from four US cohorts (Framingham Offspring, ARIC, MESA & REGARDS) published after this analysis was completed also concluded that the discriminative capacity of R-FSRP and REGARDS models and PCE, for predicting strokes among White adults 60y and older was similarly modest, and not improved upon even by machine learning models.

The poorer discrimination is somewhat expected because of the less heterogenous case-mix of BRHS men (286), particularly with regards to age, the main driver of risk.

Between stroke-specific tools, predictors like BMI, cholesterol:HDL ratio, family history of CHD and CKD, none of which form part of the FSRP model, help QStroke discriminate IS and TIAs marginally better. However, these additional variables do not appear to improve discrimination as part of QRISK3 that was developed to predict composite risk. This suggests that newer markers being explored for improving CVD risk stratification in older adults should be tested for stroke-specific prediction. Coronary artery calcium (CAC) is one such biomarker which has shown promise for improving risk stratification of CHD but not similarly for stroke (343, 458). Additionally, as discussed in Chapter 2 while evidence suggests NT-proBNP can improve stroke risk discrimination (77, 346), whether this is the case when NT-proBNP is added to established stroke risk prediction tools for predicting the risk of *stroke and TIA* in *older* adults needs to be formally examined.

5.6.3 Accuracy of Stroke Risk Prediction by Stroke-Specific and Composite-CVD Tools in Older Men

It is suggested that predicted risk – hence calibration may be more important for clinical decisions than discrimination (459) especially in older populations whose risk distribution is narrower. In this analysis, stroke risk prediction by composite-CVD tools was comparable to, if not better than by stroke-specific tools.

In BRHS men, as in older Dutch men of the Rotterdam cohort (295), FSRP tended to over-predict risk of stroke/TIA at higher probabilities but estimated risk well across low-mid deciles. This could be because although BRHS men were similar in age to FSRP men, with similar mean prognostic index (69, 287), they were more frequently using BP medication and fewer of them smoked. Algorithms for QStroke, QRISK3 and PCE include a number of age-predictor interactions. Considering this and its derivation from a UK population that was more concurrent with this BRHS sample (20) QStroke was well calibrated except for over-estimation in the highest risk group.

In comparison, QRISK3 and even PCE, developed using North American cohorts, displayed better mean calibration with slight misestimation through the low-intermediate risk range. Mean calibration for PCE in BRHS men was in fact better (1.12) than that reported by Hong et al (311) among US White adults 60y and older (1.27). As mentioned, theirs was a pooled analysis and participants were recruited

over a wider period 1983-2008. Baseline characteristics for those >60y are not available to make a comparison with BRHS men.

Considering intervention decisions are often made at intermediate risk ranges, the over-prediction by stroke-specific tools in higher deciles may not be of consequence (314). However, adjustment for non-stroke mortality as a competing event worsened calibration. And in general, CIF diverged more from KM risk with increasing predicted risks. This magnified overestimation by FSRP and QStroke, which also became apparent at lower predicted risks.

Additionally, both predicted risks and competing mortality increase with ageing (435). Accordingly, when comparing prediction of IS and TIAs in men without wide-ranging CVD, overestimation relative to CIF by stroke-specific FSRP and QStroke was clearly evident in successive age groups. Yet, QRISK3 showed better calibration in those >70y. Interestingly, this contrasts with recent findings based on primary care data by Livingstone et al (312), who report systematic overestimation of composite-CVD risk by QRISK3 when validated while accounting for non-CVD competing deaths. Admittedly the BRHS sample is much smaller in comparison, but the observation draws attention to the possibility that predictions of composite-CVD and individual components may be operating differently in older populations.

The effect any of this has on clinical usefulness would depend on the cut-off for intervention. There are no agreed thresholds for stroke risk alone. Using 8% CIF in CVD-free men (solid blue cut-off Figure 5.2 and Figure 5.4), FSRP appeared more likely than QSTROKE and QRISK3 to misclassify low-risk men (intermediate deciles) as being at high risk, although classification across age bands was comparable.

5.6.4 Using Current Composite-CVD Risk Thresholds to Classify Stroke Risk

Older adults with clinically manifest CHD, HF, arrhythmias and claudication are generally in receipt of preventive therapies to reduce future CVD events, including strokes. Hence the need for risk stratification becomes more relevant for those ageing without a history of these conditions in whom clinical decisions on interventions are a challenge (460). In this context, composite-CVD tools like QRISK3 and PCE, developed to aid primary prevention using cohorts that exclude most CVD conditions also seem more appropriate for stroke risk prediction. QRISK3 has been recommended for use in adults up to 84y (32), and PCE up to 75y (30), and in this

BRHS analysis, these tools do appear reasonably well calibrated for stroke events beyond midlife.

From a clinical and policy perspective, this suggests that QRISK3 may be utilized for providing stroke specific risk to older adults using scaling factors. This can be facilitated by including such an option on the current platform that estimates total CVD risk.

However, at current CVD intervention thresholds of QRISK3 (10%) and PCE (7.5%), which are directed at addressing composite-CVD risk, nearly all older men would become eligible for preventive interventions, with excellent sensitivity but a very high false positive rate for stroke. Arguably some of these men may be at high risk of CHD when an intervention such as statin is justified. However, strokes comprise an increasing proportion of first CVD events with increasing age (66). In BRHS itself, the fraction of hard CVD occurring over 20y that were strokes increased from 30% when men were followed from a baseline age of 50-70y; to 50% when followed from 70-90y. Considering the benefit of statins for the primary prevention of stroke in older adults is debatable for a number of reasons (315, 461, 462), this suggests that men may be considered eligible for an intervention that they don't need/benefit from and could be harmed by.

Post hoc analysis suggests this is again owing to poor discriminating power of the risk tools in older age. BRHS men who suffered a stroke were noted to have very similar predicted probabilities to those who did not, further highlighting that newer age-relevant predictors may be needed to have a more granular separation of risk.

Additionally, while disaggregated risks may help direct focus of care and monitoring towards events which are of greater concern to or more likely to afflict older adults e.g., tighter control of blood pressure for stroke; to inform risk stratification regarding eligibility for interventions such that overtreatment can be minimised, age-specific thresholds reflecting proportional stroke burden in older adults would need to be established for stroke specific management.

In this respect, cohorts of older adults similar to that used for developing QRISK3, created from more recent electronic health records linking primary and secondary care data may help to (1) derive more contemporary scaling factors, and (2) arrive at thresholds with improved specificity which may then be further investigated from a

health economics perspective (463). These points, strategies for enhancing performance and areas for additional research are discussed further in Chapter 8.

5.6.5 Limitations and Strengths

There are some key limitations to these analyses. First, although HS have been excluded from models predicting IS and TIAs based on mortality and verification of primary care data; it is possible this may not have captured all cases of cerebrovascular bleeds as BRHS linkage to hospital episodes is still in progress. However, because of their higher case-fatality, it is likely that this would be a small number.

Second, TIAs have been based on primary care reports according to clinical, time-based criteria. This may have included TIA mimics. However, TIAs present less frequently to hospital; and even within the QRISK development data, majority of TIAs were identified only through primary care records (20).

Third, some predictors of the two Q-models were not available in BRHS (e.g., Townsend scores and valvular heart disease as mentioned earlier). Type 1 diabetes was also not separately measured. However, based on self-reported use of insulin only up to 35 men could potentially be type 1 diabetic. Further, SLE and severe mental illness were not directly inquired about, and none of the men had the respective conditions coded as the indication for any reported medication use. As a result, the BRHS values for these predictors were effectively 0. Reassuringly the prevalence of SLE among men of the QRISK3 development sample was also 0 (58). Although the prevalence of severe mental illness among QRISK3 men was 4%, it may not be unreasonable to assume that BRHS men who participated in the Q20 follow-up by completing extensive questionnaires and undergoing physical examination were less likely to be suffering from severe mental illness. Additionally, predictors like steroid use and erectile dysfunction were reported by few men so it is unclear to what extent they would have contributed to performance regarding stroke. Nevertheless, others have highlighted that complex models do not necessarily have an advantage over simpler ones (464). This was in fact here indicated by PCE, based on a handful of core predictors, discriminating somewhat better than other tools – and perhaps relates to PCE predicting a more definite outcome of hard strokes only.

Fourth, some comparisons between model performances are based on subjective observation of calibration plots. However (non-test based) visual judgement on calibration to determine the better model is widely used (432-434).

Despite these limitations, this comparison of four risk tools with regards to stroke prediction has been conducted in a reasonably large sample of older men with near complete 10y follow-up. To my knowledge, the external validation of QStroke, QRISK3 and PCE for stroke risk prediction is the first in a prospective independent older cohort. The recent study by Hong et al is as yet the only other validation which reported performance measures of a scaled composite-CVD risk tool (PCE) for predicting stroke risk in older adults (311), but this focuses more on discrimination, with only a global measure of calibration reported as opposed to decile based calibration which can reveal finer performance details. Importantly, BRHS findings add to the debates on disaggregating CVD risk and intervention thresholds in older adults, and are worth verifying in a larger, multi-ethnic, mixed-gender primary prevention cohort.

5.7 Conclusion

In older British men, both stroke-specific and composite-CVD risk tools discriminate stroke risk weakly and should be improved. Non-stroke deaths influence accuracy of predicted risks, but intervention thresholds determine if competing events are strong enough to limit use of tools. In those without a history of CVD or statin use, QRISK3 remains relatively well calibrated for stroke events. However, existing models and/or thresholds should be re-examined to reflect proportional stroke burden in older adults.

Table 5.1 Definitions of outcome events and predictors in stroke-specific risk tools and BRHS

	FSRP (69, 287)	QStroke (20)	BRHS (86, 393)
Outcome Event	All types of fatal and non-fatal strokes and TIA	Ischaemic fatal and non-fatal strokes and TIA based on Read codes in GP-EHR and ICD10 codes in ONS linked data.	Matched. See section 3.3.5 for details on case ascertainment.
Exclusions	Prevalent stroke (and TIA)	Prevalent stroke, TIA and use of anticoagulant medication	Matched, see section 3.3.4 for criteria. Anticoagulants identified by self-reported use of warfarin BNF code 2.8.2
Age (y)	Self-report in Questionnaire	From GP-EHR at study entry	Self-report in Questionnaire
Townsend Score (continuous)	-	Postcode linked (Output Area level), 2001 census data.	Not available for 20y re-examination. (Excluded)
Ethnicity (categorical)	-	Self-assigned in GP-EHR.	Questionnaire based, self-reported, BRHS limited to British White participants. (Excluded)
Atrial Fibrillation (Y/N)	By ECG	As recorded in GP-EHR before start of study.	From Q20 ECG and primary care records
Family history of premature coronary heart disease (Y/N)	-	GP-EHR showing coronary disease in first degree relative <60y.	Self-report of a parent's death from heart disease before age 60y.
Type 1 Diabetes (Y/N)	-	As recorded in GP-EHR	Not specifically asked - those taking only insulin and could potentially be Type 1 are only 35 men. (Excluded)
Type 2 Diabetes (Y/N)	-	As recorded in GP-EHR	Not specifically asked. (Published coefficient used for all Diabetes)
Diabetes (Y/N)	Treatment with insulin or oral medication, or random glucose $\geq 150\text{mg/dl}$ on ≥ 2 occasions	-	Self-report of physician diagnosis or diabetes medication or fasting glucose $>7\text{ mmol/l}$
Rheumatoid Arthritis (Y/N)	-	As recorded in GP-EHR	Based on self-reported medication linked to selected BNF codes 10.1.2.1,

5 Prediction of Stroke Risk in Older Adults

	FSRP (69, 287)	QStroke (20)	BRHS (86, 393)
			10.1.2.2, 10.1.3, and 10.1.5. Plus, reason for taking medication coded to ICD9 714.xx
Chronic Kidney Disease (Y/N)	-	As recorded in GP-EHR	eGFR <60 ml/min/1.73m ² calculated using MDRD Study equation.
Hypertension Treatment (Y/N)	Self-report	GP-EHR diagnosis of hypertension and ≥1 concurrent prescription of ≥1 BP medication	Self-report of selected BNF BP medication codes 2.2.1, 2.2.8, 2.4, 2.5, 2.6.2
Coronary Heart Disease (Y/N)	-	As recorded in GP-EHR	Self-report of doctor diagnosed or GP record-based MI, Angina, CABG or PTCA
Heart Failure (Y/N)	-	As recorded in GP-EHR	Self-report of doctor diagnosed or GP record-based HF
Intermittent Claudication (Y/N)	-	-	Self-report of doctor-diagnosed or Edinburgh Claudication Questionnaire based claudication (406)
Cardiovascular Disease (Y/N)	Coronary Heart Disease (MI, Angina, Coronary Insufficiency), Heart Failure and Intermittent Claudication as per Framingham criteria (465)	-	Matched (see above for ascertainment)
Valvular Heart Disease	-	As recorded in GP-EHR	Not measured directly (Excluded) (use of anticoagulants indicated some men with valvular disease, but these get excluded)
Body Mass Index (kg/m²)	-	GP-EHR value closest to study entry.	From weight and height examined at Q20
Total Chol:HDL Chol Ratio	-	GP-EHR value closest to study entry.	Fasting blood sample at Q20
Cigarette Smoking	Self-report – yes/no	GP-EHR value closest to study entry. Ordinal variable	Self-reported at Q20 (derived as both binary and ordinal to match definitions)

5 Prediction of Stroke Risk in Older Adults

	FSRP (69, 287)	QStroke (20)	BRHS (86, 393)
		(non-, ex-, light-, moderate-, heavy- smoker)	
Systolic Blood Pressure (mmHg)	Average of two measurements on clinic visit	GP-EHR value closest to study entry.	Mean of two seated readings at Q20 exam
Left Ventricular Hypertrophy (Y/N)	ECG-based - definite	-	ECG-based - definite

BNF: British National Formulary, BRHS: British Regional Heart Study, EHR: electronic health record, GP: general practitioner, ICD: International Classification of Disease, MDRD: modification of diet in renal disease, ONS: Office of National Statistics, Y/N: Yes/No

Table 5.2 Definitions of outcome events and predictors in composite-CVD risk tools and BRHS

	PCE (57)	QRISK3 (58)	BRHS (86, 393)
Outcome Event	First hard atherosclerotic CVD – coronary death or fatal stroke or non-fatal MI or stroke.	Coronary Heart Disease (angina, acute MI, subsequent MI, complications after MI, other acute IHD, chronic IHD), Ischaemic Stroke and TIA based on Read codes in GP-EHR records, and ICD9/10 codes in HES and ONS linked data.	Matched for stroke and TIA events. Section 3.3.5 for details on case ascertainment.
Exclusions	Prevalent MI, stroke, congestive heart failure, percutaneous coronary intervention, coronary bypass surgery and AF and those older than 79 because of complex age interactions.	Prevalent CVD (heart attack, angina, stroke or TIA) & use of statins noted in GP-EHR or hospital linked records at baseline	Matched. See section 3.3.4 for criteria.
Age (y)	From ARIC, CHS, CARDIA and Framingham Original and Offspring cohorts	From GP-EHR at study entry	Self-report in Questionnaire
Townsend Score (continuous)	-	Postcode from GP-EHR linked (Output Area level) to 2011 census data.	Not available for Q20 re-examination. (Excluded)
Ethnicity (categorical)	-	Self-assigned in GP-EHR.	Questionnaire based, self-reported, BRHS limited to British White participants. (Excluded)
Atrial Fibrillation (Y/N)	-	Atrial fibrillation, atrial flutter and paroxysmal atrial fibrillation recorded in GP-EHR before start of study.	From Q20 ECG and primary care records
Family history of premature coronary heart disease (Y/N)	-	GP-EHR showing coronary disease in first degree relative <60y.	Self-report of a parent's death from heart disease before 60y.
Type 1 Diabetes (Y/N)	-	As recorded in GP-EHR	Not specifically asked - those taking only insulin and could

5 Prediction of Stroke Risk in Older Adults

	PCE (57)	QRISK3 (58)	BRHS (86, 393)
			potentially be Type 1 are only 35 men. (Excluded)
Type 2 Diabetes (Y/N)	-	As recorded in GP-EHR	Not specifically asked. (Published coefficient used for all Diabetes)
Diabetes (Y/N)	Cohort specific	-	Self-report of physician diagnosis or diabetes medication or fasting glucose >7 mmol/l
Rheumatoid Arthritis (Y/N)	-	RA, Felty's syndrome, Caplan's syndrome, adult-onset Still's disease, inflammatory polyarthropathy not otherwise specified - noted in GP-EHR	Based on self-reported medication linked to selected BNF codes 10.1.2.1, 10.1.2.2, 10.1.3, and 10.1.5. Plus, reason for taking medication coded to ICD9 714.xx
Chronic Kidney Disease (Y/N)	-	Stage 3-5 CKD, nephrotic syndrome, chronic glomerulonephritis, chronic pyelonephritis, renal dialysis, renal transplant as noted in GP-EHR	eGFR <60 ml/min/1.73m ² calculated using MDRD Study equation.
Hypertension Treatment (Y/N)	Cohort specific	GP-EHR diagnosis of hypertension and concurrent prescription of ≥1 BP medication	Self-report of selected BNF BP medication codes 2.2.1, 2.2.8, 2.4, 2.5, 2.6.2
Migraine	-	Classic/atypical/abdominal migraine, cluster headache, basilar migraine, hemiplegic migraine and migraine with or without aura in GP-EHR	From self-reported medication BNF code 4.7.4, plus reason for taking medication coded as ICD-9 code 346
Corticosteroid use	-	BNF Chapter 6.3.2 (oral or parenteral) noted in GP-EHR	Self-reported. BNF code 6.3.2
Atypical antipsychotic use	-	Second generation antipsychotics noted in GP-EHR	Self-reported. BNF code 4.2.1
Systemic Lupus Erythematosus	-	Systemic Lupus Erythematosus, Disseminated Lupus, Libman-Sacks disease noted in GP-EHR	Only possible by linking self-reported medication to reason for taking coded as ICD9 code 710.0

5 Prediction of Stroke Risk in Older Adults

	PCE (57)	QRISK3 (58)	BRHS (86, 393)
Severe Mental Illness	-	Psychosis, schizophrenia, bipolar affective disorder in GP-EHR	Only possible by linking self-reported medication to reason for taking coded as ICD9 code 295, 296, 298.
Erectile dysfunction or treatment	-	Diagnosis or treatment BNF 7.4.5 in GP-EHR	Self-reported. BNF code 7.4.5, Reason for taking coded as ICD-9 607.84
Cigarette Smoking	Self-report – yes/no	GP-EHR value most recent before study entry. Ordinal variable (non-, ex-, light-, moderate-, heavy-smoker)	Self-reported at Q20 (derived as both binary and ordinal to match definitions)
Body Mass Index (kg/m²)	-	GP-EHR value most recent before study entry.	From weight and height examined at Q20
Total Chol:HDL Chol Ratio or separate	TC and HDL measures from cohorts	GP-EHR value closest to study entry, restricting those after entry date to ones that were before CVD diagnosis, statin prescription or censoring.	Fasting blood sample at Q20 examination
Systolic BP (mmHg)	Cohort specific	GP-EHR value most recent before study entry.	Mean of two seated readings at Q20 examination
Variability in Systolic BP	-	SD from all SBP values recorded in GP-EHR 5y before study entry	-

BNF: British National Formulary, BRHS: British Regional Heart Study, EHR: electronic health record, GP: general practitioner, ICD: International Classification of Disease, MDRD: modification of diet in renal disease, ONS: Office of National Statistics, Y/N: Yes/No, PCE: Pooled cohort equations. QRISK3 Use of drugs at baseline: 2 or more prescriptions, most recent ≤28 days before study entry.

Table 5.3 External validation of stroke-specific and composite-CVD risk tools in older men of the BRHS.

Risk Tool	FSRP	QStroke	QRISK3	PCE
Men free of	Stroke, TIA	Stroke, TIA, Anticoagulant use	Stroke, TIA, Coronary Heart Disease, Statin use	Stroke, Myocardial Infarction, Heart Failure, Atrial Fibrillation
No. of men	3762	3376	2669	3047
Number of events	366 Strokes and TIAs	307 Ischaemic Strokes and TIAs	232 Ischaemic Strokes and TIAs	184 Strokes
Slope of CPI [95% CI]	0.66 ^a [0.52-0.80]	0.88 ^b [0.69-1.08]	0.82 ^c [0.58-1.06]	0.92 ^d [0.68-1.16]
Harrell's C [95% CI]	0.6346 [0.6068-0.6624]	0.6431 [0.6136-0.6726]	0.6317 [0.5970-0.6664]	0.6606 [0.6215-0.6997]
Mean Calibration	1.24	1.16	1.03	1.12
Cut-off for high risk* (%)	10.97	10.18	9.59	6.77
Sensitivity (%)	67	71	63	73
Specificity (%)	54	52	56	52
Observed risk (%)	15.5	14.6	13.7	10.3

CPI: centred prognostic index. CR: adjusted for competing non-stroke deaths. FSRP: Framingham Stroke Risk Profile. PCE: Pooled Cohort Equations. TIA: Transient Ischaemic Attack

For slope = 1: ^ap <0.001. ^bp 0.25. ^cp 0.14. ^dp 0.50.

*Global estimate of failure by Kaplan-Meier method.

Table 5.4 External Validation of FSRP, QStroke and QRISK3 in a common BRHS sample of men without CVD (N=2441, mean age 68y), *adjustment for competing non-stroke deaths in italics*.

Risk Tool	FSRP		QStroke		QRISK3 calibrated for stroke/TIA	
Men free of	Stroke, TIA, CHD, HF, IC, AF, Anticoagulant use & Statin use					
Number of events	Ischaemic Strokes (113) and TIA (83) N=196					
Number of competing events	474					
Slope of CPI [95% CI]	0.83 [0.60-1.05]		1.05 [0.78-1.31]		0.90 [0.64-1.17]	
P test for slope CPI=1	0.13		0.73		0.46	
<i>Slope of CPI [95% CI]</i>	<i>0.72 [0.50-0.93]</i>		<i>0.91 [0.66-1.16]</i>		<i>0.78 [0.54-1.03]</i>	
<i>P test for slope CPI=1</i>	<i>0.0091</i>		<i>0.4850</i>		<i>0.09</i>	
Harrell's C [95% CI]	0.6400 [0.6016-0.6783]		0.6584 [0.6220-0.6949]		0.6408 [0.6033-0.6783]	
<i>Harrell's C [95% CI]</i>	<i>0.6267</i>		<i>0.6411</i>		<i>0.6254</i>	
<i>Adj. for competing risks</i>	<i>[0.5884-0.6650]</i>		<i>[0.6046-0.6777]</i>		<i>[0.5878-0.6631]</i>	
10y Pred. Probability (%)						
Mean [Range]	10.6 [2.3-68.5]		10.2 [2.16-33.5]		9.57 [2.14-29.9]	
Median [Interquartile range]	8.77 [6.1-13.2]		9.06 [6.1, 13.2]		8.87 [6.26, 12.0]	
Mean Calibration	1.21		1.16		1.09	
<i>Adj. for competing risks</i>	1.32		1.27		1.19	
Time-dependent ROC Analysis	Sens/Spec	Obs. Risk	Sens/Spec	Obs. Risk	Sens/Spec	Obs. Risk
KM cut-off 8.79%	69/52	12.4	76/51	13.3	69/51	12.2
CIF cut-off 8.03%	72/46	10.4	78/44	10.8	74/44	10.4

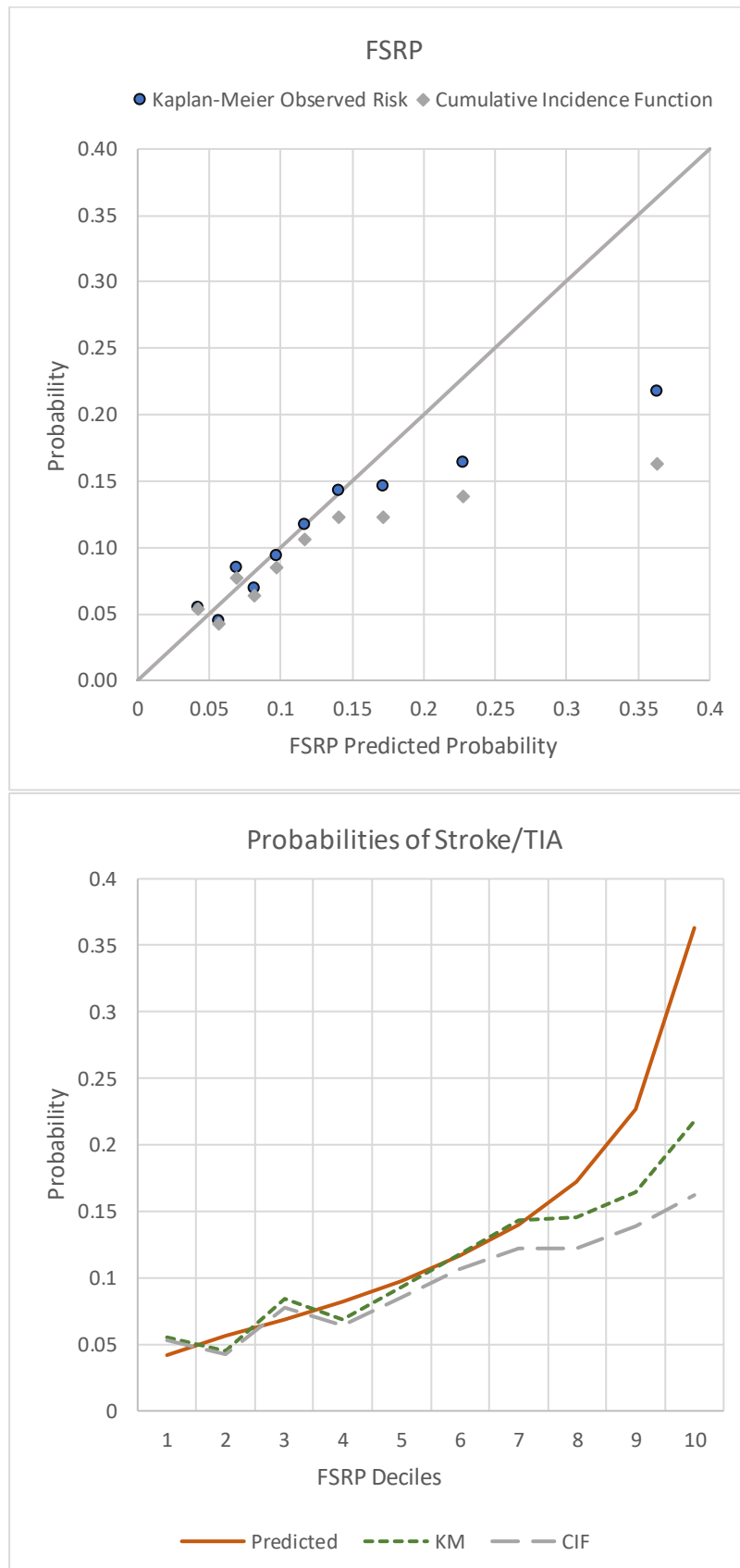
CIF: cumulative incidence function; CPI: centred prognostic index; KM: Kaplan-Meier method

Table 5.5 Observed and predicted risks among 2441 BRHS men (mean age 68y), free of CVD

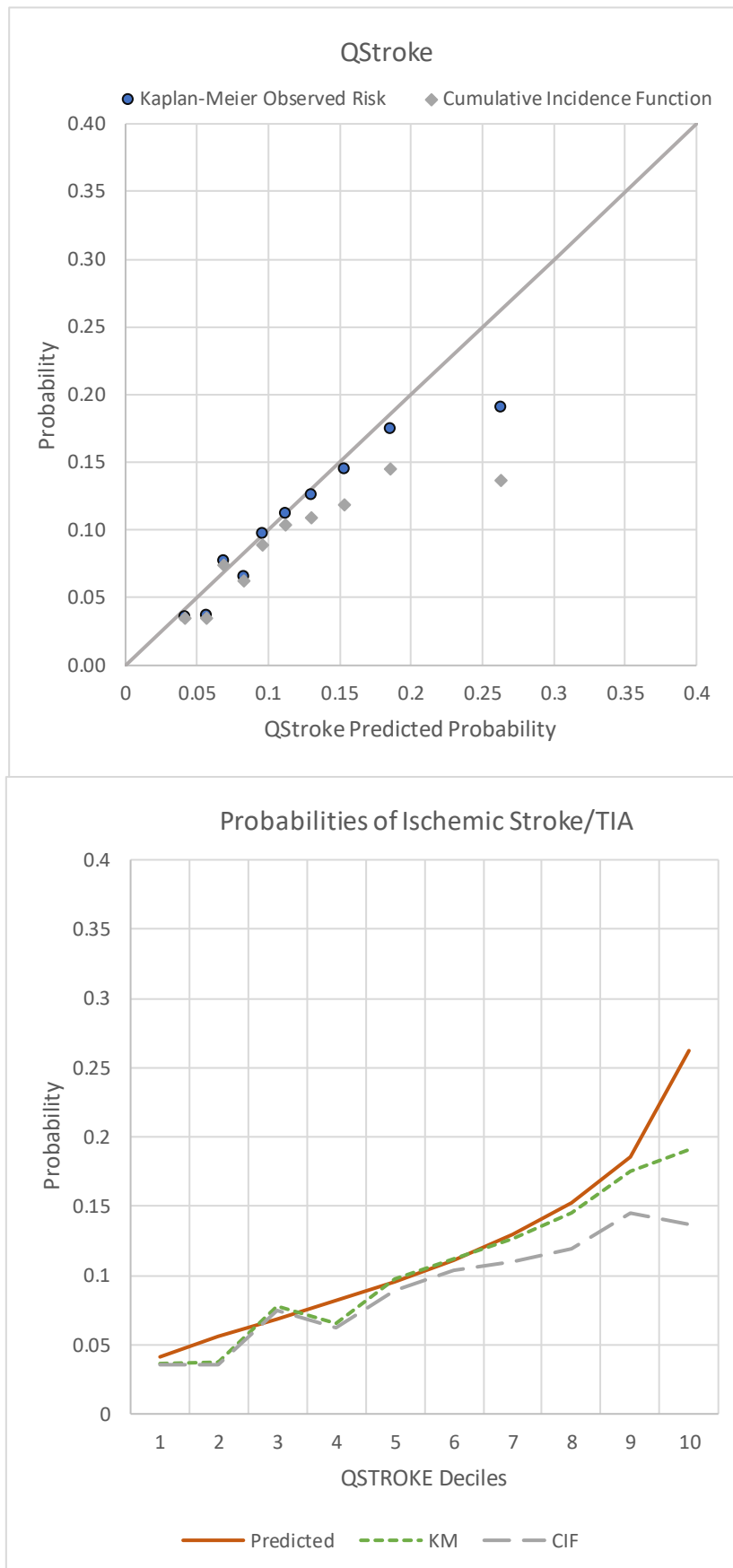
Age group (years)	No. of Events/N	Cumulative Incidence (%)	Kaplan-Meier Risk (%)	FSRP Predicted Risk (%)	QStroke Predicted Risk (%)	QRISK3 Predicted Risk (%)
≤65	42/876	4.79	4.99	7.1	6.03	6.81
>65 - ≤70	57/746	7.64	8.26	10.1	9.5	9.46
>70 - ≤75	52/521	9.98	11.34	13.3	13.54	11.7
>75	45/298	15.1	19.08	17.4	18.4	14.2

Figure 5.1 Calibration plots of observed vs predicted risk in deciles of predicted risk

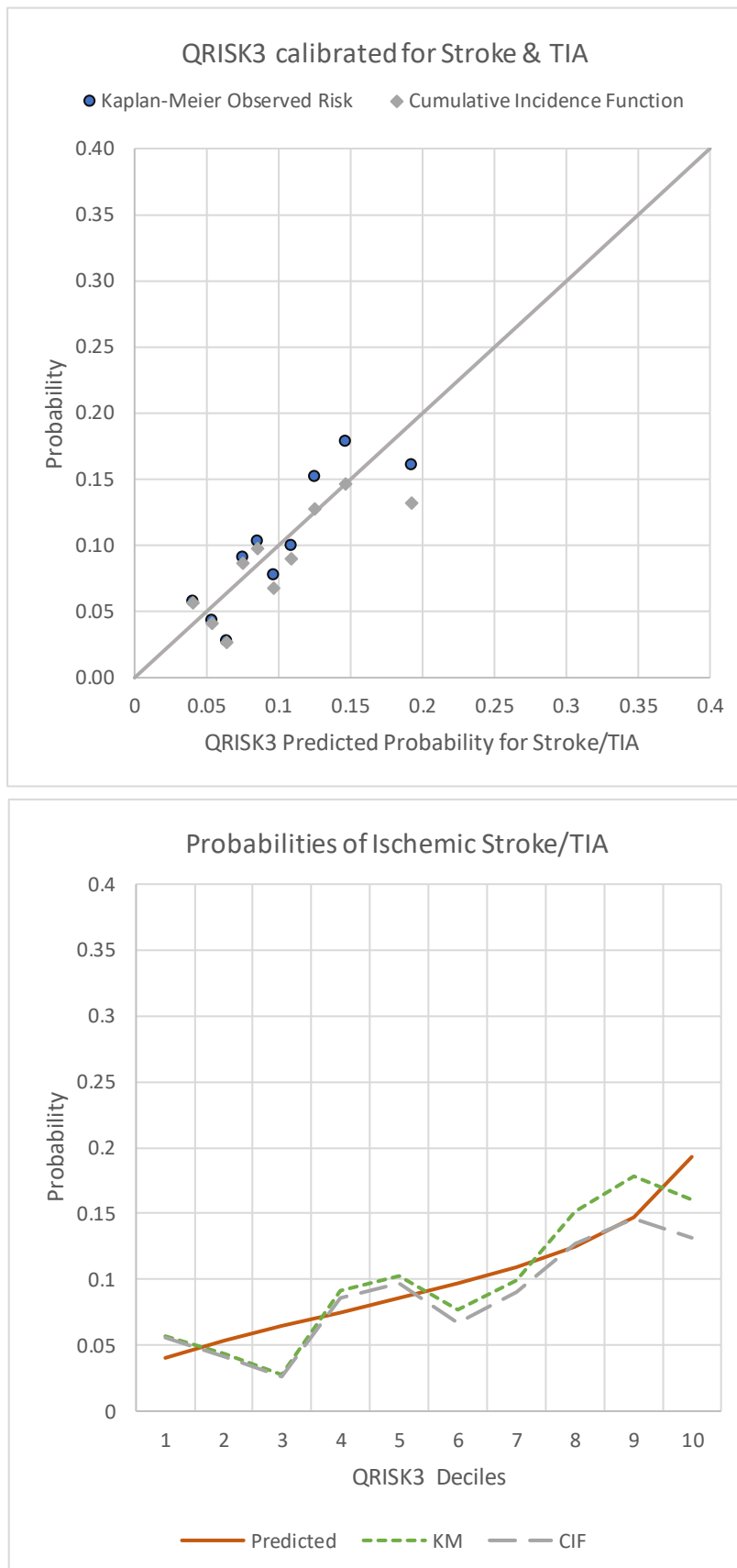
(a) FSRP



(b) QStroke



(c) QRISK3



(d) PCE

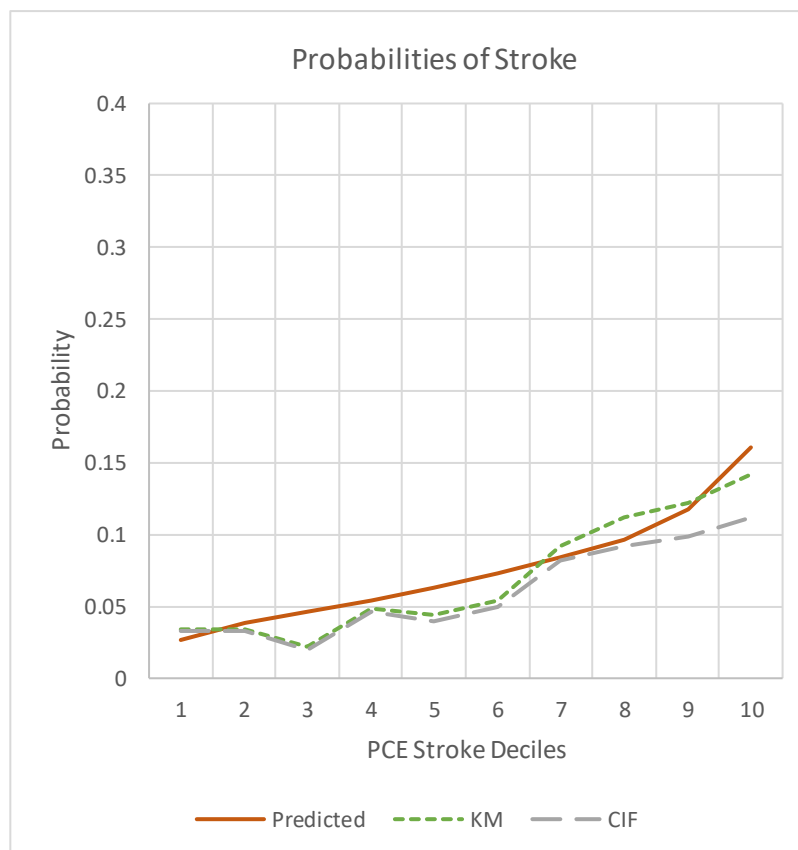
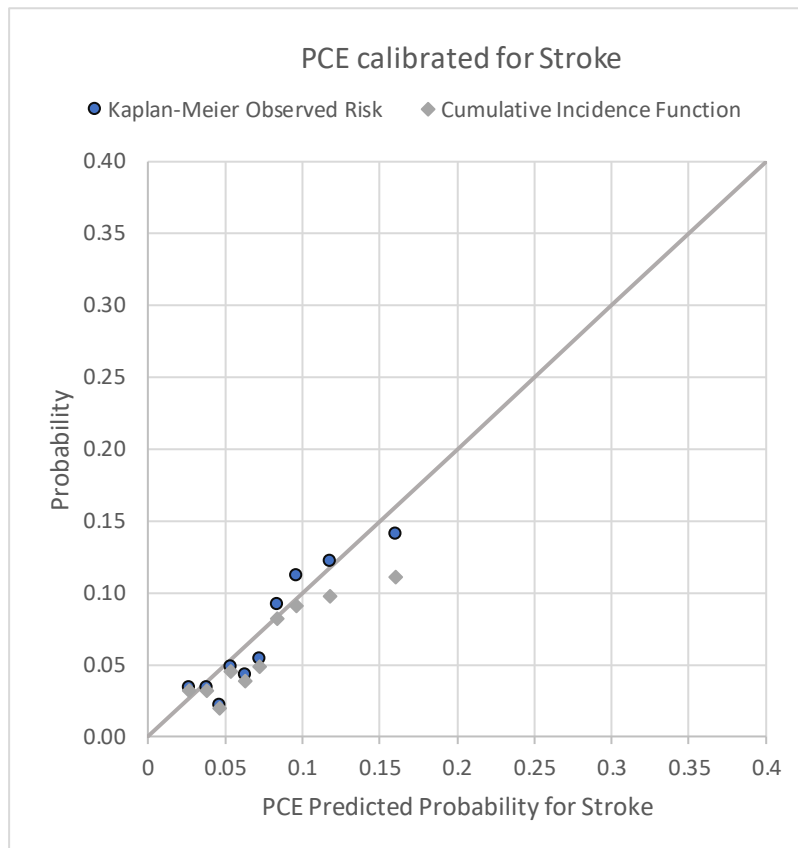
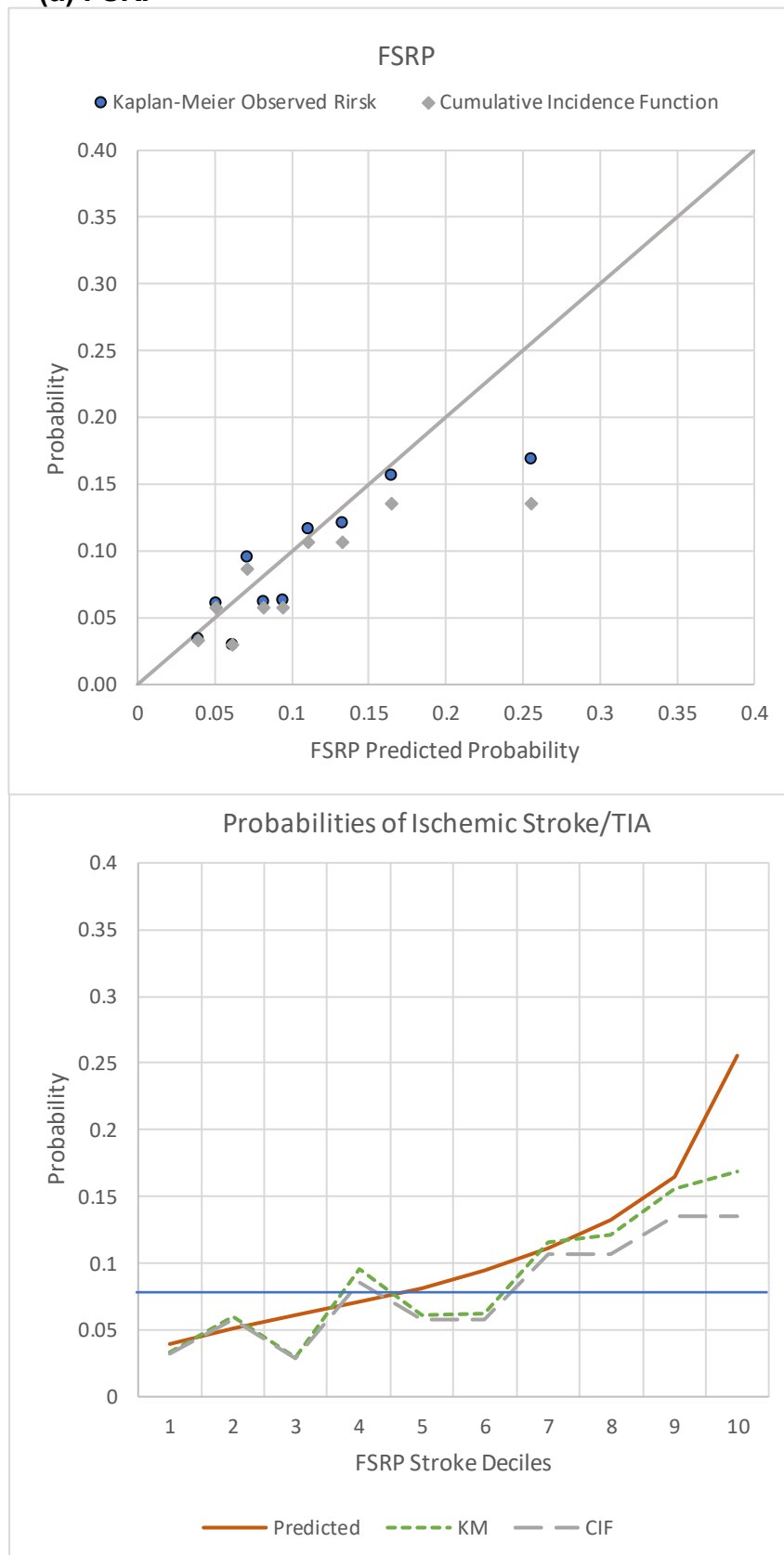
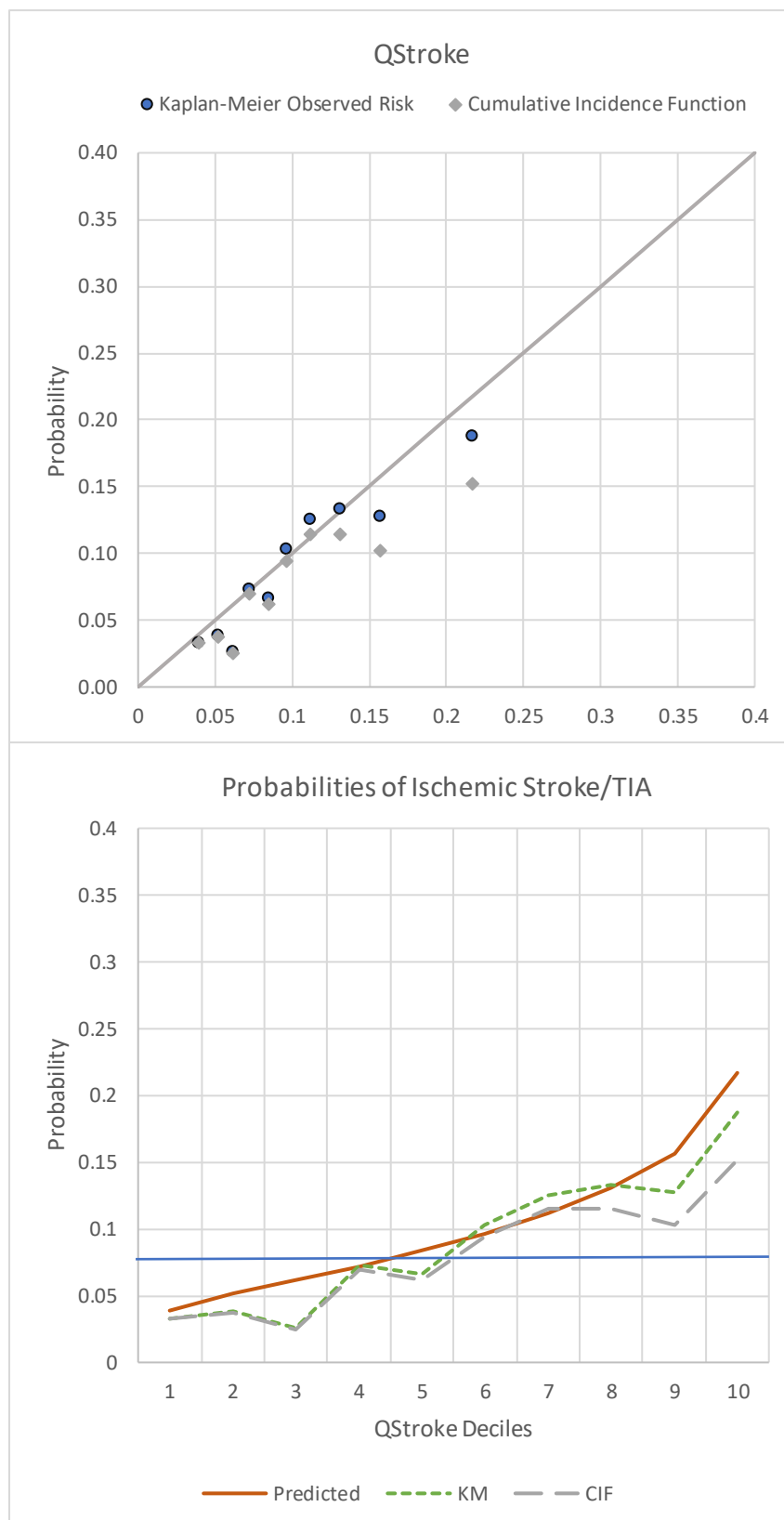


Figure 5.2 Calibration in a common BRHS sample of 2441 men without CVD, experiencing 196 incident stroke and TIA events over 10y

(a) FSRP



(b) QStroke



(c) QRISK3

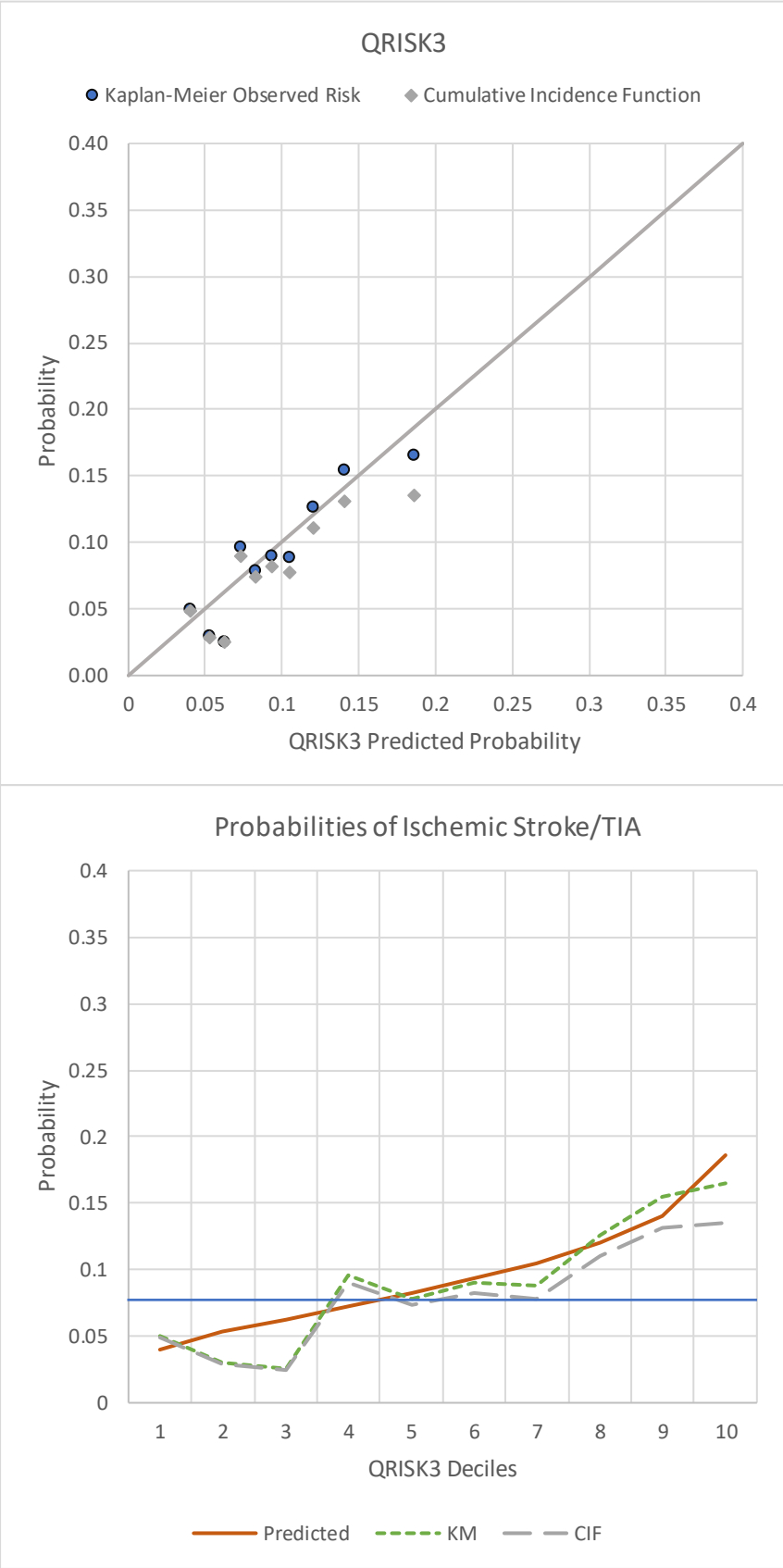


Figure 5.3 Scatterplot matrix of the FSRP, QStroke and QRISK3 mean predicted probabilities in a common BRHS sample of 2441 men without CVD, experiencing 196 incident stroke and TIA events over 10y

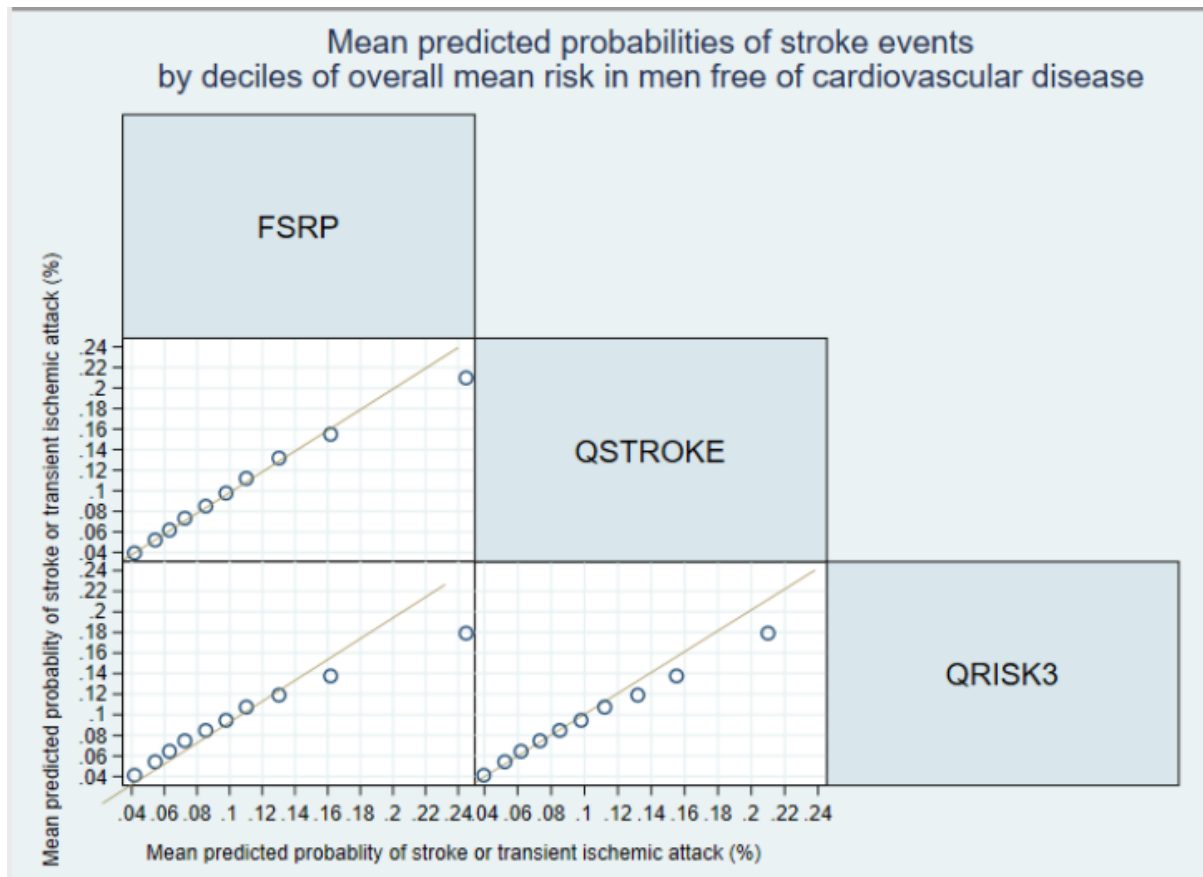
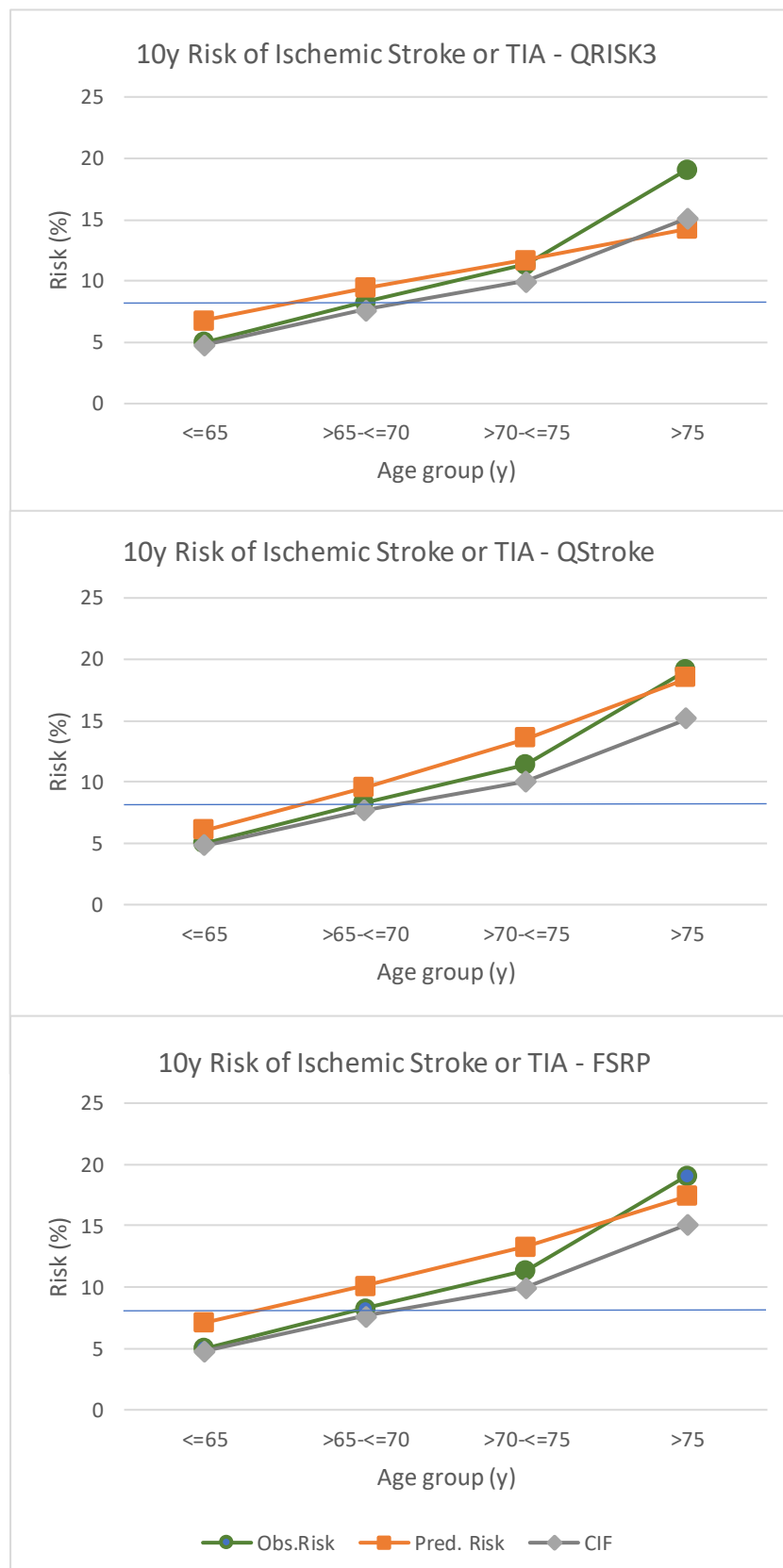


Figure 5.4 Calibration of QRISK3, QStroke and FSRP across age-groups in 2441 BRHS men without CVD, experiencing 196 incident stroke and TIA events over 10y



Chapter 6. Prospective Associations of NT-proBNP with Stroke Events

6.1 Summary

Traditional risk factors weaken in their ability to discriminate stroke risk with increasing age when natriuretic peptide (NP) biomarkers reflecting subclinical cardiac dysfunction may be more useful. Whether NPs are also useful for predicting stroke risk in SAs has not been examined. To explore the utility of NPs in primary prevention of stroke in older adults and SAs, this chapter explores the associations of NT-proBNP with stroke events in CVD free participants of BRHS and SABRE, over a 20y follow-up. NT-proBNP was associated with TIAs, fatal and non-fatal strokes, and a composite outcome of cerebrovascular accident in older BRHS men, and with all strokes in middle-aged SABRE SAs. Associations were independent of classical stroke risk factors, and of Troponin T as a complementary cardiac biomarker. Associations were also generally robust to adjustment of cardiac events occurring during follow-up prior to a stroke, and observed irrespective of the presence of hypertension, diabetes, and CKD. Findings suggest that the utility of NT-proBNP in improving stroke risk discrimination and guiding primary prevention strategies among older adults and SAs should be examined formally.

6.2 Introduction

Chapter 5 alludes to the need for improving stroke risk discrimination among older adults using age-relevant novel predictors. As discussed in section 2.2.4.2, arrhythmias such as AF, and HF become progressively important precursors in stroke aetiology with age; and biomarkers reflecting early or sub-clinical stages of these conditions such as NPs (section 2.5) could be candidates for this role. However, previous studies reporting positive associations between NT-proBNP and stroke in older adults have been limited by shorter follow-up (263, 333, 370, 385), by including participants with pre-existing cardiac disease (77, 263) and in how cardiac events occurring during follow-up (346, 367) have been accounted for. This includes earlier analysis of the

current BRHS cohort based on a mean follow-up of 9y only for major strokes, and inclusive of men with a history of AF (466). Additionally, evidence of association between NT-proBNP and TIAs, which increase in incidence with age (79) and contribute to overall stroke risk (80), either as an individual outcome (81) or a composite outcome with stroke (370) is scant.

Recent studies suggest a rising trend of HF and asymptomatic left ventricular dysfunction among SAs (83, 467), which indirectly also portends a mechanism for increased stroke risk. Although positive prospective associations between NT-proBNP and stroke risk have been observed in some non-White ethnic groups, this remains to be confirmed among SAs (section 2.5.5). In the absence of prediction tools derived from SA cohorts, cardiovascular risk prediction among them relies on models derived from predominantly White participants and is noted to be suboptimal (section 2.4.5). Evidence on whether NT-proBNP can independently predict stroke risk in SAs would be a necessary step for establishing whether it is useful in improving stroke risk stratification beyond traditional risk factors in this ethnic group as well (165).

Further, as recognised indicators of cardiac muscle injury, Troponins (I and T) have also been extensively investigated as markers of future manifest heart disease and stroke (377-380). Levels of Troponins and NPs appear to be moderately correlated (366). However, their release is associated with different underlying pathophysiological mechanisms (355, 358, 374, 468), and it is thought the biomarkers provide complementary clinical information (348). It would hence be useful to establish if NPs have a role in predicting long term stroke risk in ostensibly healthy older adults and SAs, independent of Troponins.

This chapter investigates the prospective associations of NT-proBNP with a range of incident stroke events in older White British men, and with total stroke among middle-aged Europeans and SAs, without pre-existing clinical cardiovascular disease.

6.3 Objectives

1. To examine long-term associations of NT-proBNP with incident all, fatal and non-fatal strokes; TIAs; and a composite outcome of stroke or TIAs in older BRHS men free of MI, Stroke, HF and AF.

2. To examine long-term associations of NT-proBNP with incident all strokes among middle-aged European and SA participants of SABRE without a history of CHD and stroke.
3. To examine, in both cohorts, if these associations were independent of baseline high sensitivity cardiac Troponin-T (hs-cTnT) levels.
4. To examine whether associations were independent of intervening episodes of MI, HF and AF in BRHS, and of intervening CHD in SABRE.
5. To examine, in both cohorts, whether associations persisted across clinical subgroups defined by presence/absence of hypertension, diabetes and CKD.

6.4 Methods

The study design, data collection and follow-up methodology for BRHS and SABRE have been detailed in Chapter 3. Analyses described in this chapter use data on blood biomarkers and covariates collected via physical exams and questionnaires in

- the BRHS from the 20-year follow-up examination Q20 (1998-2000, age 60-79y).
- the Southall arm of the SABRE study from the baseline visit V1 (1998-91, age 40-69y).

6.4.1 Assessment of Blood Biomarkers

In both cohorts, NT-proBNP and hs-cTnT were measured in plasma samples on an automated clinically validated immunoassay analyser (e411, Roche Diagnostics, Burgess Hill UK). All assays used the manufacturer's calibration and quality control materials. The limit of detection for NT-proBNP was 5pg/ml; for hs-cTnT 3pg/ml in BRHS and 2.5pg/ml in SABRE.

In BRHS, no adjustment was needed for values of NT-proBNP and samples reported as hs-cTnT <3 were assigned 2.99pg/ml. In SABRE values below limit of detection were numerically replaced by limit of detection divided by square root of 2 (421) i.e., for NT-proBNP 3.5355pg/ml and for hs-cTnT 1.732051pg/ml.

6.4.2 Covariates

Covariates were selected based on stroke risk factor (section 2.2.3) and biomarker literature (77, 263, 366, 466), and included age (and sex in SABRE), LS7 metrics which could affect cardiac health and stroke risk including diet (469), medications for BP, diabetes (and statins in BRHS); markers of inflammation, kidney function (and lung function in BRHS (470, 471)), and social class and alcohol intake. Section 3.3 and 3.6 have further details on covariate measurements.

6.4.3 Prevalent Conditions

In BRHS, prevalent stroke, TIA, and MI at Q20 were ascertained through GP reports and primary care record reviews from prior to Q20. AF at Q20 was determined using a 12-lead ECG at the physical examination and prior primary care records. HF at Q20 was determined using self-report of doctor diagnosed HF and from primary care records. Prevalent diabetes was based on reported physician diagnosis and/or diabetic medication or fasting glucose $>7\text{mmol/l}$.

In SABRE, CHD or stroke occurring prior to study participation was identified by self-report of doctor diagnosed disease from V1 questionnaire, along with presence of pathological Q waves on ECG for determining CHD. Prevalent diabetes was defined using the WHO criteria (423), self-report of doctor diagnosed disease or use of diabetic medication.

In both cohorts, prevalent hypertension was defined as SBP $>140\text{mmHg}$ and/or DBP $>90\text{mmHg}$ and/or receipt of BP medications. CKD was defined as $\text{eGFR} >60\text{ml/min/1.73m}^2$.

6.4.4 Incident Events and Mortality

Mortality and morbidity follow-up for both studies have been described in Chapter 3.

In BRHS, incident stroke events (section 3.3.5) have been classified into fatal and non-fatal strokes and TIAs which were analysed in this chapter together and as individual outcomes. However, TIAs have not been recorded in SABRE (section 3.6.5) and the outcome was limited to an aggregate of all fatal and non-fatal strokes.

6.4.5 Statistical Methods

In both cohorts, analyses were limited to participants with a measure of NT-proBNP. In BRHS, all analyses excluded men with a history of stroke, MI, AF and HF, while

analyses examining TIAs or a composite of TIA and stroke i.e., cerebrovascular accident (CVA) also excluded men with a history of TIA. In SABRE, analyses were based on data from European and SA participants who were free of CHD and stroke, from the Southall arm of SABRE.

6.4.5.1 Descriptive Statistics

Baseline characteristics of participants were compared across low, intermediate, and high categories of NT-proBNP, using oneway ANOVA or Kruskal Wallis tests depending on distribution and homogeneity of variances for continuous characteristics, and Chi square tests for categorical traits.

NT-proBNP levels vary with age (74). Categories were created among BRHS men free of stroke, MI, AF and HF, using tertiles T1-T3, with <55pg/ml as cut-off for T1 and ≥ 123 pg/ml for T3. The latter coincided with 125pg/ml, below which the probability of having left ventricular dysfunction among the general population in a non-acute setting is considered to be very low (irrespective of age) (350, 472, 473).

In SABRE, the cut-off for high NT-proBNP was chosen based on evidence of ≥ 100 pg/ml being high for a middle-aged CVD free population (351, 474). The cut-off for low NT-proBNP was based on the median value in the overall CHD and stroke free sample (<34pg/ml). Preliminary analysis had compared baseline characteristics between Europeans and SAs free of CHD and stroke, including cumulative distribution plots of log-transformed NT-proBNP levels. The association between ethnicity (exposure) and log-NT-proBNP was assessed in a multivariable linear regression model, as also described for African Americans and Caucasians (82) adjusting for age, sex, BMI, SBP, DBP, cholesterol, glucose, eGFR, diabetes, hypertensive group, smoking, physical activity, diet, CRP and social class. Based on (1) ethnic differences in baseline NT-proBNP levels from this preliminary analysis and (2) ethnic differences in distribution/associations with stroke of covariates (50, 211) all further descriptive and inferential analyses were conducted separately for Europeans and SAs a priori. Interactions between NT-proBNP and sex were not significant in any ethnic group.

6.4.5.2 Survival Analysis and Cox Proportional Hazards Regression

In both cohorts, crude incidence of all strokes (and additionally of first TIA and CVA in BRHS) per 1000 person-years (/1000PY) was compared as a trend across categories

of NT-proBNP through survival analysis. Age-adjusted event-free survival probabilities are presented using KM-survival curves.

Using Cox models, HRs of respective stroke events were estimated for intermediate and high categories of NT-proBNP with reference to low; as trends; as well as per standard deviation (SD) of log NT-proBNP (derived for each ethnicity separately in SABRE). In BRHS time to event was calculated from baseline date of examination (in 1998-2000) to a first stroke, death, or 1st June 2018, whichever came first. For associations with fatal/non-fatal strokes, participants with the alternate type were censored. For TIAs time was calculated from the baseline date of examination to the earliest of a first TIA, death or 1st June 2018; and participants with stroke were censored. For CVA, the first of either TIA or stroke events was used. In SABRE, time to event was calculated from the baseline year of examination (1988-1991) to a first fatal/non-fatal stroke event, non-stroke death, or year of morbidity follow-up (2008-2011) – whichever came first.

For objectives 1 and 2, HRs were estimated for crude associations, adjusted for age (and sex in SABRE), and after accounting for confounding variables (Figure 6.1) as follows: **model 1:** known cardiovascular risk factors that form the LS7 metrics (SBP, BMI, cholesterol, glucose, PA as continuous; and current smoking and poor diet as binary variables); **model 2:** further adjusted for social class, alcohol intake and medications for BP, diabetes (and statins in BRHS); **model 3:** further adjusted for inflammation (IL-6 in BRHS, CRP in SABRE), eGFR for kidney function (and FEV1 for lung function in BRHS). To examine if associations were independent of baseline Troponin-T (objective 3), model 3 was further adjusted for SD-log-hs-cTnT. To examine if the effect of NT-proBNP was explained by incident cardiac events antecedent to stroke (objective 4), model 3 was adjusted for MI, HF and AF in BRHS and CHD in SABRE as time-varying covariates. Analyses were based on available complete cases. A p-value <0.05 was considered significant for HRs and linear trends.

Linearity of associations was tested for all respective outcomes in both cohorts using likelihood ratio tests with the ordinal variable and with quadratic term of continuous SD-log NT-proBNP. There was no evidence of departure from linearity. Dose-response relationship between NT-proBNP and risk of study-specific stroke events were characterized using restricted cubic splines in model 1, with knots at 5th, 27.5th,

50th, 72.5th and 90th percentiles of NT-proBNP range (which were ethnicity specific in SABRE).

Proportional hazards assumptions were assessed using post estimation tests, examination of Schoenfeld residuals and log-log plots, and were found to be valid in both studies except for a slight weakening of effect of the highest NT-proBNP category in SABRE Europeans towards the end of follow-up time.

6.4.5.3 Subgroup Analyses

In relation to objective 5, absolute rates of stroke events were estimated in subgroups stratified by categories of NT-proBNP and presence/absence of diabetes, hypertension, and CKD. HRs of stroke events with reference to the subgroup without each condition and having low NTproBNP were estimated for the remaining subgroups adjusted for model 1 variables. Interactions ($p < 0.10$ considered significant) between categories of NT-proBNP and each prevalent condition were also explored using the Wald chi-square test.

6.4.5.4 Sensitivity Analyses

To examine the effect of any undiagnosed HF, analyses were repeated in both cohorts excluding participants with NT-proBNP ≥ 400 pg/ml which represents suspected chronic heart failure (345).

6.4.5.5 Consideration of Missing Data

Characteristics of participants with complete data on NT-proBNP and covariates were compared to those with missing data using appropriate statistical tests in both cohorts. The probability of being a missing case was examined in logistic regression models.

In BRHS, analyses were repeated using models exclusive of diet which had the greatest proportion of missing data from all covariates, after NT-proBNP.

6.4.5.6 Supplementary Analyses

To account for competing non-stroke mortality, associations of NT-proBNP with stroke events were examined while adjusting for the competing risk of non-stroke deaths both in BRHS and in SABRE.

The risk of stroke across low, intermediate and high categories of hs-cTnT, and per SD-log-hs-cTnT in models mutually adjusted for NT-proBNP were also tabulated.

6.5 Results

6.5.1 Baseline Participant Characteristics and Incidence of Stroke Across Levels of NT-proBNP

BRHS

The average age of BRHS men free of stroke, MI, AF, and HF at baseline was 69y. NT-proBNP values (5-9771pg/ml) were available for 3241 men. Men with higher NT-proBNP values were older and more socioeconomically deprived (Table 6.1). Across increasing tertiles of NT-proBNP levels of SBP, BP medication and statin use, inflammation, and hs-cTnT increased; while kidney function, lung function and PA decreased. Of note, levels of BMI and DBP; and prevalence of poor diet, smoking, alcohol use, diabetes (10-12%) and diabetes treatment (4-5%) were similar.

Across tertiles of NT-proBNP, crude incidence of all strokes (median follow-up 16y), TIAs and CVAs increased as a significant trend; incidence of all strokes doubled and then tripled across T2 and T3 relative to T1 (Table 6.1). Similarly, age-adjusted event-free survival for all outcomes was worse for men with intermediate and high levels of NT-proBNP (Figure 6.2a-e).

SABRE

There were 1219 Europeans (87% men, mean age 53y) and 1225 SAs (83% men, mean age 51y) free of CHD and stroke with data on NT-proBNP (Table 6.2). SAs had 1.3 times higher [95% CI 1.00-1.69] age and sex adjusted risk of stroke. They also had slightly higher levels of SBP, DBP, glucose and inflammation; poorer PA; and lower levels of cholesterol, smoking, and alcohol intake. More SAs were diabetic and on treatment for diabetes and high BP. Plasma NT-proBNP levels were slightly lower in SAs, median (Q1, Q3) 31.1pg/ml (19, 55); Europeans 37.1pg/ml (24, 64) $p < 0.001$ (Table 6.2, Figure 6.3). SA ethnicity was associated with 18% lower log NT-proBNP levels (beta coefficient for SAs -0.193 $p < 0.0001$ in multivariable adjusted model).

Higher categories of NT-proBNP were associated with increasing age, SBP and use of BP medication, inflammation; and decreasing GFR and PA in both ethnic groups. Prevalence of smoking and diabetes was similar across levels of NT-proBNP in both ethnic groups although the proportion of smokers was lower among SAs, while the proportion with diabetes higher (18-22%) (Table 6.3 and Table 6.4).

During a median follow up of 20y, stroke incidence increased across categories of NT-proBNP in both ethnic groups. In particular, SAs with high NT-proBNP ($\geq 100\text{pg/ml}$) had an incidence of 14/1000PY compared to Europeans with high NT-proBNP having 9/1000PY. Among SAs, age adjusted stroke free survival was mainly worse for those with high NT-proBNP (Figure 6.4a-b).

6.5.2 Long-term Associations of NT-proBNP with Stroke Events

BRHS

NT-ProBNP was associated with increased risk of stroke events as a statistically significant trend across increasing categories in all models (Table 6.5). The greatest attenuation to crude HRs was brought about by adjustment for age. Fully adjusted (model 3) HRs of all strokes for intermediate and high categories were 1.68 [1.23-2.29] and 2.22 [1.60-3.08] respectively (p trend <0.0001). Further adjustment for hs-cTnT made little difference (HR intermediate 1.65 [1.21-2.26] and high 2.12 [1.52-2.94], p trend <0.001). Associations remained similarly strong on adjustment for MI, AF and HF antecedent to stroke (intermediate 1.65 [1.20-2.26] and high 1.96 [1.40-2.74], p trend <0.001). The pattern of associations was similar for TIAs, non-fatal and fatal strokes, and for CVAs; with magnitude of associations slightly smaller for TIAs and larger for fatal events.

Statistically significant associations with all event types were also noted per SD-log NT-proBNP. HRs ranged from 1.26 [1.05-1.50] for TIAs to 1.59 [1.22-2.06] for fatal strokes in fully adjusted models. Associations persisted after adjustment for hs-cTnT and incident cardiac events, except in case of TIAs for which the risk became statistically non-significant on accounting for the latter.

Dose response relationships between NT-proBNP and stroke events (model 1) are displayed in Figure 6.5a-e; and indicate a sharper increase in risk with initial rise in NT-proBNP levels, leading to a plateau.

SABRE

Among Europeans, increasing NT-ProBNP levels were associated with increasing risk of stroke as a trend robust to full adjustment (HR model 3: intermediate 1.45 [0.91-2.30] and high 1.99 [1.09-3.62] p trend 0.03) (Table 6.6). Separate further adjustments for hs-cTnT and CHD antecedent to stroke attenuated HRs slightly, and while the trend

lost statistical significance, risk among participants in the highest category remained roughly 1.8 times the lowest.

In SAs, increased risk of stroke was evident mainly among those with high NT-proBNP (HR model 3: intermediate 0.88 [0.55-1.42] high 2.67 [1.49-4.79] p trend <0.001). This risk attenuated only slightly, on adjusting for hs-cTnT (HR high NT-proBNP 2.37 [1.30-4.33]) and for incident CHD (HR high NT-proBNP 2.27 [1.20-4.31]) remaining statistically significant (Table 6.6).

In fully adjusted models, HRs of stroke per SD-log NT-proBNP among Europeans (1.38 [1.15-1.66]) and SAs (1.49 [1.21-1.83]) were similar (Table 6.6), with little change on adjusting for hs-cTnT, and slight attenuation on adjusting for incident CHD. Dose-response relationships across the continuous range of NT-proBNP were also similar in both groups, except for a steeper rise in HRs to 50pg/ml in Europeans vs a slower rise to 100pg/ml in SAs, followed in both by a gradual increase in risk (Figure 6.6a-b).

6.5.3 Associations with Stroke in Key Cardiovascular Risk Factor Groups

BRHS

Table 6.7 and Table 6.8 show absolute rates and HRs of stroke and CVA in BRHS men grouped according to low/intermediate/high NT-proBNP and hypertension, diabetes and CKD status. Higher NTproBNP levels were associated with higher absolute rates of stroke and CVA irrespective of presence of hypertension, or diabetes or CKD. Statistical interactions between subgroups were generally not significant. However, the adjusted (model 1- known cardiovascular risk factors from the LS7 metrics) risk of stroke and CVA in men without hypertension but with high NT-proBNP was nearly twice that among men with hypertension who had low levels. Additionally, the risk of stroke and CVA in men without diabetes but with high NT-proBNP was as high as risk among diabetic men.

SABRE

Considering event numbers, subgroup analyses in SABRE were conducted for NT-proBNP groups dichotomised at the 100pg/ml cut-off. Table 6.9 shows absolute rates and HRs of stroke in SABRE participants grouped according to low/high NT-proBNP and hypertension, diabetes and CKD status.

Among Europeans high NTproBNP levels were clearly associated with higher absolute rates of stroke in hypertensives – in whom covariate adjusted risk doubled compared to those with low NT-proBNP without hypertension (p interaction 0.05). High NT-proBNP appeared to be associated with higher absolute rates of stroke irrespective of diabetes and CKD, but adjusted HRs were statistically significant only in those without the risk factor condition.

Among SA participants, absolute rates of stroke were higher for those with high NT-proBNP regardless of hypertension, or diabetes or CKD. Adjusted risk of stroke appeared especially high among those who had high NT-proBNP and were hypertensive (~fourfold) and diabetic (fivefold).

6.5.4. Sensitivity Analyses

BRHS

In BRHS, excluding men with NT-proBNP ≥ 400 pg/ml slightly reduced the magnitude of risk associated with the highest category of the biomarker, but overall relationships remained similar and statistically significant (Appendix 6.1).

SABRE

On excluding participants with NT-proBNP ≥ 400 pg/ml in SABRE, HR of stroke associated with NT-proBNP ≥ 100 pg/ml in Europeans, and the trend across categories became weaker and non-significant when fully adjusted for covariates. Among SAs, HR of stroke associated with NT-proBNP ≥ 100 pg/ml remained elevated and significant (Appendix 6.2). However, HRs associated with SD-log NT-proBNP were marginally affected and remained statistically significant in both ethnic groups.

6.5.5. Consideration of Missing Data

BRHS

Of 4252 men who took part in Q20, 3614 were free of MI stroke HF and AF, of which 10% (n=373) did not have a measure of NT-proBNP. These men had slightly higher levels of mean SBP and BP medication use, were more frequently smokers, but were similar to those with a measure of NT-proBNP on other characteristics, with no statistically significant differences in rate of incident events including all-cause mortality (Appendix 6.3).

Of the 3614 men, 76% (n=2736) had complete data on NT-proBNP and all covariates. Variables other than NT-proBNP with missing data included diet (7%), cholesterol glucose and eGFR (5%), IL-6 (4%) and PA (3%). In comparison to complete cases, men with missing data were slightly older, with higher rates of socioeconomic deprivation, hypertension, and all-cause mortality, as well as higher median value of NT-proBNP, but no difference in stroke event rates (Appendix 6.4).

In this sample, the probability of missingness was associated both with the exposure (NT-proBNP) and multiple baseline covariates, some of which were fully observed and others which had data missing. The missing data mechanism was hence assumed to be missing not at random. In logistic regression models comprising predictors of missingness and each stroke event type, missingness was not associated with either of stroke, TIA or CVA outcomes.

Analyses additionally repeated without including the diet variable in models indicated HRs that remained robust (Appendix 6.5). Diet was hence retained in the main models to keep BRHS and SABRE analyses consistent with LS7 metrics.

SABRE

Of 1562 Europeans and 1509 SAs participating in the baseline Southall SABRE visit with follow up data on stroke available, 1404 Europeans and 1376 SAs had no history of CHD and stroke. Among these, 13% EU and 11% SAs had missing values on NT-proBNP. In each ethnic group, nearly all participants missing NT-proBNP were also missing eGFR, CRP and hs-cTnT, with negligible missing data for other variables. Overall complete data were available for 82% EU and 81% SAs. Europeans with missing data were similar to those with complete data except for slightly better kidney function and lower median hs-cTnT levels and fewer participants on BP medication. The cardiovascular profile of SAs with and without missing data was also very similar, except for statistically non-significant slightly higher rate of stroke events and all cause deaths among missing cases (Appendix 6.6).

In SABRE Europeans, the probability of missingness overall was associated with age, sex, BP medication use, eGFR and hs-cTnT; assumed to be missing not at random; and independent of strokes in a logistic regression model containing these variables. Among SABRE SAs, the probability of missingness overall was only associated with sex which was fully observed, and hence assumed to be missing at random.

Additionally, missingness was independent of the stroke outcome for both ethnicities, in models containing NT-proBNP and relevant covariates, rendering complete case analysis non-biased, albeit less precise.

6.5.5. Supplementary Analyses

Associations on Adjusting for Competing Risk of Non-Stroke Death

Appendix 6.7 shows risk of stroke events associated with NT-proBNP while accounting for competing non-stroke deaths. In fully adjusted models and models additionally adjusted for hs-cTnT, HRs for the high NT-proBNP category were slightly weaker in magnitude but overall trends remained statistically significant in BRHS, and among SABRE SAs. Among SABRE Europeans, the incremental risk of stroke across categories of NT-proBNP became non-significant but HR per SD-log NT-proBNP was little affected.

Associations of Troponin-T with Stroke Events

Appendix 6.8 gives (cut-offs for and) HRs of stroke across low intermediate and high categories of hs-cTnT in models adjusted for all covariates and NT-proBNP (model 3 + NT-proBNP). hs-cTnT was not associated with TIAs and CVAs in BRHS men, nor with all strokes in SABRE participants.

6.6 Discussion

6.6.1 Summary of Key Findings

Among older BRHS men without clinically manifest heart disease or stroke, over a median follow up of 16y, values of NT-proBNP falling within the clinically normal reference range were incrementally associated with all severities of stroke events independent of a number of risk factors, of baseline hs-cTnT levels and of cardiac events occurring prior to a stroke event. NT-proBNP appeared to stratify stroke risk irrespective of the presence/absence of hypertension, diabetes, and kidney dysfunction.

Among middle-aged CVD free participants of the SABRE study, increasing NT-proBNP levels were also independently associated with the risk of stroke over a median follow up of 20y in both SAs and Europeans. However, associations appeared

stronger in SAs for $\geq 100\text{pg/ml}$ as a potential threshold for increased risk, and more robust to baseline hs-cTnT levels and to intervening CHD events.

6.6.2 Comparison with Studies Examining NT-proBNP as a Risk Marker of Stroke in Older Adults

Evidence regarding the long-term association of NT-proBNP with the range of stroke events in older adults without a history of CHD, HF and AF, and hence its role in risk prediction and primary prevention of stroke has been limited (81, 346, 370).

Magnitude of association with strokes noted for the top tertile of NT-proBNP in BRHS (HR 2.22 [1.60-3.08]) is slightly larger than that reported for the top third of the NT-proBNP distribution (1.81 [1.58-2.07]) in an individual-participant data meta-analysis of 30 prospective studies (346). Given BRHS men were older (mean age 69y vs 61y among meta-analysis participants); followed for a median period twice as long (16y vs 8y); and with median(Q1, Q3) NT-proBNP 82pg/ml(43, 159) in BRHS compared to 64pg/ml(30,135) in the meta-analysis sample, this confirms NT-proBNP remains a robust marker of the long-term risk of a first stroke event in CVD naïve older adults.

This BRHS finding is corroborated by very recent work among older Dutch men of the Rotterdam study, (mean 68y); free of CHD, stroke, HF; and followed for a similar (14y) mean duration (368). Authors reported HR for all strokes (fatal and non-fatal) of 1.38 [1.19-1.61] per SD-log NT-proBNP - almost identical to that noted in BRHS (1.36 [1.19-1.56]).

Although the latter work did not examine TIAs, an earlier shorter follow-up (mean 9y) of the same Dutch men, excluding only those with stroke/TIA and HF, while noting associations with IS and HS, did not record an association with TIAs (81). Authors suggested this might mean sub-clinical heart disease prospectively related to more severe events in men. However, increasing NT-proBNP levels independently predicted increased risk of TIA, as well as CVA in BRHS men. This may likely be related to a narrower baseline distribution of NT-proBNP in the Dutch men (median 65pg/ml(35, 133) leading to lower tertile cut-offs (T1 42pg/ml and T3 104pg/ml) compared to BRHS men; and/or their shorter follow-up leading to a lower TIA event rate across tertiles. Additionally, the Dutch sample included men with AF and reported baseline anticoagulant use of 3.7% although this was adjusted for. In comparison

BRHS analysis excluded men with AF, with <1% of the remaining men reporting warfarin use, adjusting for which made no difference to stroke or TIA risk estimates.

The risk of CVA associated with NT-proBNP was also examined among community dwelling older adults free of CVD (but not AF) in the Canterbury Health Volunteers Study, New Zealand (370). However, findings for categorical associations did not reach statistical significance because of a short 5y follow-up limiting the number of events (to only 70 in a sample of 2528), although HR per ln-NT-proBNP (1.43 [1.08-1.89]) was noted to be similar to risk of CVA per SD-log-NT-proBNP in BRHS men.

Pathways underlying Associations between NT-proBNP and Stroke in Older Age

Associations with the spectrum of stroke events were independent of a range of known confounders/shared risk factors that can lead to elevated NT-proBNP and to stroke. This suggests the increased stroke risk may be linked to wider metabolic (348) or inflammatory states (475) that can trigger cardiac strain and cerebrovascular pathology and were not completely accounted for, or indeed to broader physiologic influence of NT-proBNP and the raised NP activity it reflects.

For example, while NPs are secreted to reduce volume and pressure overload on the heart by causing vasodilation, diuresis and natriuresis, and effects are mainly anti-hypertensive in the short term; NT-proBNP levels >99pg/ml have been linked to development of hypertension in normotensive individuals over longer term (357). NPs have also been noted to varyingly influence endothelial permeability (356). Both can be precursors to neurovascular endothelial dysfunction and atherosclerosis. Interestingly, BNP has been found to protect against diabetes (360), and to stimulate angiogenesis in extra-cardiac hypoxic tissue (356), both of which may potentially protect against CVAs. It is likely a cumulative effect of these mechanisms, which results in the range of stroke manifestations.

Among CVD free older adults in whom NT-proBNP levels indicate subclinical cardiac dysfunction, it is plausible that the pathway to stroke involves eventual clinical manifestation of that dysfunction, such as HF, AF or MI with which NT-proBNP is noted to be associated (476, 477) and which then lead to a preponderance of thromboembolic stroke events in late life (72, 73, 173). However only a small aspect of the prospective association of NT-proBNP with stroke appeared to be mediated through the occurrence of cardiac events. This has been noted in other older cohorts

with a shorter follow up (77, 263). BRHS findings suggest NT-proBNP may be signalling age related atrial substrate changes and remodelling, that create a thrombogenic environment leading to CE strokes without the occurrence of manifest cardiac conditions up to 20y later (189).

6.6.3 Comparison with Evidence on NT-proBNP as a Risk Marker of Stroke in South Asians

To my knowledge, this is the first comparison of NT-proBNP levels between middle-aged European and SA individuals from a CVD free general population, and the first examination of its association with stroke events in SAs.

Statistically non-significant lower levels of NT-proBNP have been noted among Asian-Americans relative to White participants in post hoc analyses of the Diabetes Prevention Program (Gupta 2020). However, this recruited a diabetes prone sample with impaired glucose tolerance, with Asian Americans being only a small fraction. In contrast, The SABRE analysis compares SAs and Europeans in almost equal numbers. Given NT-proBNP has a protective role against development of diabetes (360) and NPs are anti-hypertensive in the short term (74, 357) - the finding that middle-aged as yet CVD free SAs have lower levels of NT-proBNP than Europeans may have value in explaining some of their higher prevalence of diabetes and high BP, and greater future risk of CVD including stroke. However, it is difficult to say if an 18% difference in log-NT-proBNP is clinically significant. Further, echocardiographic data was not available for baseline SABRE participants, and so the comparison could not control for differences in LV mass (219) between the two ethnic groups. It is worth pointing out that in a later analysis of SABRE (373), an older subset of SAs had higher NT-proBNP levels compared to Europeans, but this included participants with CVD which itself raises NT-proBNP.

Notwithstanding this, independent incremental association of NT-proBNP with stroke was noted in SAs, of a magnitude comparable to that in Europeans – both within SABRE and elsewhere (76, 363). In SABRE, baseline history of HF and AF was not available and data on first ever AF and HF could not be ascertained, so models could only adjust for intermediate CHD events. However, given SAs have a lower burden of AF and relatively higher burden of CHD (10); the robustness of associations to adjustment of incident CHD is useful to note.

Potential Pathways underlying Associations between NT-proBNP and Stroke in South Asians

Although subtyping of strokes was not possible in SABRE, a greater proportion of the IS burden in SAs is known to be comprised of LAA and SVD (23, 205, 209). Mechanisms underlying the association between NT-proBNP and stroke may therefore differ from those in older adults in whom CE strokes become more frequent (41, 114, 169). SAs are thought to harbour a pro-inflammatory milieu, possibly linked to greater central adiposity (478, 479), which may be a precursor for both NP release (355) and LAA and SVD strokes (158). SABRE models did adjust for CRP, but this alone may not be able to capture the contribution of inflammation to NT-proBNP levels and/or stroke.

6.6.4 NT-proBNP Predicts Stroke Independent of Troponin-T

Troponins representing chronic cardiac injury and NPs representing hemodynamic cardiac overload may provide complementary perspectives on cardiac status. NT-proBNP and hs-cTnT were found to be correlated modestly in older British men (Spearman's ρ 0.31 $p < 0.001$) and weakly in middle-aged participants of SABRE (Spearman's ρ 0.19 $p < 0.001$). In models adjusting for both markers, NT-proBNP retained its significant associations with stroke events in both cohorts, while associations of hs-cTnT were null for TIAs and CVAs in BRHS and for all strokes in SABRE. Studies assessing Troponins alongside NT-proBNP in older adults have generally focused on a global CVD outcome (333, 364, 370, 480). However, examination of associations with stroke mortality of NT-proBNP, hs-cTnT and CRP adjusted mutually, in a mixed-race CVD free older North American cohort also reported robust significant associations only for NT-proBNP (78). It is possible that hs-cTnT levels in older CVD free adults result more often from physiological cardiac muscle turnover and not pathological injury (348, 374). To my knowledge there are no such comparisons available for SAs. For most SABRE participants, hs-cTnT levels were below 14pg/ml (the 99th centile for general population) and similarly may not be reflecting a cardiac pathology.

6.6.5 NT-proBNP as a Stroke Risk Marker across Risk Factor Sub-Groups

In agreement with previous research (76, 346) NT-proBNP was able to signal a greater relative risk of stroke/CVA irrespective of hypertension and diabetes status and kidney function, in older men followed for a longer duration of 20y. This makes it worth

investigating as criteria for targeted stroke risk investigations such as cardiac or carotid imaging (481, 482) or rhythm monitoring (483).

Additionally, BRHS men with hypertension but NT-proBNP <123pg/ml appeared to be at lower risk of stroke compared to those without hypertension but with higher NT-proBNP. The potential of NT-proBNP to stratify stroke risk across finer categories of blood pressure has also been suggested by Hussein et al (484) examining a larger sample of older CVD free ARIC participants. In geriatric clinical practice, this may have relevance for deciding when to (not) escalate BP treatment.

NT-proBNP >100pg/ml appeared to especially increase risk of stroke in SAs; and may similarly warrant more aggressive management of risk factors across relevant risk factor subgroups. This appeared especially true for SAs with high NT-proBNP and diabetes, which continues to remain a worrying risk for CVD morbidity (485) and carries an especially high risk of stroke (210, 211).

The ability of NT-proBNP to stratify risk of stroke irrespective of the presence/absence of hypertension, diabetes and kidney dysfunction likely comes down to the sensitivity of the NP system to reflect cardiac and hemodynamic stress across physiological states. Higher BNP levels have been associated with abnormal left ventricular function and silent ischemia in people with type 2 diabetes (486, 487). Individuals with CKD have been found to have a range of NT-proBNP values suggesting mechanisms for its elevation beyond (and despite) reduced renal clearance can still be reflected (488). And evidence indicates a complex interplay between NT-proBNP and systolic BP (484) representing cardiac wall stress from the effects of existing hypertension, as well as indirectly through long term effects of BNP on vasculature that may potentially promote hypertension (357). A useful consequence of this sensitivity to a myriad of influences means NT-proBNP remains a robust prognostic marker for stroke.

6.6.6 Strengths and Limitations

General strengths and limitations of the two data sets have been presented in sections 3.4 and 3.7.

The BRHS analysis explored a range of stroke manifestations including TIAs over an extended follow-up, focusing exclusively on a CVD free older group most likely to

benefit from informed primary prevention of stroke. Models adjusted for conventional stroke risk factors as well as covariates relevant to health of older adults such as inflammation (308) and lung function (489). The number of fatal strokes was limited, and formal tests of strength of associations between fatal/non-fatal events were not conducted. But similar strong associations of stroke mortality with NT-proBNP have been recorded in a multi-ethnic North American cohort with an even smaller number of events (78). In SABRE, subgroup analyses were limited by number of stroke events however findings are in expected directions.

In both cohorts, time varying adjustment for incident cardiac events controlled for the increased risk of a stroke resulting from the pathophysiology of such events (and therefore the change in lifestyle/medication use that follows them and could influence risk associations). This allowed for such participants to remain in the risk set instead of being lost to censoring (346). To account for non-stroke mortality during the lengthy follow up (and due to participant age in BRHS), competing risks models provided a more realistic assessment and confirmed robust associations in both vulnerable groups.

Classification of stroke subtypes to explore finer etiologic associations was not possible and although earlier evidence indicates similar HRs for IS and HS (346), and particularly strong association with CE strokes, the association with SVD is less clear (77, 263) and may be worth investigating among SAs who have a greater burden of this stroke subtype.

Only a single measure of biomarkers was available so the effect of change in biomarker levels over time could not be examined. Baseline echocardiographic measures of heart structure that could confound biomarker associations were not available; but in BRHS adjusting for ECG based left ventricular hypertrophy did not change results (not shown).

Additionally, although analysis used available cases which reduced sample size, missing data mechanisms suggested this would not be biased. Previous evidence to compare associations in SAs is not available but for BRHS, comparison with latest evidence available for older adults suggests similar magnitude and direction of associations (368).

6.7 Conclusion

NT-proBNP incrementally and independently predicts the risk of a range of stroke events in older British men without a history of stroke, MI, HF and AF, for up to 20y. NT-proBNP is also a robust independent marker of long-term stroke risk in middle-aged SAs who are free of CVD. Importantly, findings suggest that NT-proBNP may add discriminatory power to conventional risk factors for stratification of stroke risk in the two high-risk populations. This is examined further in the next chapter of this doctoral research.

6 Associations of NT-proBNP with Stroke Events

Table 6.1 Baseline characteristics of BRHS men free of stroke, MI, HF and AF, across low, intermediate and high NT-proBNP categories

Trait	Tertile1-Low		Tertile2-Intermediate		Tertile3-High		P value
	N		N		N		
Age (y)	1094	66.02 (4.53)	1067	68.32 (5.27)	1080	70.81 (5.39)	<0.001
BMI (kg/m ²)	1092	26.93 (3.42)	1059	26.82 (3.54)	1076	26.59 (3.83)	0.08
SBP (mmHg)	1094	136.03 (20.21)	1066	140.97 (23.24)	1071	148.96 (25.59)	<0.001
DBP (mmHg)	1094	85.24 (9.85)	1066	85.02 (10.72)	1071	85.87 (12.22)	0.18
Cholesterol (mmol/l)	1092	6.22 (1.07)	1066	6.05 (1.03)	1075	5.87 (1.06)	<0.001
Glucose (mmol/l)	1091	5.61 (5.25, 6.06)	1062	5.62 (5.24, 6.07)	1073	5.63 (5.22, 6.14)	0.90
IL-6 (pg/ml)	1084	1.89 (1.37, 2.87)	1061	2.17 (1.54, 3.27)	1066	2.53 (1.79, 4.03)	<0.001
eGFR (ml/min/1.73m ²)	1092	78.33 (11.57)	1066	76.16 (12.92)	1077	72.66 (14.66)	<0.001
FEV1 (L)	1089	2.79 (0.63)	1056	2.63 (0.64)	1065	2.46 (0.65)	<0.001
NTproBNP (pg/ml) mean (SD)	1094	32 (13)	1067	84 (19)	1080	382 (543)	
Range		5-54		55-122		123-9771	<0.001
Median (Q1, Q3)		32 (22, 43)		82 (67, 98)		218 (160, 374)	
Troponin T (pg/ml) mean (SD)	1089	11 (4.9)	1058	12 (6.00)	1074	17 (40.7)	<0.001
Median (Q1, Q3)		10.1 (7.6, 13.4)		10.80 (8.50, 14.70)		13.6 (10.4, 18.2)	
Physical Activity (%)	1056		1031		1041		
Inactive		7		8		14	
Occasional-Light		39		42		45	<0.001
Moderate-Vigorous		53		49		41	
Poor Diet (%)	1022	38	1005	38	975	41	0.34
Current Smokers (%)	1093	12	1065	13	1078	14	0.14
Alcohol Intake (%)	1079		1055		1060		
None		9		8		12	
Occasional-Light		71		72		68	0.14
Moderate-Heavy		20		20		20	
IMD (%)	1092		1065		1080		
Most deprived		15		16		18	
2		14		17		20	
3		21		18		20	0.001
4		25		23		22	
Least deprived		24		26		20	
BP medications (%)	1081	16	1054	27	1061	38	<0.001
Statin use	1094	3	1067	4	1080	6	0.001
Diabetes treatment (%)	1081	4	1054	4	1061	5	0.69

6 Associations of NT-proBNP with Stroke Events

Trait	Tertile1-Low		Tertile2-Intermediate		Tertile3-High		P value
	N		N		N		
Prevalent Diabetes (%)	1065	11	1018	10	1043	12	0.20
Crude Incidence	Event/N		Event/N		Event/N		
All strokes/1000PY [95%CI]	80/1094	4.66 [3.74-5.80]	131/1067	8.63 [7.27-10.24]	156/1080	12.7 [10.86-14.86]	<0.001
TIAs/1000PY [95%CI]	61/1078	3.69 [2.87-4.74]	65/1046	4.49 [3.52-5.73]	80/1033	7.12 [5.72-8.86]	<0.001
CVAs/1000PY [95%CI]	133/1078	8.04 [6.78-9.53]	183/1046	12.65 [10.95-14.63]	212/1033	18.86 [16.49-21.58]	<0.001

Abbreviations: BMI: body mass index, CVA: cerebrovascular accident (stroke or TIA), DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, FEV1: forced expiratory volume in 1 second, IL-6: interleukin 6, IMD: index of multiple deprivation, SBP: systolic blood pressure. TIA: transient ischaemic attack

Table 6.2 Comparing Europeans (n=107/1219) and SAs (n=118/1225) without CHD and stroke, with available biomarkers

	Europeans	South Asians	P value
Crude Stroke Incidence Rate/1000PY [95%CI]	4.67 [3.9-5.6]	5.06 [4.2-6.1]	
Age sex adjusted HR [95%CI]	1	1.30 [1.00-1.69]	0.05
Age (y)	53 (7)	51 (7)	<0.001
Male (%)	87	83	0.01
BMI (kg/m²)	26 (4)	26 (4)	0.87
Systolic BP (mmHg)	123 (17)	125 (18)	0.03
Diastolic BP (mmHg)	77 (11)	80 (10)	<0.001
Cholesterol (mmol/l)	6.1 (1.1)	5.9 (1.0)	<0.001
Glucose (mmol/l)	5.3 (5.0, 5.8)	5.5 (5.1, 6.1)	<0.001
Physical Activity (MJ/wk)	10.5 (7, 16)	9 (4, 13)	<0.001
Poor Diet (%)	7	5	0.01
Current Smokers (%)	31	13	<0.001
CRP (mg/l)	1.2 (0.5, 2.7)	1.5 (0.7, 3.2)	<0.001
eGFR (ml/min/1.73m²)	93 (39)	97 (35)	0.02
Alcohol Intake (units/wk)	9 (2, 20)	1 (0, 12)	<0.001
Social Class Manual (%)	61	76	<0.001
BP medications (%)	9	13	0.002
Diabetes treatment (%)	2	9	<0.001
Prevalent Diabetes	6	20	<0.001
NTproBNP (pg/ml)			
Mean (sd), Range	68.9 (147), 5-2280	55.6 (114), 4-2361	<0.001
Median (Q1, Q3)	37.1 (24, 64)	31.1 (19, 55)	
Troponin T (pg/ml)			
Mean (sd), Range	9.95 (4.4), 3-86	10.02 (3.4), 2-42	0.23
Median (Q1, Q3)	9.4 (8, 11)	9.4 (8, 11)	

Mean (sd) or median (Q1, Q3) or mean (min-max). The 99% centile for NTproBNP in EU is 704, SA 479 pg/ml. N varies slightly due to missing data; min N is for alcohol intake, European=1182, SA=1178. Abbreviations: BMI: body mass index, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate.

Table 6.3 Baseline characteristics of European SABRE participants without a history of CHD and stroke

	NT-proBNP <34pg/ml		NT-proBNP 34 to <100pg/ml		NT-proBNP ≥100pg/ml		P value
	N		N		N		
Age (y)	553	51.12 (6.84)	512	53.84 (7.18)	154	56.68 (7.05)	<0.001
BMI (kg/m ²)	553	26.12 (3.55)	511	25.94 (4.05)	154	26.57 (4.54)	0.21
Systolic BP (mmHg)	552	120.60 (14.83)	512	123.88 (17.59)	154	131.32 (21.25)	<0.001
Diastolic BP (mmHg)	552	76.68 (10.10)	512	77.15 (10.87)	154	79.05 (12.14)	0.05
Cholesterol (mmol/l)	553	6.11 (1.11)	512	6.11 (1.17)	154	6.18 (1.16)	0.76
Glucose (mmol/l)	552	5.34 (5.03, 5.73)	510	5.35 (4.93, 5.75)	154	5.33 (4.97, 5.78)	0.67
Physical Activity (MJ/week)	553	11.00 (7.27, 16.33)	512	10.00 (6.00, 15.51)	154	9.00 (5.04, 14.56)	<0.01
CRP (mg/L)	540	0.97 (0.44, 2.27)	506	1.16 (0.52, 3.06)	153	1.84 (0.99, 4.37)	<0.01
eGFR (ml/min/1.73m ²)	545	98.43 (49.58)	507	91.03 (28.45)	153	83.48 (24.81)	<0.001
Alcohol (units/week)	538	9.75 (3.12, 20.12)	496	7.74 (1.20, 19.90)	148	8.68 (0.72, 23.34)	0.07
NT-proBNP (pg/ml) mean (sd)	553	22.18 (6.97)	512	56.13 (17.38)	154	279.37 (343.59)	<0.001
median		22.70 (16.56, 28.08)		51.46 (42.07, 67.15)		151.20 (121.20, 47.10)	
Range		5.12-33.95		34.11-99.67		100-2280	
Troponin-T (pg/ml) mean (sd)	553	9.24 (2.55)	512	10.08 (4.66)	154	12.09 (7.10)	<0.001
median		9.13 (7.58, 10.39)		9.47 (8.00, 11.29)		10.33 (8.77, 13.52)	
range		4.31-26.22		3.83-85.83		3.35-61.65	
Male (%)	553	95	512	81	154	73	<0.01
Poor Diet (%)	553	5	512	9	154	9	0.02
Current smokers (%)	553	31	511	32	154	28	0.57
Manual social class (%)	550	57	510	63	153	68	0.02
BP medications (%)	552	4	512	10	154	23	<0.001
Prevalent Diabetes (%)	553	5	512	5	154	8	0.23
Crude Stroke Incidence/1000PY		2.94		5.47		9.12	<0.001
[95% CI]		[2.08- 4.16]		[4.17-7.18]		[6.06-13.73]	

Mean (sd) or median (Q1, Q3). Abbreviations: BMI: body mass index, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate.

Table 6.4 Baseline characteristics of South Asian SABRE participants without a history of CHD and stroke

	NT-proBNP <34pg/ml		NT-proBNP 34 to <100pg/ml		NT-proBNP ≥100pg/ml		P value
	N		N		N		
Age (y)	667	49.12 (6.63)	446	52.23 (6.88)	112	54.46 (6.78)	<0.001
BMI (kg/m ²)	666	25.97 (3.30)	446	26.32 (4.09)	112	26.21 (4.13)	0.80
Systolic BP (mmHg)	667	121.43 (15.10)	446	126.78 (18.26)	112	137.73 (23.30)	<0.001
Diastolic BP (mmHg)	667	79.93 (9.76)	446	79.74 (10.89)	112	82.22 (12.22)	0.09
Cholesterol (mmol/l)	666	5.95 (1.07)	446	5.85 (1.02)	112	5.83 (1.02)	0.20
Glucose (mmol/l)	664	5.54 (5.12, 6.08)	445	5.51 (5.03, 6.18)	112	5.38 (5.03, 5.97)	0.50
Physical Activity (MJ/week)	667	9.00 (5.00, 13.00)	446	8.50 (4.00, 11.78)	112	7.00 (1.50, 12.63)	0.001
CRP (mg/L)	655	1.15 (0.56, 2.59)	439	1.80 (0.81, 3.75)	109	2.19 (1.05, 4.55)	<0.001
eGFR (ml/min/1.73m ²)	660	98.53 (34.19)	441	96.80 (35.90)	112	89.41 (36.54)	0.04
Alcohol (units/week)	641	1.62 (0.00, 12.17)	429	0.12 (0.00, 9.06)	108	0.00 (0.00, 6.88)	<0.01
NT-proBNP (pg/ml) mean	667	20.20 (7.62)	446	55.86 (17.47)	112	264.99 (300.67)	<0.001
median		20.17 (13.96, 26.48)		52.06 (40.89, 67.99)		166.55 (119.30, 263.35)	
Range		3.54-33.98		34-99.83		100-2361	
Troponin-T (pg/ml) mean	667	9.44 (2.49)	446	10.40 (3.89)	112	11.91 (4.73)	<0.001
median		9.16 (7.77, 10.64)		9.59 (8.18, 11.61)		10.89 (8.63, 14.58)	
Range		4.37-25.97		1.73-42.29		3.55-35.3	
Male (%)	667	91	446	74	112	71	<0.001
Poor Diet (%)	660	~	443	~	110	~	0.79
Current smokers (%)	666	*	445	*	111	*	0.11
Manual social class (%)	654	75	426	76	108	79	0.69
BP medications (%)	667	7	446	16	112	35	<0.001
Prevalent Diabetes (%)	667	18	446	22	112	21	0.225
Crude Stroke Incidence/1000PY		3.92		4.88		13.63	<0.001
[95% CI]		[2.98-5.16]		[3.59-6.62]		[9.28-20.02]	

Mean (sd) or median (Q1, Q3). Suppressed cells indicate proportions across biomarker categories that are: ~similar, *decreasing. Abbreviations: BMI: body mass index, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate.

6 Associations of NT-proBNP with Stroke Events

Table 6.5 HR [95% CI] of stroke events across NT-proBNP categories in BRHS men free of CVD followed for a median of 16 years.

NTproBNP			Crude + age	Model 1	Model 2	Model 3	Model 3 + Troponin T	Model 3 + Incident events
(a) All strokes								
	Events/N	367/3241	367/3241	319/2867	312/2792	309/2755	308/2736	309/2755
<55 pg/ml	80/1094	1	1	1	1	1	1	1
55 - 122 pg/ml	131/1067	1.89 [1.43-2.50]	1.66 [1.25-2.20]	1.64 [1.21-2.22]	1.69 [1.24-2.30]	1.68 [1.23-2.29]	1.65 [1.21-2.26]	1.65 [1.20-2.26]
≥123 pg/ml	156/1080	2.92 [2.23-3.83]	2.24 [1.69-2.98]	2.19 [1.60-3.01]	2.31 [1.67-3.19]	2.22 [1.60-3.08]	2.12 [1.52-2.94]	1.96 [1.40-2.74]
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.001	<0.001
HR per sd-log		1.54 [1.38-1.70]	1.37 [1.22-1.53]	1.35 [1.19-1.53]	1.39 [1.23-1.59]	1.36 [1.19-1.56]	1.32 [1.15-1.51]	1.30 [1.13-1.49]
(b) Non-Fatal Strokes								
	Events/N	275/3241	275/3241	237/2867	231/2792	230/2755	229/2736	230/2755
<55 pg/ml	66/1094	1	1	1	1	1	1	1
55 - 122 pg/ml	94/1067	1.64 [1.19-2.24]	1.50 [1.09-2.06]	1.59 [1.12-2.25]	1.63 [1.14-2.32]	1.60 [1.12-2.28]	1.58 [1.10-2.25]	1.57 [1.10-2.24]
≥123 pg/ml	115/1080	2.56 [1.89-3.48]	2.14 [1.55-2.95]	2.11 [1.47-3.03]	2.24 [1.55-3.24]	2.12 [1.46-3.08]	2.06 [1.41-3.00]	1.86 [1.40-2.73]
P for trend		<0.001	<0.001	<0.001	<0.0001	<0.001	<0.001	<0.01
HR per sd-log		1.42 [1.25-1.60]	1.30 [1.14-1.48]	1.28 [1.10-1.48]	1.33 [1.14-1.55]	1.29 [1.11-1.51]	1.26 [1.08-1.48]	1.24 [1.06-1.45]
(c) Fatal Strokes								
	Events/N	92/3241	92/3241	82/2867	81/2792	79/2755	79/2736	79/2755
<55 pg/ml	14/1094	1	1	1	1	1	1	1
55 - 122 pg/ml	37/1067	3.10 [1.67-5.73]	2.38 [1.27-4.43]	1.82 [0.95-3.47]	1.87 [0.98-3.59]	1.96 [1.00-3.82]	1.92 [0.99-3.75]	1.98 [1.00-3.90]
≥123 pg/ml	41/1080	4.63 [2.52-8.51]	2.78 [1.47-5.24]	2.50 [1.30-4.84]	2.55 [1.31-4.98]	2.60 [1.30-5.19]	2.39 [1.19-4.78]	2.35 [1.15-4.80]
P for trend		<0.001	<0.01	<0.01	<0.01	<0.01	0.01	0.02
HR per sd-log		1.94 [1.59-2.38]	1.60 [1.28-2.00]	1.58 [1.24-2.02]	1.61 [1.25-2.07]	1.59 [1.22-2.06]	1.48 [1.14-1.93]	1.50 [1.15-1.97]
(d) TIAs								
	Events/N	206/3157	206/3157	186/2795	182/2720	180/2685	178/2666	180/2685
<55 pg/ml	61/1078	1	1	1	1	1	1	1
55 - 122 pg/ml	65/1046	1.24 [0.88-1.76]	1.14 [0.80-1.62]	1.17 [0.80-1.70]	1.18 [0.81-1.72]	1.17 [0.80-1.71]	1.19 [0.82-1.74]	1.15 [0.78-1.69]
≥123 pg/ml	80/1033	2.04 [1.46-2.86]	1.71 [1.20-2.44]	1.83 [1.25-2.69]	1.78 [1.20-2.64]	1.72 [1.15-2.56]	1.71 [1.14-2.56]	1.60 [1.06-2.43]
P for trend		<0.001	<0.01	<0.01	<0.01	<0.01	<0.01	0.03
HR per sd-log		1.32 [1.15-1.52]	1.22 [1.05-1.42]	1.25 [1.06-1.48]	1.26 [1.06-1.50]	1.26 [1.05-1.50]	1.26 [1.05-1.51]	1.18 [0.98-1.42]
(e) CVAs								
	Events/N	528/3157	528/3157	465/2795	455/2720	450/2685	447/2666	450/2685
<55 pg/ml	133/1078	1	1	1	1	1	1	1
55 - 122 pg/ml	183/1046	1.61 [1.28-2.01]	1.42 [1.13-1.78]	1.42 [1.11-1.81]	1.45 [1.14-1.86]	1.43 [1.12-1.84]	1.43 [1.12-1.83]	1.41 [1.10-1.80]
≥123 pg/ml	212/1033	2.49 [2.00-3.10]	1.96 [1.56-2.46]	1.96 [1.53-2.53]	2.03 [1.57-2.62]	1.94 [1.49-2.52]	1.87 [1.44-2.44]	1.75 [1.34-2.29]
P for trend		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001
HR per sd-log		1.45 [1.33-1.59]	1.31 [1.19-1.44]	1.31 [1.18-1.46]	1.35 [1.22-1.51]	1.33 [1.19-1.49]	1.31 [1.17-1.46]	1.27 [1.13-1.42]

Model 1: Age plus SBP, BMI, cholesterol, glucose, physical activity, current smoking, diet. Model 2: Further adjusted for social class, alcohol intake and medications for BP, diabetes and statins. Model 3: Further adjusted for IL-6, eGFR and FEV1. Incident events include AF, HF and MI before stroke. For TIA and CVA analysis which also excludes men with history of TIA, the tertile cut-offs (pg/ml) were 53 and 122, so original ones were retained.

6 Associations of NT-proBNP with Stroke Events

Table 6.6 HR [95% CI] of stroke events across NT-proBNP categories in middle-aged SABRE participants free of CHD and stroke followed for a median of 20y.

NTproBNP pg/ml		Crude	Crude + age, sex	Model 1	Model 2	Model 3	Model 3 + Troponin T	Model 3 + Incident CHD
(a) Europeans								
	Events/N	107/1219	107/1219	107/1213	103/1172	102/1150	102/1150	102/1150
<34	32/553	1	1	1	1	1	1	1
34 - <100	52/512	1.94 [1.25-3.02]	1.69 [1.08-2.65]	1.54 [0.97-2.43]	1.51 [0.95-2.40]	1.45 [0.91-2.30]	1.41 [0.89-2.25]	1.42 [0.88-2.28]
≥100	23/154	3.49 [2.04-5.97]	2.60 [1.48-4.57]	2.38 [1.35-4.20]	2.11 [1.17-3.82]	1.99 [1.09-3.62]	1.85 [1.00-3.43]	1.81 [0.96-3.38]
P for trend		<0.0001	<0.001	0.003	0.01	0.03	0.05	0.065
HR per sd-log		1.64 [1.41-1.91]	1.49 [1.26-1.75]	1.45 [1.23-1.72]	1.42 [1.19-1.69]	1.38 [1.15-1.66]	1.36 [1.12-1.66]	1.29 [1.06-1.56]
(b) South Asians								
	Events/N	118/1225	118/1225	114/1207	104/1131	101/1109	101/1109	101/1109
<34	51/667	1	1	1	1	1	1	1
34 - <100	41/446	1.30 [0.86-1.96]	1.03 [0.67-1.59]	1.02 [0.65-1.58]	0.94 [0.59-1.49]	0.88 [0.55-1.42]	0.82 [0.51-1.33]	1.12 [0.69-1.82]
≥100	26/112	3.85 [2.39-6.19]	2.73 [1.64-4.54]	2.81 [1.63-4.87]	2.45 [1.38-4.36]	2.67 [1.49-4.79]	2.37 [1.30-4.33]	2.27 [1.20-4.31]
P for trend		<0.0001	<0.001	<0.001	<0.01	<0.001	<0.01	0.01
HR per sd-log		1.60 [1.37-1.87]	1.45 [1.22-1.72]	1.46 [1.21-1.75]	1.42 [1.17-1.73]	1.49 [1.21-1.83]	1.43 [1.15-1.78]	1.34 [1.10-1.63]

Model 1: Age, sex plus SBP, BMI, cholesterol, glucose, physical activity as continuous; and current smoking and poor diet as binary variables.

Model 2: Further adjusted for social class, alcohol intake and medications for BP and diabetes. Model 3: Further adjusted for CRP and eGFR.

Table 6.7 Stroke Incidence and Hazard Ratios [95% CIs] in BRHS men free of MI, Stroke, HF and AF stratified by prevalent conditions and categories of NT-proBNP

Subgroup	Low NT-proBNP	Intermediate NT-proBNP	High NT-proBNP
Non-hypertensive			
Events/N	28/391	33/298	23/174
Incidence(/1000PY)	4.36 [3.01-6.31]	7.54 [5.36-10.60]	10.59 [7.04-15.94]
HR [95% CI]	1	1.57 [0.91-2.71]	2.21 [1.21-4.03]
Hypertensive			
Events/N	52/699	97/763	133/900
Incidence(/1000PY)	4.87 [3.71-6.39]	9.04 [7.41-11.03]	13.22 [11.16-15.67]
HR [95% CI]	0.86 [0.51-1.45]	1.42 [0.86-2.33]	1.90 [1.14-3.16]
P for interaction		0.88	0.99
Non-diabetic			
Events/N	63/950	111/916	136/913
Incidence(/1000PY)	4.18 [3.26-5.35]	8.42 [6.99-10.14]	12.84 [10.86-15.20]
HR [95% CI]	1	1.86 [1.33-2.62]	2.49 [1.76-3.54]
Diabetic			
Events/N	13/115	14/102	17/130
Incidence(/1000PY)	8.02 [4.66-13.81]	10.80 [6.40-18.23]	13.40 [8.33-21.56]
HR [95% CI]	2.17 [1.08-4.34]	2.33 [1.14-4.77]	2.88 [1.52-5.44]
P for interaction		0.21	0.14
No CKD			
Events/N	74/1037	118/962	124/886
Incidence(/1000PY)	4.54 [3.62-5.70]	8.60 [7.18-10.30]	11.87 [9.96-14.16]
HR [95% CI]	1	1.74 [1.26-2.38]	2.20 [1.58-3.05]
CKD			
Events/N	6/55	13/104	32/191
Incidence(/1000PY)	7.11 [3.19-15.83]	9.00 [5.23-15.50]	17.74 [12.55-25.09]
HR [95% CI]	1.55 [0.62-3.86]	1.26 [0.64-2.48]	2.52 [1.54-4.14]
P for interaction		0.18	0.56

Models adjusted for age, SBP, BMI, cholesterol, glucose, physical activity, smoking and poor diet. CKD: chronic kidney disease with eGFR<60 ml/min/1.73m². Cut-off for NT-proBNP low <55pg/ml and high ≥123 pg/ml

Table 6.8 CVA Incidence and Hazard Ratios [95% CIs] in BRHS men free of MI, Stroke, TIA, HF and AF stratified by prevalent conditions and categories of NT-proBNP

Subgroup	Low NT-proBNP	Intermediate NT-proBNP	High NT-proBNP
Non-hypertensive			
Events/N	42/389	58/298	34/169
Incidence(/1000PY)	6.67 [4.93-9.02]	13.86 [10.72-17.93]	16.99 [12.14-23.77]
HR [95% CI]	1	2.01 [1.32-3.07]	2.35 [1.44-3.83]
Hypertensive			
Events/N	91/685	124/742	178/858
Incidence(/1000PY)	8.96 [7.29-11.00]	12.15 [10.19-14.49]	19.37 [16.73-22.44]
HR [95% CI]	1.12 [0.73-1.69]	1.33 [0.88-2.00]	1.99 [1.31-3.03]
P for interaction		0.04	0.34
Non-diabetic			
Events/N	109/940	155/896	180/873
Incidence(/1000PY)	7.48 [6.20-9.03]	12.37 [10.57-14.48]	18.50 [15.99-21.41]
HR [95% CI]	1	1.55 [1.19-2.03]	2.08 [1.58-2.74]
Diabetic			
Events/N	19/109	18/101	25/125
Incidence(/1000PY)	12.74 [8.13-19.98]	14.29 [9.00-22.68]	22.31 [15.08-33.02]
HR [95% CI]	2.07 [1.18-3.63]	1.78 [0.96-3.29]	2.99 [1.79-5.00]
P for interaction		0.11	0.28
No CKD			
Events/N	126/1022	165/944	168/846
Incidence(/1000PY)	8.03 [6.75-9.57]	12.60 [10.82-14.68]	17.58 [15.12-20.45]
HR [95% CI]	1	1.45 [1.13-1.87]	1.91 [1.47-2.48]
CKD			
Events/N	7/54	18/101	44/184
Incidence(/1000PY)	8.55 [4.07-17.93]	13.25 [8.35-21.03]	26.65 [19.83-35.82]
HR [95% CI]	1.04 [0.46-2.38]	1.18 [0.68-2.04]	2.32 [1.54-3.48]
P for interaction		0.61	0.74

Models adjusted for age, SBP, BMI, cholesterol, glucose, physical activity, smoking and poor diet. CKD: chronic kidney disease with eGFR<60 ml/min/1.73m². Cut-off for NT-proBNP low <55pg/ml and high ≥123 pg/ml

6 Associations of NT-proBNP with Stroke Events

Table 6.9 Stroke Incidence and Hazard Ratios [95% CIs] among SABRE participants free of CHD and Stroke stratified by prevalent conditions and low/high NT-proBNP

Subgroup	Europeans		South Asians	
	Low NT-proBNP	High NT-proBNP	Low NT-proBNP	High NT-proBNP
Non-hypertensive Events/N Incidence(/1000PY) HR [95% CI]	63/853 3.79 [2.96-4.85] 1	7/83 4.80 [2.29-10.07] 1.04 [0.47-2.29]	54/809 3.40 [2.60-4.44] 1	4/39 5.80 [2.18-15.45] 2.05 [0.73-5.74]
Hypertensive Events/N Incidence(/1000PY) R [95% CI]	21/211 5.62 [3.66-8.61] 0.85 [0.45-1.61]	16/71 15.05 [9.22-24.57] 2.47 [1.24-4.92]	38/304 6.88 [5.00-9.45] 1.30 [0.77-2.17]	22/73 18.08 [11.90-27.45] 3.74 [1.96-7.17]
P for interaction		0.05		0.57
Non-diabetic Events/N Incidence(/1000PY) HR [95% CI]	77/1010 3.97 [3.17-4.96] 1	21/141 8.95 [5.83-13.72] 1.83 [1.10-3.02]	52/891 2.97 [2.26-3.90] 1	17/88 10.69 [6.65-17.20] 2.68 [1.48-4.84]
Diabetic Events/N Incidence(/1000PY) HR [95% CI]	7/55 7.23 [3.45-15.17] 0.96 [0.35-2.60]	2/13 11.49 [2.87-45.96] 1.57 [0.31-7.91]	40/222 10.23 [7.50-13.95] 1.76 [0.98-3.17]	9/24 28.39 [14.78-54.57] 5.32 [2.40-11.78]
P for interaction		0.90		0.80
No CKD Events/N Incidence(/1000PY) HR [95% CI]	79/993 4.14 [3.32-5.16] 1	21/139 9.22 [6.01-14.14] 1.83 [1.11-3.02]	85/1059 4.17 [3.37-5.16] 1	22/98 12.85 [8.46-19.52] 2.66 [1.59-4.46]
CKD Events/N Incidence(/1000PY) HR [95% CI]	5/59 4.87 [2.03-11.70] 0.83 [0.33-2.07]	2/14 8.87 [2.24-35.86] 1.37 [0.33-5.68]	4/42 4.99 [1.87-13.31] 0.79 [0.25-2.50]	4/14 20.51 [7.7.-54.65] 3.90 [1.37-11.11]
P for interaction		0.91		0.44

Models adjusted for age, sex, SBP, BMI, cholesterol, glucose, physical activity, smoking and poor diet. Cut-off for NT-proBNP 100pg/ml. CKD: chronic kidney disease with eGFR<60 ml/min/1.73m²

Figure 6.1 Association between NT-proBNP and Stroke Events

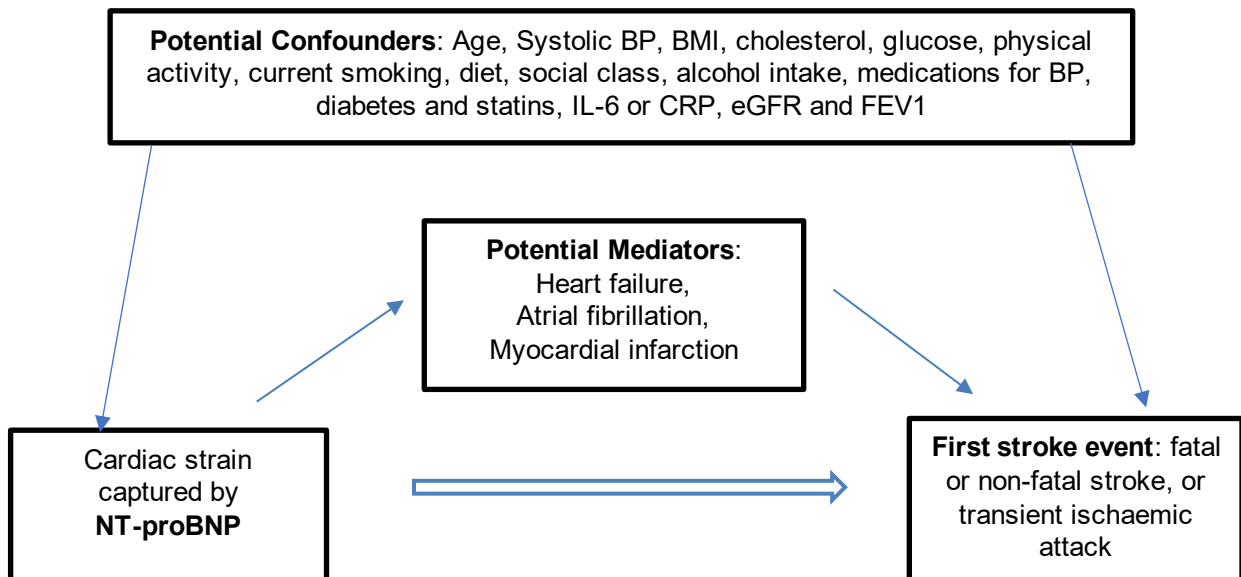
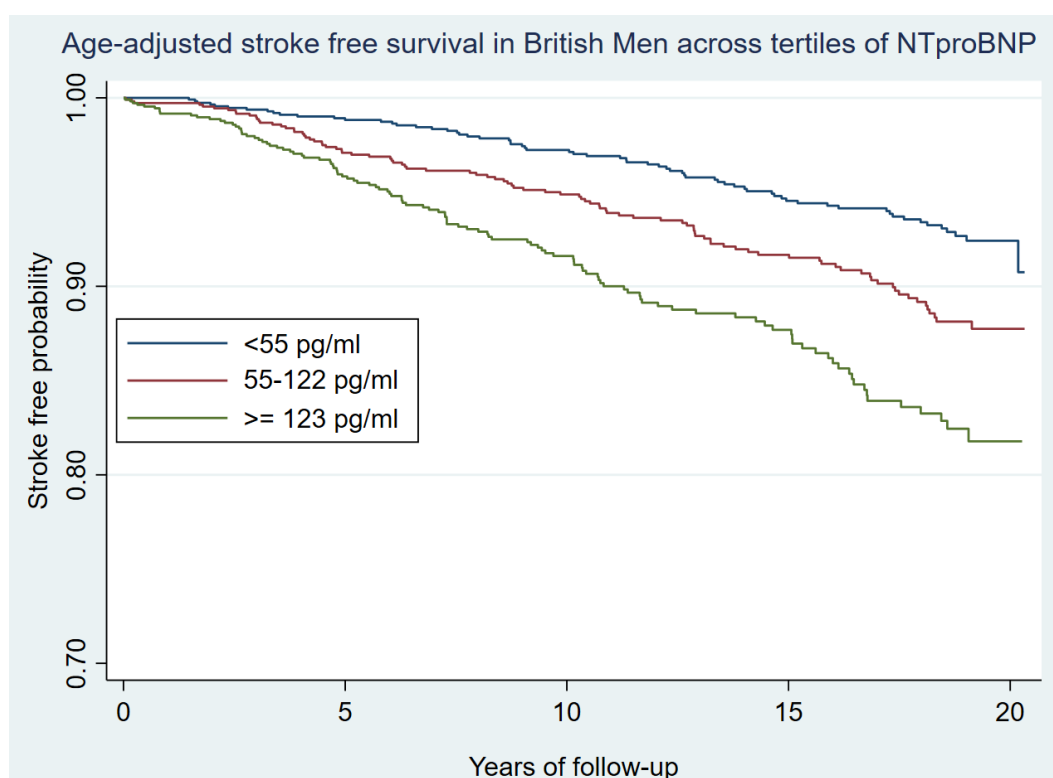


Figure 6.2 Age adjusted KM survival curves across tertiles of NT-proBNP in BRHS men free of MI, stroke, HF and AF followed for 20y.

6.2a: All strokes



6.2b: Non-fatal strokes



6.2c: Fatal strokes



6.2d: TIAs



6.2e: CVAs

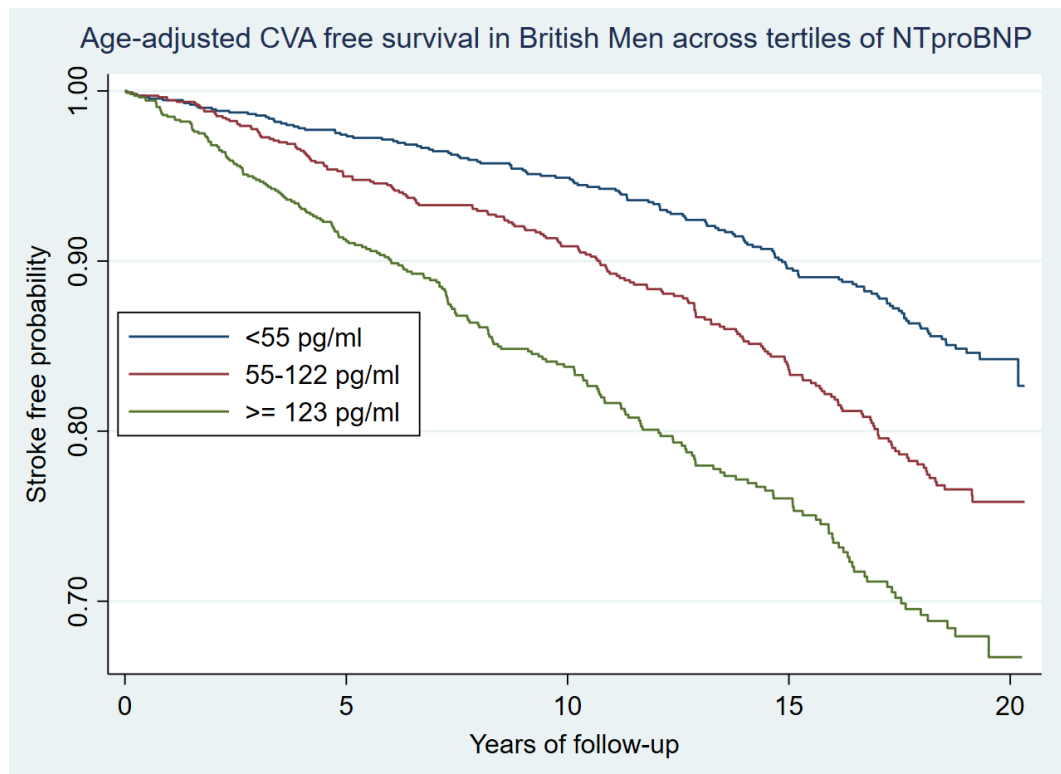


Figure 6.3 Comparison of NT-proBNP levels in middle-aged European and South Asian participants of SABRE.

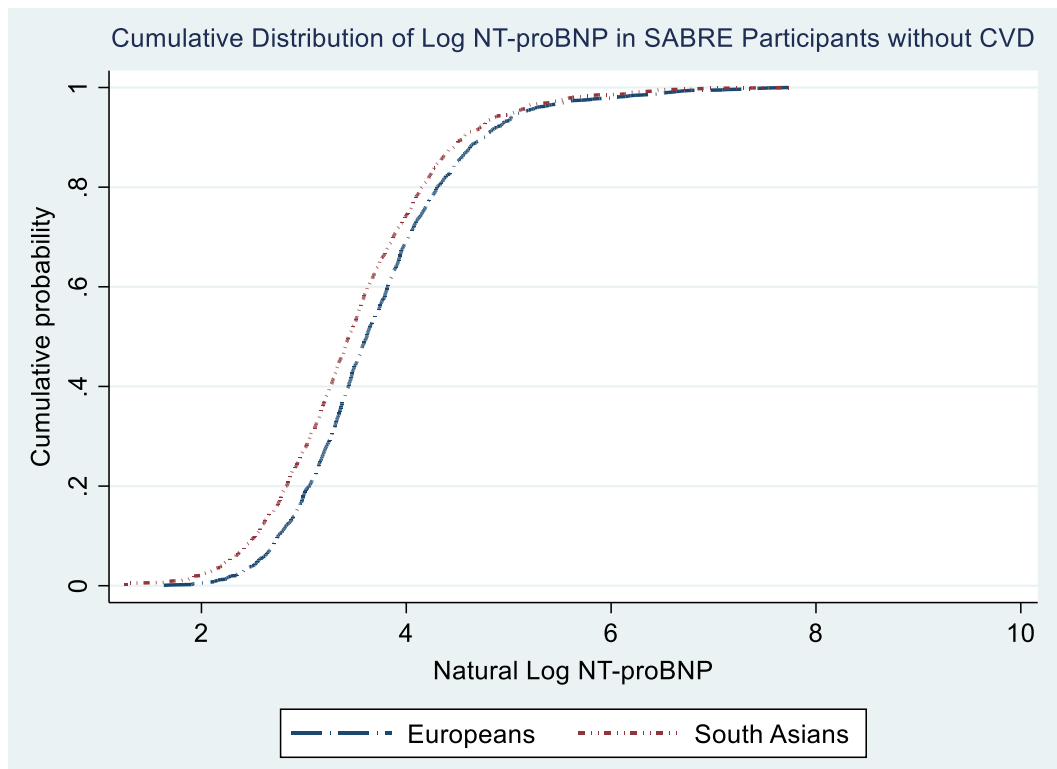
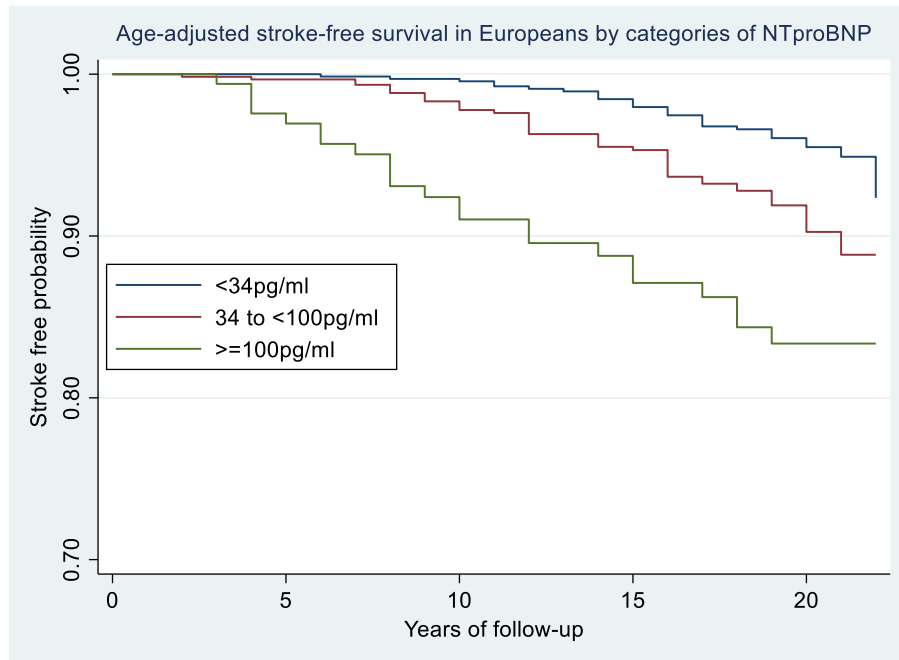


Figure 6.4 Age adjusted KM survival curves across categories of NT-proBNP in SABRE participants free of CHD and, stroke, followed for 22y.

6.4a Europeans



6.4b South Asians

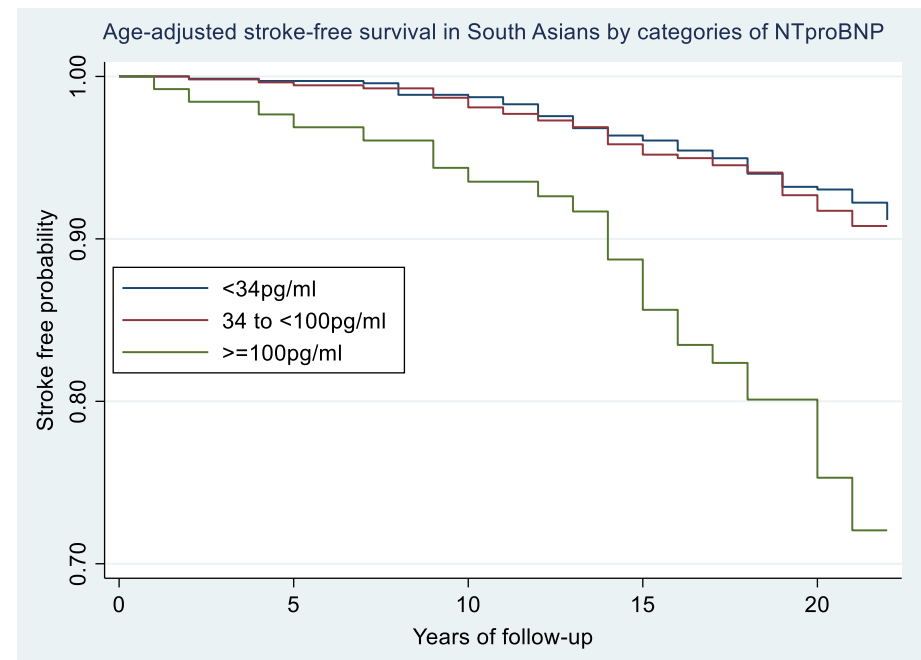
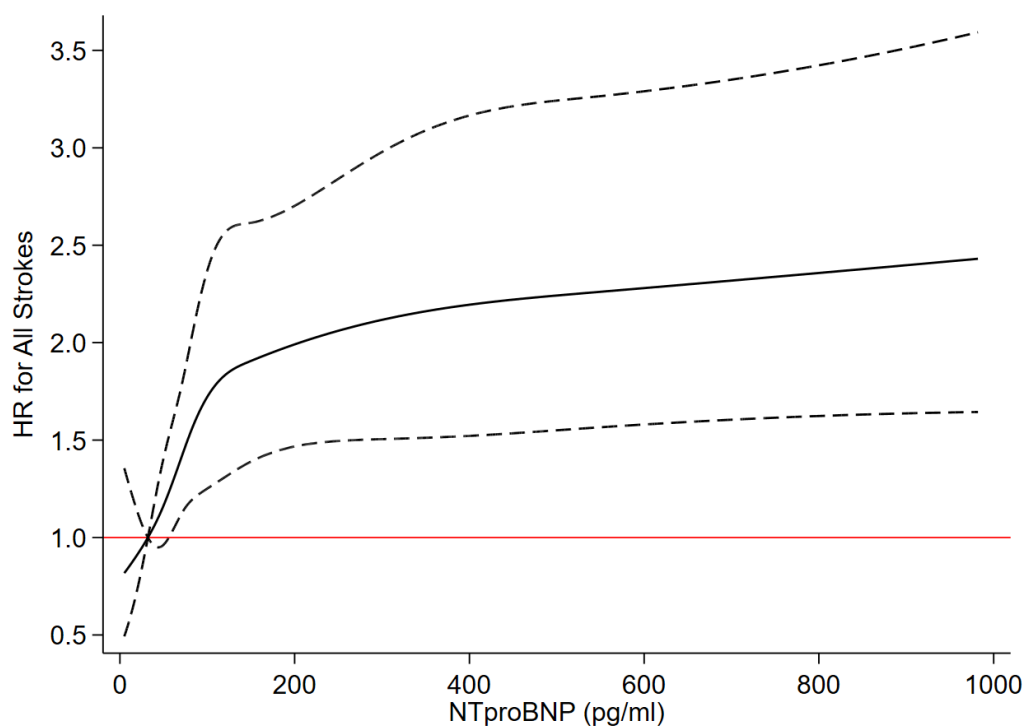


Figure 6.5 Risk of stroke displayed as restricted cubic splines in BRHS men free of CVD followed for a median of 16y.

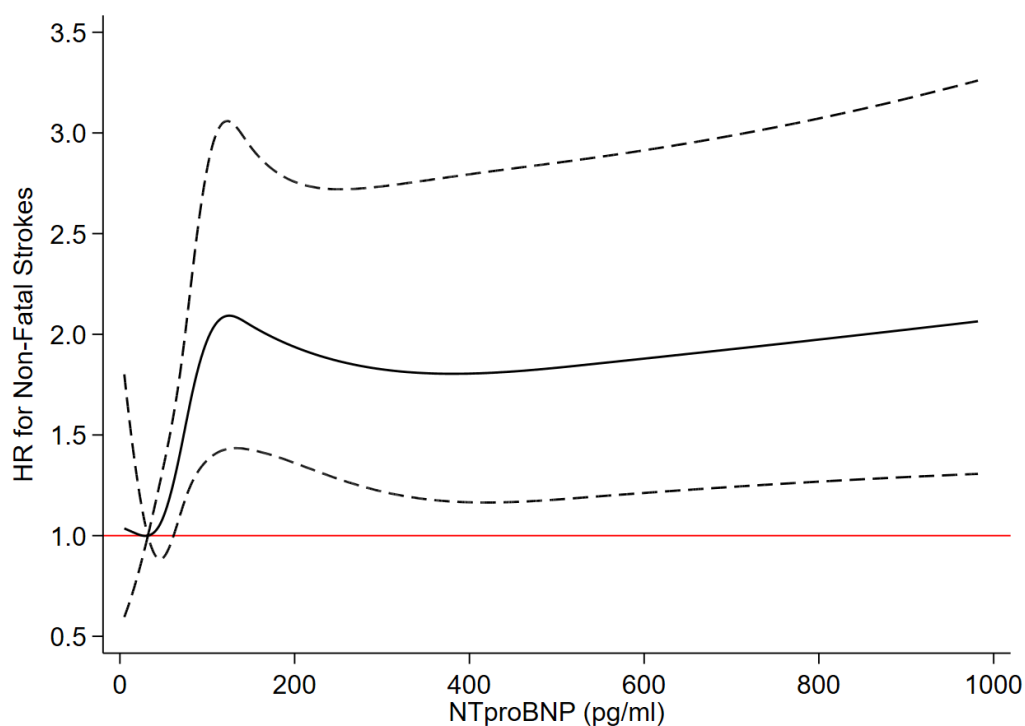
Adjusted for Age, SBP, BMI, cholesterol, glucose, physical activity, smoking, diet.

NT-proBNP reference value 32pg/ml

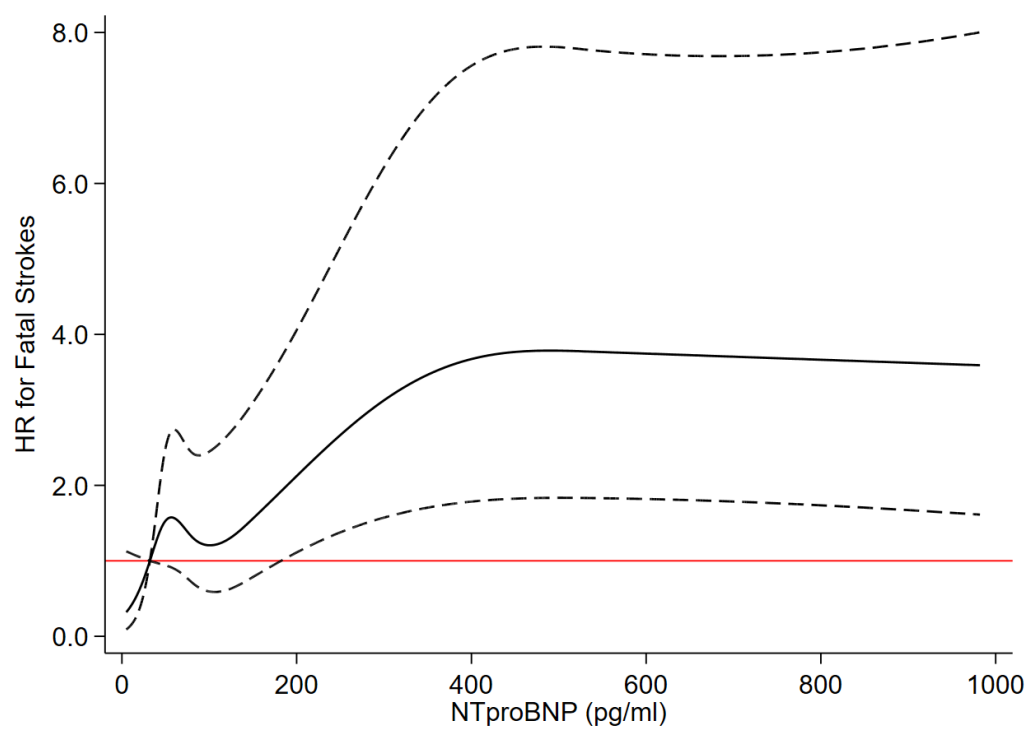
6.5a: All strokes



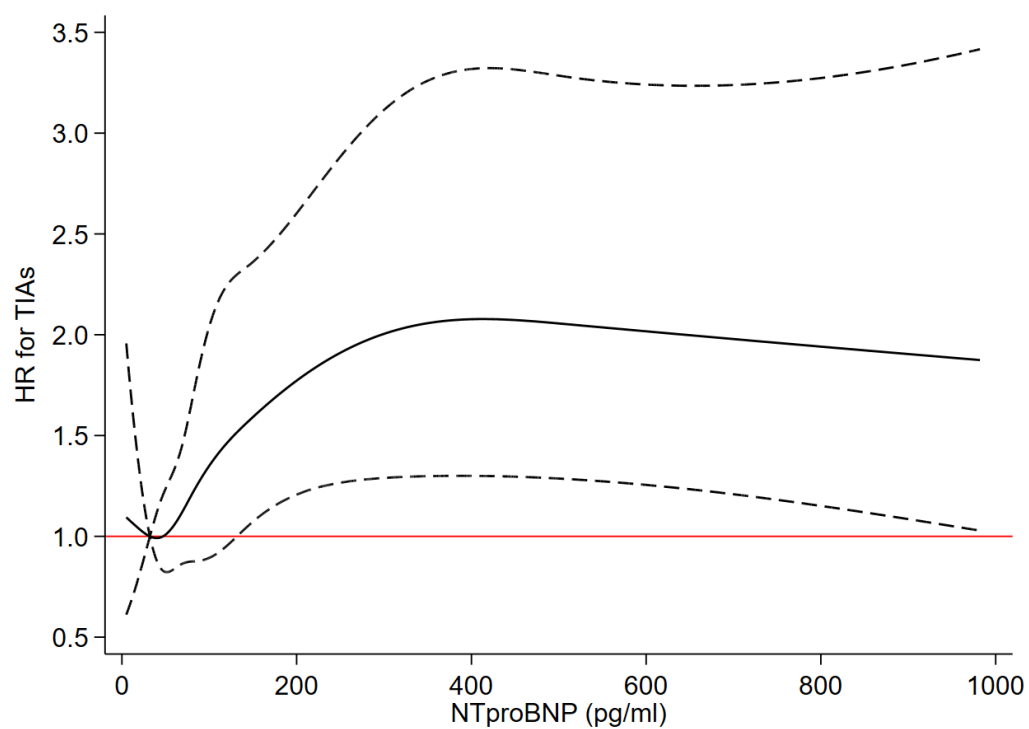
6.5b: Non-fatal strokes



6.5c: Fatal strokes



6.5d: TIAs



6.5e: CVAs

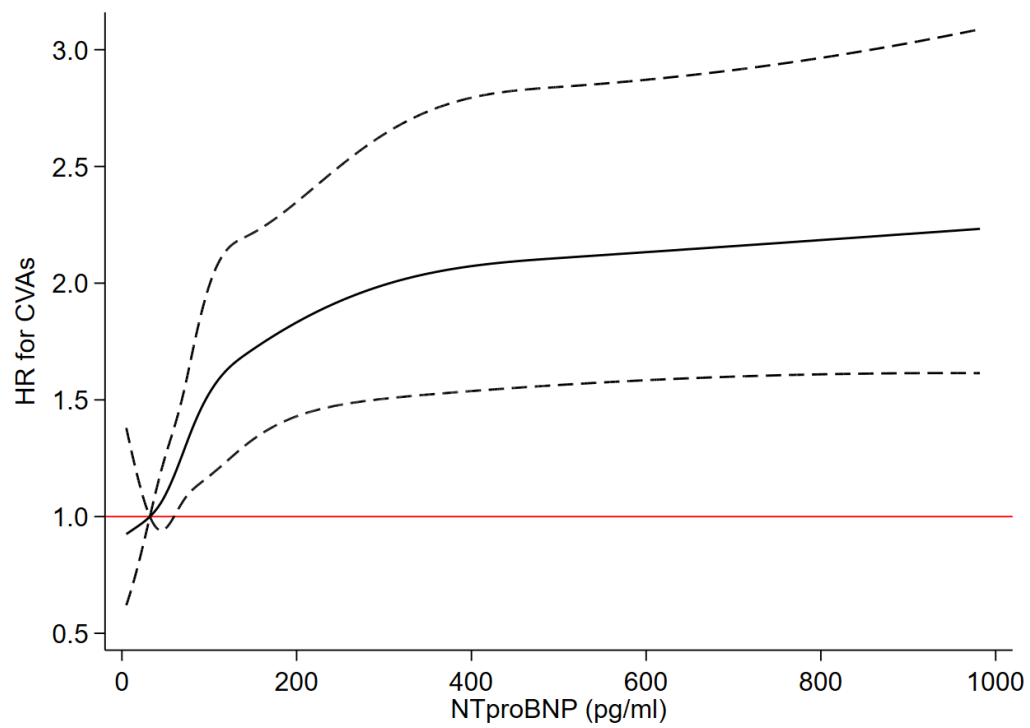
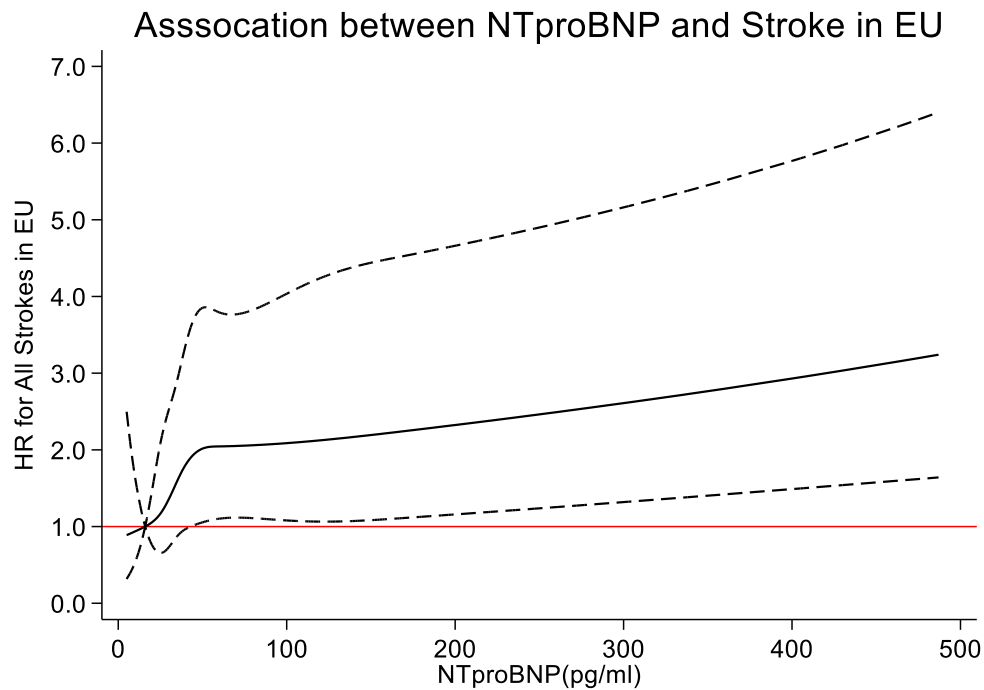


Figure 6.6 Risk of stroke displayed as restricted cubic splines in SABRE participants free of CHD and stroke, followed for a median of 20y.

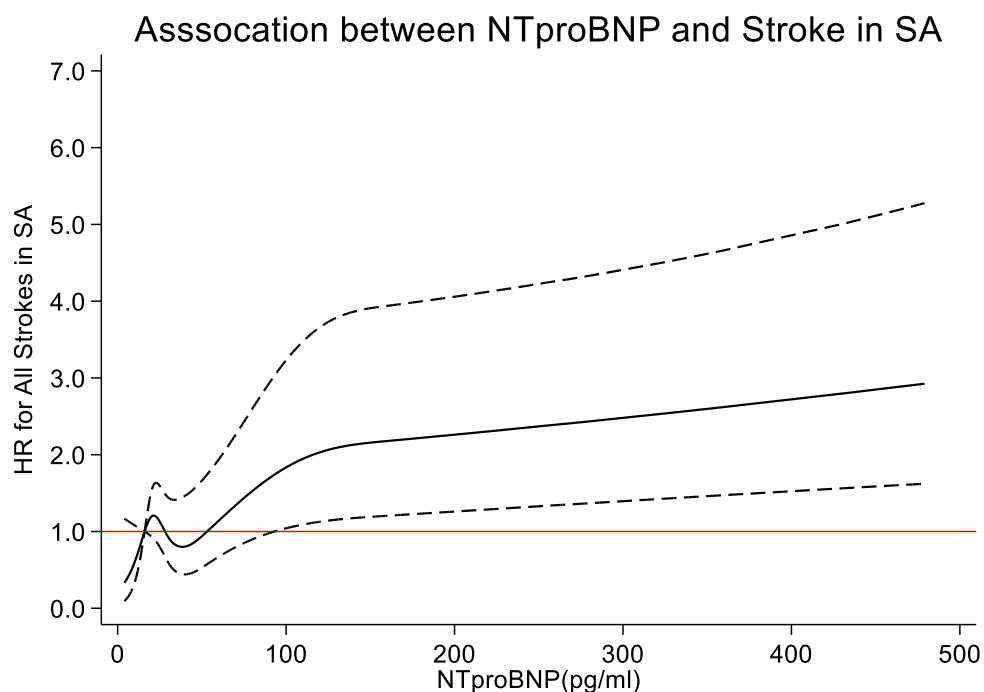
Adjusted for Age, SBP, BMI, cholesterol, glucose, physical activity, smoking, diet.

NT-proBNP reference value 16pg/ml

6.6a: Europeans



6.6a: South Asians



Chapter 7. Incremental Performance of NT-proBNP in Stratifying Stroke Risk

7.1 Summary

NT-proBNP has been observed to add discriminatory power to composite-CVD risk prediction models, but there is little evidence if NT-proBNP can specifically improve stratification of stroke risk among older adults and SAs who are free of CVD. The previous chapter confirmed robust independent long-term associations of NT-proBNP with stroke events in both population groups. This chapter examines the incremental value of NT-proBNP when added to the FSRP and QStroke equations in BRHS men for predicting the composite risk of stroke or TIA over 10y; and when added to a SABRE specific model containing available predictors of QStroke for predicting stroke risk over 22y. Measures of discrimination included C-index and net reclassification improvement for events and non-events across low, intermediate and high-risk categories defined by 5% and 10% risk thresholds, NT-proBNP resulted in a modest increase in discrimination among older men (change in C-index +0.02) and among middle-aged SAs (change in C-index +0.01). Depending on the model, NT-proBNP reclassified up to 7% of older men with incident stroke to a higher risk category. However, it appeared to have a more modest (albeit consistent) ability to downgrade risk among older men and SA adults who did not go on to experience stroke i.e., NT-proBNP improved the specificity of stroke risk prediction. Findings, especially those relating to SAs need to be validated in larger independent cohorts.

Findings from this work related to SAs have been presented as a poster (101) at the American Heart Association's Epidemiology and Prevention/Lifestyle and Cardiometabolic Health 2023 Scientific Sessions *N-terminal Pro B-type Natriuretic Peptide Improves Stratification of Cardiovascular Disease and Specifically Stroke Risk in South Asians* https://www.ahajournals.org/doi/10.1161/circ.147.suppl_1.P334

7.2 Introduction

NT-proBNP has been previously recommended for augmenting risk stratification of composite-CVD outcomes (346, 370). As argued earlier in section 2.2.4, stroke events form a greater proportion of CVD with age (13, 67, 171) and among SAs (194). Studies examining any predictive performance of NT-proBNP among SAs are lacking. And while NT-proBNP has been noted to modestly improve stroke-specific risk discrimination among predominantly European CVD free adults (346); a single C-statistic cannot capture clinical usefulness of a biomarker (440). Whether NT-proBNP-inclusive risk models assign a more appropriate risk category to older adults who do/do not go on to have stroke events has been rarely reported (77, 368).

As a preliminary step to assessing the contribution of NT-proBNP to stroke risk stratification, Chapter 6 confirmed independent long-term associations of NT-proBNP with stroke events among CVD free older men and middle-aged SAs. The aim of the current chapter is to take this further, by formally examining whether NT-proBNP adds value beyond traditional risk factors to stroke risk discrimination and reclassification in these groups.

7.3 Objectives

1. To examine incremental performance of NT-proBNP for 10y stroke risk prediction among older CVD free BRHS men, when added to FSRP and QStroke equations.
2. To examine incremental performance of NT-proBNP for 22y stroke risk prediction among middle-aged CVD free SA (and European) participants of SABRE, beyond a self-calibrated model containing available predictors of QStroke.

7.4 Methods

The study design, data collection and follow-up methodology for BRHS and SABRE have been detailed in Chapter 3. Analyses described in the current chapter use data on NT-proBNP and predictors collected via questionnaires and physical exams in

- the BRHS from the 20-year follow-up examination Q20 (1998-2000, age 60-79y).
- the Southall arm of the SABRE study from the baseline visit V1 (1998-91, age 40-69y).

Assessment of NT-proBNP, predictors, prevalent conditions and follow-up stroke and TIA events, and mortality in both cohorts has been described in Chapter 3 and again in Chapter 6.

7.4.1 Statistical Analyses

In both cohorts, analyses were restricted to participants without prevalent stroke and CHD, with complete data on NT-proBNP and relevant model predictors. In BRHS, analyses also excluded TIA, HF and AF a priori. This was to create a true primary prevention sample in which the added value of NT-proBNP for informing intervention decisions could be appropriately assessed. Additional exclusion for FSRP was intermittent claudication which formed part of the definition of CVD (287); and for QStroke men with anticoagulant use or with HS during follow-up (20).

7.4.1.1 Descriptive Statistics

For both cohorts baseline characteristics were examined as mean (SD) or median (Q1, Q3) for continuous variables and percentages for categorical traits. Baseline characteristics of SABRE SAs and Europeans were compared using t-tests for continuous variables and Chi square tests for categorical traits. NT-proBNP was compared between ethnic groups using Kruskal Wallis test.

7.4.1.2 Predictive Performance of NT-ProBNP

Predictive performance of NT-proBNP was examined in each study population using nested (*base* and *base + NT-proBNP*) Cox models.

BRHS

Incremental value of NT-proBNP was assessed with reference to 2 separate base models comprising (i) FSRP (287) and (ii) QStroke (20) equations. These risk equations were chosen because they have been derived specifically for prediction of *stroke* events and so better suited to assess the added value of a new *stroke* risk predictor. They also include as an outcome TIAs which have a rising incidence with age (79). FSRP models predicted the risk of a composite outcome of stroke (IS and

HS) or TIA; and QStroke models predicted the composite risk of IS or TIA. The follow-up for these predictions was limited to 10y, as is the time horizon for these risk tools. Both equations were re-calibrated (490) to BRHS data. This involved first generating a prognostic index using respective published predictor beta coefficients multiplied by BRHS values of predictor variables, which was centred using its *BRHS* mean. This was then used as a single variable in Cox models to update (i) its beta coefficient; (ii) the 10y baseline survival function for the relevant risk tool.

SABRE

Incremental value of NT-proBNP was assessed with reference to a single base model comprising those QStroke predictor variables which were available in SABRE (age, sex, BMI, cholesterol:HDL ratio, SBP, antihypertensive use, smoking, diabetes, CKD and social class). QStroke has self-assigned ethnicity as part of its equation and predicts 10yr risk of IS and TIA. However, limiting the follow-up period to match this time horizon markedly reduced the number of stroke events in each ethnic group. Additionally, SABRE does not have a reliable record of TIAs at baseline or follow-up. Hence separate models were fitted *de novo* for SAs and Europeans, thus utilising ethnicity-specific predictor coefficients to generate a centred prognostic index and ethnicity-specific baseline survival functions. These models predicted the 22y risk of any stroke (HS or IS). QStroke includes all predictors of the FSRP except LVH which was not available in SABRE.

In both cohorts, each base model was then extended by adding SD-log NT-proBNP (derived from the respective sample), and a centred prognostic index and baseline survival function was estimated for this base+NT-proBNP model.

7.4.1.2 Indicators of Incremental Performance

Likelihood Ratio Test

Improved model fit on adding NT-proBNP to base models was initially confirmed using likelihood ratio tests (71).

Fraction Of New Information Provided by NT-proBNP

The amount of variation explained by predictors in a base model relative to an extended model can be captured by the *adequacy index*, given by the ratio

$$\frac{\text{Likelihood Ratio } \chi^2 \text{ of the base model}}{\text{Likelihood Ratio } \chi^2 \text{ of the base + biomarker model}}$$

The fraction of new information provided by the added biomarker (438), in this case NT-proBNP, was then estimated by using the formula

$$1 - \text{Adequacy Index}$$

C-Index

Improvement in separation of participants who do/not experience the outcome was assessed by comparing Harrell's C-index of discrimination between each base and extended model. Further details have been described in section 3.8.6.1. The C-index ranges from 0.5 (as good as chance) to 1 (perfect discrimination), with a value <0.7 considered suboptimal (291).

Risk Reclassification

Individual predicted probability or risk of stroke event (P) was generated for the base and extended models using

$$P = 1 - S_0(t)^{\exp(\text{Centred Prognostic Index})}$$

where $S_0(t)$ was the 10y baseline survival function of the relevant model in BRHS, and 22y baseline survival for the relevant model in SABRE SAS and Europeans.

Predicted risks were categorised according to study specific a priori thresholds into 3 risk categories – low, intermediate and high, using cut-offs based roughly on the KM-observed risk and half-KM-observed risk (71), suggested when there is no conventionally recommended threshold for classifying risk of an event type.

Difference in the ability of the base and base+NT-proBNP models to assign individuals with and without events to a more appropriate risk category was assessed using Net Reclassification Improvement or NRI for events (NR_{Ie}) and non-events (NR_{Ie}) (440). This involved cross tabulating the risk categories for both models to enumerate changes in risk classification across categories. The following formulae provide an estimate of NR_{Ie} and NR_{Ie}:

$$NR_{Ie} = \frac{\text{Number of events moving up} - \text{Number of events moving down}}{\text{Number of events}}$$

$$NRI_{ne} = \frac{\text{Number of nonevents moving down} - \text{Number of nonevents moving up}}{\text{Number of nonevents}}$$

NRI_e and NRI_{ne} have been reported separately as an a priori decision. This is because an overall sum NRI is hard to interpret and can result from different combinations of movement across risk categories. Further, changes in predictions for non/events can have different implications and are more meaningful when reported on their own. Cross tabulation also allowed for comparing marginal classifications between models of proportions of participants assigned to each risk category.

Confidence intervals for C-indices and NRI were obtained using 1000 bootstrap samples (439)

Integrated Discrimination Improvement

IDI is a further comparison of the discriminative ability of models which does not rely on categorisation of risk. It measures the difference in means of predicted probabilities for events and non-events between the base and extended models (440).

$$IDI = (P_{biom} \text{ among events} - P_{biom} \text{ among nonevents}) - (P_{base} \text{ among events} - P_{base} \text{ among nonevents})$$

Where, P_{biom} is the mean predicted probability estimated using the model containing NT-proBNP, and P_{base} the mean probability estimated using the base model.

The relative IDI (rIDI), calculated by dividing the IDI by the difference in predicted probabilities estimated by the base model, allows a standardised comparison between studies with differing event rates (71, 491). Further, an rIDI value greater than the inverse of the number of uncorrelated predictors in the base model suggests a new predictor biomarker better than the average of the rest (492).

7.4.1.3 Sensitivity Analysis

Methods to estimate NRI were originally developed for logistic regression models. To account for the effect of censored follow-up in time to event data, NRI was additionally estimated by updated methods (493), using the following formulae:

$$NRI_e = \frac{[p(event|up) * p(up)] - [p(event|down) * p(down)]}{p(event)}$$

$$NRI_{ne} = \frac{[(1 - p(event|down)) * p(down)] - [(1 - p(event|up)) * p(up)]}{1 - p(event)}$$

Where proportions moving up or down i.e., $p(up)$ and $p(down)$ are calculated from the overall sample; and probabilities $p(event)$, $p(event|up)$ and $p(event|down)$ are based on KM-estimates.

Incremental performance was also assessed in models that adjusted for competing risk of death from non-stroke causes, using Fine and Gray method for obtaining sub-hazard ratios (436) and recommendations by Wolbers et al for calculating predicted probabilities and estimating C-indices (435). NRI was then estimated by applying the standard NRI formulae to 1000 bootstrap cross tabulations.

7.4.1.4 Consideration of Missing Data

Missingness for the BRHS FSRP sample was 16%, and for the BRHS QStroke sample 17%. There were no differences in event rate between men with/out complete data. In logistic regression models comprising relevant predictors of missingness (i.e., age, BP medication, smoking and NT-proBNP in the FSRP model, and age and social class in the QStroke model), and the outcome variable, missingness was not associated with the outcome for either sample. Complete case analysis was hence assumed to be unbiased (442, 443).

Missingness among SABRE Europeans was 16% with participants with complete information being a year older, having a higher use of BP medication, lower prevalence of diabetes, and more likely to be women. Missingness among SABRE SAs was 17% with lower prevalence of diabetes, CKD and fewer women among those with complete data. There were no statistically significant differences in stroke rates in participants with/out complete information. In logistic regression models comprising these identified predictors of missingness, stroke outcome variable and NT-proBNP; missingness was not associated with the outcome for either ethnic group. Again, complete case analysis was hence assumed to be unbiased (442, 443) but with lower precision.

A comparison of mean predicted probability with KM-observed risk overall; and of KM-observed risk within the different risk categories indicated that calibration of all models was reasonable.

7.5 Results

7.5.1 Baseline Characteristics of Participants

BRHS

Characteristics of BRHS men contributing to FSRP and QStroke models are shown in Table 7.1. Men had an average age of 68y (± 5), with a crude event incidence of 10/1000PY. The average SBP was 142mmHg and a fifth were on BP treatment. Around 10% had CKD and a similar proportion were diabetic.

SABRE

Characteristics of SABRE participants contributing to self-calibrated QStroke models are shown in Table 7.2. SA participants were on average 2y younger than Europeans with a similar crude stroke incidence of 5/1000PY. More SAs were diabetic and on BP treatment, with a slightly higher mean cholesterol:HDL ratio. Nearly a third of Europeans but only 14% of SAs were smokers.

7.5.2 Incremental Performance of NT-proBNP

BRHS

Table 7.3 shows incremental performance of NT-proBNP for stroke risk prediction in CVD free BRHS men, as measured by fraction of new information provided by NT-proBNP, C-indices and NRI. Both the FSRP and QStroke models had a KM-observed risk of 9%. The thresholds for low, intermediate and high-risk categories were taken as 5% and 10%. NT-proBNP improved the model fit for both FSRP and QStroke, contributing 17% and 24% of the extended models' information respectively. It improved the base C-index for FSRP (0.6428) by 0.0156, and of QStroke (0.6404) by 0.0168, with some overlap of C-index CIs between base and extended models. NT-proBNP also slightly widened the range of predicted probability for both tools.

The FSRP+NT-proBNP model on balance re-classified 2% [95% CI -4.5 – 8.4] of events to a higher risk category and 3% [-1.3 – 7.5] of non-events to a lower risk

category. The QStroke+NT-proBNP model correctly upgraded 5% [-2.4 – 12.4] of events and correctly downgraded 4% [-0.5– 9.4] of non-events. The rIDI indicated that NT-proBNP was likely as good as the predictors in FSRP, and better on average than predictors in QStroke.

Reclassification between nested models is shown in Table 7.4. Marginal classifications suggested a small increase in the number of participants classified as low risk for both FSRP (2%) and QStroke (4%) overall without much change in the proportion of men with high risk.

SABRE

Table 7.5 shows performance measures of NT-proBNP for stroke risk prediction in CVD free SABRE participants. Both the SAs and Europeans had a KM-observed risk of 11%. The thresholds for low, intermediate and high-risk categories were taken as 5% and 10%. NT-proBNP improved model fit for both SAs and Europeans, contributing 12% and 17% of the extended models' information in the ethnic groups respectively. Among SAs, NT-proBNP improved base C-index (0.7610) by 0.009, and among Europeans (0.7270) by 0.016, with some overlap of C-index CIs between base and extended models. NT-proBNP also slightly widened the range of predicted probability in both ethnic groups.

The extended model on balance re-classified 4% [-3.5 – 11.1] of events to a higher risk category and 5% [-0.6 – 10.3] of non-events to a lower risk category in SAs. Among Europeans, it *incorrectly* re-classified 4% [-12.5 – 4.8] of events to a lower risk category and correctly re-classified 6% [0.2 - 11.5] of non-events to a lower risk category. rIDI indicated NT-proBNP was better on average than the QStroke variables included in the base model in both ethnic groups.

Reclassification between nested models is shown in Table 7.6. Marginal classifications suggested a 3% increase in the number of SAs classified as low risk overall when NT-proBNP was included in the model with little change in the proportion of SAs at high risk. And a 2% increase in Europeans at low risk with a 3% decrease in Europeans at high risk overall (Table 7.6a-b).

7.5.3 Sensitivity Analyses

NRI using Methods to Account for Censoring

For both cohorts, the NRI measures were almost identical when estimated using methods that account for censoring (Table 7.3 and Table 7.5, *italicised*), as also noted in other studies estimating NRI with/out censoring taken into consideration (493-495).

Incremental Performance while Adjusting for Competing Mortality

In analyses adjusting for competing risks of death, thresholds for risk categories were retained as 5% and 10% to make an informative comparison of the effect of competing events. Compared to the main analyses, C-indices were lower for all models for both cohorts - however, increments in C-indices brought about by NT-proBNP were of similar magnitude.

Among BRHS men, NR_{Ie} and NR_{Ine} for the FSRP+NT-proBNP model were 7% [1.6-11.9] and 2% [0.5-4.1] respectively. NR_{Ie} and NR_{Ine} for the QStroke extended model were 4% [-2.4 – 10.4] and 2% [0.3-4.2] respectively (Appendix 7.1).

In SABRE, on adjusting for competing deaths in SAs, NR_{Ie} was -1% [-2.9 – 1.0] and NR_{Ine} 2% [1.3-3.0]. NR_{Ie} and NR_{Ine} among Europeans were 1% [-6.3 – 8.2] and 6% [3.4-8.6] respectively (Appendix 7.2).

7.6 Discussion

7.6.1 Summary of Key Findings

This chapter examined if NT-proBNP added more discriminative power to models based on established risk factors for stratification of stroke risk in two population subgroups experiencing a high burden of stroke. Findings indicated that the added prognostic value of NT-proBNP in both cohorts was consistent but limited.

In older British men free of a wide range of CVD conditions, NT-proBNP improved stratification of the composite risk of stroke or TIA when added to FSRP and QStroke equations, correctly reclassifying up to 5% events and 4% of non-events as part of QStroke. However statistically significant improvement was mainly seen on adjustment for competing deaths as 7% upward reclassification for men with events when NT-proBNP was added to FSRP for the prediction of all types of stroke and TIA;

and 2% downward reclassification for men without events on adding NT-proBNP to both FSRP and QStroke.

In middle-aged SAs without CVD, NT-proBNP improved stroke risk stratification when added to variables of QStroke, re-classifying 4% of events and 5% of non-events into a more appropriate risk category. However statistically significant improvement was only seen on adjustment for competing deaths as a downgrading of risk in 2% of SAs who did not experience an event. In European participants of SABRE, NT-proBNP was consistent in significantly contributing only to correct reclassification of non-events (6%) in both regular and competing risk models, while the direction of net reclassification of events was less consistent.

7.6.2 Comparison with Studies Examining Incremental Performance of NT-proBNP for Stroke Risk Prediction in Older Adults

To place findings from the BRHS in context, previous studies have reported similarly small increments in C-statistics/indices (77, 346, 368) when examining incremental performance of NT-proBNP for predicting the 10y risk of stroke in older populations in base models comprising various predictors. However, only one recent study has reported stroke specific NRI for events and non-events (368).

In the Rotterdam study NT-proBNP was added to variables of the PCE model to predict the 10yr risk of stroke as defined by the WHO (368). Male participants of the Dutch cohort were of a similar age to BRHS men, and free of CHD, stroke and HF (but not TIA or AF). The extended model caused a similar +0.014 increment in C-index although the base model in Dutch men had a much better discrimination (0.712) than in BRHS. NT-proBNP also brought about a net upward re-classification of 9% of men with incident stroke, but also *incorrectly* assigned higher risk to net 3% of men without incident stroke. This was based on thresholds used for stratifying atherosclerotic CVD risk (30), across 4 categories. Given the difficulty in comparing NRI between studies which differ in the number and definitions of risk categories and outcomes (493), the ability of NT-proBNP to upgrade risk in those with events was also noted in BRHS, especially strongly in the FSRP-extended model which adjusted for competing deaths. This is of value since it considers a more realistic probability of experiencing a stroke in late life. In addition to this, in BRHS men, NT-proBNP was consistently noted to

correctly downgrade 2% (up to a maximum of 4%) of BRHS men who did not go on to have a stroke event, in both FSRP and QStroke competing risk models.

The ability of NT-proBNP to mainly correctly (*down-*)classify *composite-CVD* risk among older adults not experiencing such events has been noted by others (346, 370). Findings from the current chapter corroborate this specifically for *stroke*. And suggest NT-proBNP may be useful to improve stroke-specificity of composite-CVD risk prediction tools in old age (as raised as a concern in Chapter 5). Moreover, the possibility that NT-proBNP could better classify both stroke events and non-events in CVD free older BRHS men i.e., potentially improve both sensitivity and specificity, can have useful implications for clinical decision making among older adults in general. This is discussed further in Chapter 8.

It is important to also mention that despite some improvement in risk stratification, the discrimination of NT-proBNP extended models remained suboptimal (<0.7) and calls for continued research into age-linked stroke risk markers.

7.6.3 Performance of NT-proBNP for Stroke Risk Prediction in South Asians

There are no previous reports comparing stroke risk prediction by conventional variables and NT-proBNP-extended models in SAs. In the current analysis, magnitude of association between the biomarker and stroke was similarly strong in middle-aged European and SA participants, and NT-proBNP was able to accurately reclassify a modest proportion of non-events in both ethnic groups. However, in SAs the C-index of the reference model already appeared better and hence improvement by NT-proBNP was to a lesser degree than that observed among SABRE Europeans. This was accompanied by a slightly reduced ability of NT-proBNP to improve specificity of risk prediction compared to Europeans.

The potential for NT-proBNP to correctly reclassify events in SAs (and Europeans) was less clear. This may be linked to NT-proBNP being less associated with co-morbid pathologies than with physiological maintenance responses in middle age (366). There is also the possibility that the especially lengthy follow up in SABRE may have influenced results. From the BiomarCaRE Consortium, a NR1e of 2% was reported among a very large sample of middle-aged European men and women followed for 10y for all strokes. However, this analysis did not exclude CVD conditions other than prevalent stroke at baseline (76). It may therefore be necessary to examine the

incremental performance of NT-proBNP in middle age more widely, especially in CVD free SAs. This is because they experience stroke events a decade earlier than Europeans (23). If enhanced event reclassification can be confirmed in larger SA cohorts, it may guide (often limited) resource allocation for enhanced preventive interventions to select individuals earlier.

7.6.4 Strengths and Limitations

General strengths and limitations of the two data sets have been presented in sections 3.4 and 3.7.

In both cohorts, incremental performance of NT-proBNP was examined as a continuous biomarker which provides more information for risk stratification as opposed to a cut-off based binary predictor, and as part of competing risk models which has rarely been examined. But for both BRHS and SABRE participants, only a baseline measure of NT-proBNP was available. And although risk prediction is based on single one-off values, risk factor levels can vary during follow up giving some degree of inaccuracy to all prediction models.

In this context, the use of repeat NT-proBNP measurements has been shown to improve prediction and risk stratification of HF related outcomes in individuals with (496) and without (497) HF at baseline. Similarly, change in NT-proBNP between baseline and 3y was noted to add modest prognostic value above baseline NT-proBNP when predicting CVD in multi-ethnic CVD free adults, but if this works by improving reclassification of events or non-events was model dependent (371). Whether serial NT-proBNP can similarly capture the subclinical trajectory of CVD free older adults and add predictive accuracy to *stroke* risk remains to be seen. Dynamic risk prediction models (section 2.4.6.2) which get updated as sequential values for predictors become available would be ideal to investigate statistically. Since serial measurement of NT-proBNP in CVD free patients is not currently part of routine practice, perhaps this may initially require harmonized longitudinal cohorts of CVD free individuals who have had repeat NT-proBNP measured as per study protocol. The potential for artificial intelligence to draw on multiple multi-dimensional biomarkers for improving performance of risk prediction models is discussed further in Chapter 8.

All analyses were conducted on complete case samples and although bias was likely to be minimal, the effects reported may lack precision.

BRHS analysis used available equations for well-known stroke risk tools and updated their overall coefficient and baseline risk to match study parameters. BRHS analyses also excluded men with HF and AF and TIA – adults who are likely already on preventive management which can influence biomarker-stroke associations and hence discrimination ability.

An inherent limitation to using NRI measures is that NRLe and NRIne weight movements in risk categories equally which may not be realistic. Still, accompanying reclassification tables provide some detail of numbers of participants moving across (how many) categories, with marginal classifications generally indicating a small increase in the lowest risk category overall as a shift from the intermediate risk. Therefore, estimation of NRI is useful as one of a number of steps in judging the added value of a biomarker and comparing this between biomarkers (71). In this context, it is acknowledged that studies exploring the role of Troponins in predicting stroke in older adults do indicate some added discriminatory power for reclassification (368, 370). However, based on findings from Chapter 6 where hs-cTnT was noted to have weak, non-significant associations with stroke when *included with models containing NT-proBNP*, it was deemed redundant to explore its incremental value in the current Chapter. Indeed, others who have explored a combination of both biomarkers have also observed that Troponins may be adding very little to risk reclassification of stroke beyond NT-proBNP (77, 368).

7.7 Conclusion

NT-proBNP consistently downgraded a modest number of CVD free older British men without an incident stroke/TIA over a 10y follow-up to a lower risk category; with some indication that it could also help upgrade those with incident stroke to higher risk. Similar examinations should be conducted in independent cohorts inclusive of women participants. NT-proBNP also assigned a more appropriate risk category to a modest proportion of SAs without incident stroke, which is consistent with its more general ability to improve specificity. Findings require to be validated in other independent SA

studies, for a more conventional prediction horizon of 10y, to verify if they are of clinical significance.

Because current clinical practice is based on composite-CVD risk assessment, examining the added value of NT-proBNP to PCE, QRISK3 and SCORE equations for sensitivity/specificity to *stroke* events in both population groups is also a logical next step. These and other implications are further elaborated next in the final Chapter.

Table 7.1 Baseline characteristics of CVD free BRHS men contributing to FSRP and QStroke base and extended models.

Events/N	FSRP 208/2429	QStroke 199/2442
Crude Stroke Incidence Rate/1000PY [95%CI]	9.89 [8.63-11.32]	9.46 [8.23-10.87]
Age (y)	68 (5)	68 (5)
Body Mass Index (kg/m ²)	-	26.7 (4)
Systolic Blood Pressure (mmHg)	142 (24)	142 (24)
Cholesterol:HDL Ratio	-	4.80 (1.4)
Current Smokers (%)	12	13
Blood Pressure Medication (%)	20	21
Diabetes (%)	10	10
Left Ventricular Hypertrophy (%)	1	-
Rheumatoid Arthritis (%)	-	<0.5
Chronic Kidney Disease (%)	-	9
Family history of coronary death (%)	-	5
NT-proBNP (pg/ml)	129 (245)	133 (253)
Range	5-4097	5-4097
Median (Q1, Q3)	72 (39, 132)	74 (39, 138)

Mean (sd)

Table 7.2 Baseline characteristics of CVD free SABER participants contributing to a self-calibrated QStroke base and extended models.

Events/N	Europeans 104/1181	South Asians 106/1149	P value
Crude Stroke Incidence Rate/1000PY [95%CI]	4.69 [3.87-5.69]	4.84 [4.00-5.85]	0.82
Age sex adjusted HR [95%CI]	1	1.23 [0.94-1.62]	0.13
Age (y)	53 (7)	51 (7)	<0.001
Body Mass Index (kg/m ²)	26 (4)	26 (4)	0.92
Systolic Blood Pressure (mmHg)	123 (17)	125 (18)	0.048
Cholesterol:HDL Ratio	4.9 (1.6)	5.1 (1.6)	0.003
Women (%)	13	15	0.22
Current Smokers (%)	31	14	<0.001
Manual Social Class (%)	61	76	<0.001
Blood Pressure Medication (%)	9	13	0.004
Diabetes (%)	5	19	<0.001
Chronic Kidney Disease (%)	6	4	0.046
NTproBNP (pg/ml)	69.5 (149)	55.8 (117)	
Range	5-2280	4-2361	
Median (Q1, Q3)	37.4 (23.6, 64.6)	30.9 (18.9, 55.4)	<0.001

Mean (sd)

7 Role of NT-proBNP in Stratifying Stroke Risk

Table 7.3 Incremental performance measures of NT-proBNP for stroke risk prediction in CVD free BRHS men.

	BRHS-FSRP		BRHS-QStroke	
Predictors	Age, SBP, BP Treatment, Smoking, Diabetes and LVH		Age, BMI, Cholesterol:HDL ratio, SBP, BP treatment, Smoking, Diabetes, RA, CKD, and Family history of Coronary Death	
Events/N	208 Strokes & TIAs/2429		199 Ischaemic Strokes & TIAs/2442	
KM-Observed risk at 10y [95%CI]	9.40 [8.26-10.70]		8.97 [7.85-10.24]	
Model	Base	Plus NT-proBNP	Base	Plus NT-proBNP
HR [95%CI]^	-	1.32 [1.13-1.54]	-	1.36 [1.16-1.60]
P for Likelihood ratio test	-	0.0005	-	0.002
Harrell's C [95% C]	0.6428 [0.6060-0.6796]	0.6584 [0.6222-0.6947]	0.6404 [0.6050-0.6759]	0.6572 [0.6206-0.6939]
Baseline Survival	0.9137397	0.914945	0.9328129	0.9302557
Probability Event, Mean (range)	9.65 (2.56-54.43)	9.74 (2.22-65.4)	9.23 (2.42-30.30)	9.33 (1.94-45.13)
Adequacy Index	-	0.828	-	0.762
Fraction of new information from NT-proBNP		0.172		0.238
NRI Events		0.019 [-0.045-0.084]		0.050 [-0.024-0.124]
<i>NRI Events corrected for censoring</i>		<i>0.018 [-0.044-0.081]</i>		<i>0.052 [-0.021-0.124]</i>
NRI Non-events		0.031 [-0.013-0.075]		0.044 [-0.005-0.094]
<i>NRI Non-events corrected for censoring</i>		<i>0.031 [-0.013-0.075]</i>		<i>0.045 [-0.005-0.095]</i>
IDI		0.006 [-0.002-0.013]		0.007 [-0.001-0.015]
Relative IDI		0.211 [-0.122-0.544]		0.385 [-0.223-0.993]

^per SD-log NT-proBNP adjusted for centred prognostic index.

Confidence intervals obtained using 1000 bootstrap samples.

BMI: body mass index, BP: blood pressure, CKD: chronic kidney disease, IDI: integrated discrimination improvement, LVH: left ventricular hypertrophy, NRI: net reclassification improvement, RA: rheumatoid arthritis, SBP: systolic blood pressure

Table 7.4 Reclassification table comparing 10y risk categories for base and base+NT-proBNP models for stroke in older CVD free BRHS men.

(a) FSRP (n=208/2429)

Base Model	Base + NT-proBNP			Total (%)	
Events	<5%	5 to <10%	≥10%		
<5%	8	7	0	7.2	
5 to <10%	3	67	10	38.5	
≥10%	0	10	103	54.3	
Total (%)	5.3	40.4	54.3	100	
Non-events	<5%	5 to <10%	≥10%		
<5%	204	89	1	13.2	
5 to <10%	149	902	117	52.6	
≥10%	1	125	633	34.2	
Total (%)	15.9	50.3	33.8	100	
Overall	<5%	5 to <10%	≥10%		KM Risk (%)
<5%	212	96	1	12.7	4.98
5 to <10%	152	969	127	51.4	6.92
≥10%	1	135	736	35.9	15.06
Total (%)	15.0	49.4	35.6	100	
KM Risk (%)	3.11	7.54	15.22		

(b) QStroke (n=199/2442)

Base Model	Base + NT-proBNP			Total (%)	
Events	<5%	5 to <10%	≥10%		
<5%	7	5	0	6.0	
5 to <10%	4	66	17	43.7	
≥10%	0	8	92	50.3	
Total (%)	5.5	39.7	54.8	100	
Non-events	<5%	5 to <10%	≥10%		
<5%	207	93	1	13.4	
5 to <10%	196	889	137	54.5	
≥10%	2	132	586	32.1	
Total (%)	18.1	49.7	32.3	100	
Overall	<5%	5 to <10%	≥10%		KM Risk (%)
<5%	214	98	1	12.8	3.96
5 to <10%	200	955	154	53.6	7.12
≥10%	2	140	678	33.6	14.47
Total (%)	17.0	48.9	34.1	100	
KM Risk (%)	2.71	7.13	15.55		

Tables show risk categories in red; KM risk in dark blue; and absolute numbers except where marked (%) which indicate percentage of total.

KM: Kaplan-Meier estimate of observed risk.

7 Role of NT-proBNP in Stratifying Stroke Risk

Table 7.5 Incremental performance measures of NT-proBNP for stroke risk prediction in CVD free SABRE participants.

	SABRE Europeans		SABRE South Asians	
Predictors	Age, Sex, BMI, SBP, BP Treatment, Smoking, Diabetes, Cholesterol:HDL ratio, CKD and Social Class			
Events/N	104 Strokes/1181		106 Strokes/1149	
KM-Observed risk at 22y [95%CI]	11.07 [8.92-13.68]		11.03 [8.93-13.58]	
Model	Base	Plus NT-proBNP	Base	Plus NT-proBNP
HR [95%CI]^		1.45 [1.21-1.73]	-	1.40 [1.16-1.68]
P for Likelihood ratio test		0.0001	-	0.0007
Harrell's C [95% C]	0.7270 [0.6783-0.7757]	0.7430 [0.6948-0.7912]	0.7610 [0.7174-0.8046]	0.7700 [0.7262-0.8138]
Baseline Survival	0.9053863	0.9070931	0.9125711	0.915235
Probability Event, Mean (range)	12.75 (1.26-79.05)	13.15 (1.16-96.13)	12.17 (1.43-88.72)	12.21 (1.09-98.45)
Adequacy Index	-	0.826	-	0.885
Fraction of new information from NT-proBNP		0.174		0.115
NRI Events		-0.038 [-0.125-0.048]		0.038 [-0.035-0.111]
<i>NRI Events corrected for censoring</i>		<i>-0.036 [-0.134-0.062]</i>		<i>0.044 [-0.064-0.151]</i>
NRI Non-events		0.058 [0.002-0.115]		0.049 [-0.006-0.103]
<i>NRI Non-events corrected for censoring</i>		<i>0.059 [0 - 0.119]</i>		<i>0.051 [-0.006-0.108]</i>
IDI		0.024 [-0.003-0.052]		0.018 [-0.007-0.043]
Relative IDI		0.306 [-0.032-0.643]		0.174 [-0.066-0.414]

^per SD-log NT-proBNP adjusted for centred prognostic index.

Confidence intervals obtained using 1000 bootstrap samples

BMI: body mass index, BP: blood pressure, CKD: chronic kidney disease, IDI: integrated discrimination improvement, NRI: net reclassification improvement, SBP: systolic blood pressure

Table 7.6 Reclassification table comparing 22y risk categories for base and base+NT-proBNP models for stroke in CVD free SABRE participants.

(a) South Asians (n=106/1149)

Base Model	Base + NT-proBNP			Total (%)	
Events	<5%	5 to <10%	≥10%		
<5%	7	0	1	7.6	
5 to <10%	2	15	7	22.6	
≥10%	0	2	72	69.8	
Total (%)	8.5	16.0	75.5	100	
Non-events	<5%	5 to <10%	≥10%		
<5%	298	34	2	32.0	
5 to <10%	71	234	30	32.1	
≥10%	1	45	328	35.9	
Total (%)	35.5	30.0	34.5	100	
Overall	<5%	5 to <10%	≥10%		KM Risk (%)
<5%	305	34	3	29.8	2.85
5 to <10%	73	249	37	31.2	9.20
≥10%	1	47	400	39.0	19.86
Total (%)	33.0	28.7	38.3	100	
KM Risk (%)	2.84	7.26	22.21		

(b) Europeans (n=104/1181)

Base Model	Base + NT-proBNP			Total (%)	
Events	<5%	5 to <10%	≥10%		
<5%	5	1	0	5.8	
5 to <10%	3	15	4	21.2	
≥10%	0	6	70	73.1	
Total (%)	7.7	21.2	71.2	100	
Non-events	<5%	5 to <10%	≥10%		
<5%	257	35	2	27.3	
5 to <10%	65	206	36	28.5	
≥10%	0	71	405	44.2	
Total (%)	29.9	29.0	41.1	100	
Overall	<5%	5 to <10%	≥10%		KM Risk (%)
<5%	262	36	2	25.4	2.47
5 to <10%	68	221	40	27.9	8.16
≥10%	0	77	475	46.7	19.53
Total (%)	27.9	28.3	43.8	100	
KM Risk (%)	2.86	8.51	20.70		

Tables show risk categories in red; KM risk in dark blue; absolute numbers except where marked (%) which indicate percentage of total.

KM: Kaplan-Meier estimate of observed risk.

Chapter 8. Implications and Conclusion

8.1 Summary

This chapter reviews key findings and research contributions of this thesis; and discusses their implications for public health, policy and clinical practice, as well as future research.

The thesis had an overall aim of informing primary prevention of stroke in older adults and South Asians. Findings with key public health implications are that (1) the impact of CVH on stroke reduced from mid to late life underscoring the need for greater focus on detecting and managing wider age linked causes of stroke; (2) among middle-aged SA participants, optimal CVH could reduce the burden of stroke by more than a third and greater efforts to especially promote healthier BP, glucose and BMI levels were needed; (3) prediction of stroke in old age by composite-CVD risk tools was comparable to if not better than by stroke-specific tools but it was necessary to address the issues of weak discrimination, age appropriate thresholds, and stroke risk communication; and (4) in both target populations NT-proBNP was a robust independent marker of long-term stroke risk, added value to stroke risk prediction by modestly improving reclassification of non-events, and was potentially useful in guiding intensity of stroke risk factor management.

Several avenues for future primary prevention research have become available. Apart from validating thesis findings among older women and a larger more recent cohort of SAs, these include (1) investigating the impact of the updated LE8 CVH model on stroke among both groups; (2) validating newer risk predictions algorithms such as SCORE2-OP and the Stroke Riskometer; (3) developing a de novo stroke risk prediction tool for SAs using data from maturing SA cohorts; (4) exploring associations of NT-proBNP with subtypes of stroke; (5) conducting randomized controlled trials to examine the use of NT-proBNP in guiding preventive therapy for stroke; and (6) conducting net benefit analyses for comparing the clinical utility of traditional, NT-proBNP based and other novel biomarker based models for stratification of stroke risk.

8.2 Key Findings

This doctoral research analysed longitudinal quantitative data from two long-running British cohorts, BRHS and SABRE, to inform population-level and high-risk approaches for stroke prevention in older adults and SAs, both of whom experience a high burden of stroke. It estimated the population level impact of the AHA's Life's Simple 7 and Cardiovascular Health framework, the performance of common risk assessment tools for prediction of stroke; and the incremental value of NT-proBNP, as a marker of subclinical cardiac dysfunction, in refining stroke risk stratification when added to models containing conventional risk factors. Key results are as follows:

Findings from Chapter 4 indicate that among older men without CHD and stroke, ideal CVH i.e., having all LS7 metrics at ideal levels (CVH score 14) was extremely rare (<1%) and the prevalence of optimal CVH (CVH score ≥ 10) was around 20%. The association of CVH with stroke risk attenuated between mid and late adult life; and there was marked reduction in the fraction of stroke attributable to suboptimal CVH (39% to 6%) and to non-ideal levels of nearly all LS7 metrics, although BP retained the greatest impact. However, later life stroke risk was relatively lower for those who improved their CVH between middle and older age compared to those who failed to do so. In comparison to stroke, the impact of CVH on MI or a composite outcome of stroke or MI was stronger and larger.

Findings from Chapter 4 also indicate that among middle-aged CHD and stroke free SAs, the prevalence of optimal CVH was 38%, and slightly higher than among similarly recruited Europeans-33%. Underlying this overall CVH estimate among SAs was a large proportion of never-smokers, alongside a significantly lower proportion with ideal BP and ideal glucose and ideal PA. The fraction of stroke attributable to sub-optimal CVH among SAs was also larger than among Europeans (36% vs 21%), similar to the fraction of CHD attributable to sub-optimal CVH; and increased further (to 44%) when applying stricter BMI thresholds for obesity. Among individual LS7 metrics, the largest PAF of stroke in SAs was due to non-ideal BP (67%) followed by non-ideal glucose (22%).

Chapter 5 described how well stroke-specific (FSRP and QStroke) and composite-CVD (QRISK3 and PCE) risk prediction tools estimated the 10y risk of stroke events in older BRHS men. External validation findings suggest that both types of risk tools,

with a range of traditional and newer stroke risk predictors failed to efficiently discriminate between older men who did/not experience stroke (C-indices ranging from 0.63 to 0.66). Calibration i.e., the agreement between predicted and observed risks was poorer for stroke-specific tools at higher predicted risks, when they over-estimated stroke risk, and worsened on adjusting for competing non-stroke deaths. In the primary prevention sample free of a wide range of CVD conditions, performance of FSRP, QStroke and QRISK3 was similar except for the highest two to three deciles of predicted risk and in men >75y when QRISK3 appeared better calibrated. Using QRISK3 and PCE to classify older CVD free men as low/high risk based on thresholds recommended for composite-CVD was associated with excellent sensitivity (99%) but poor specificity (2-3%) for stroke.

Chapter 6 and 7 elaborated respectively on the long-term associations of NT-proBNP with stroke events in CVD free older BRHS men and middle-aged SAs; and on the incremental performance of NT-proBNP in predicting and refining stroke risk in both groups. NT-proBNP was found to have robust incremental associations with fatal and non-fatal stroke events as well as TIAs in older men free of CHD, stroke, HF and AF; independent of a broad range of potential confounders and across levels of key comorbid conditions such as hypertension, diabetes, and CKD. NT-proBNP was similarly associated with stroke in middle-aged CVD free SAs over a ~20y horizon, independent of key confounders, with levels above 100pg/ml potentially indicating especially high risk in those with diabetes. In both groups, associations persisted even after adjusting for cardiac events that occurred prior to incident stroke events, and were robust to adjustment for Troponin-T.

NT-proBNP added limited discriminatory power to 10y stroke prediction by FSRP and QStroke in older men (change in C-index +0.02) and to 22y stroke risk prediction by a QStroke based model in middle-aged SAs (change in C-index +0.01). However, depending on the model, NT-proBNP reclassified up to 7% of older men with stroke events to a higher risk category; and was more modest but consistent in its ability to downgrade non-events in both older adults and middle-aged SAs.

8.3 Novel Contributions to Stroke Research

The strengths and limitations associated with research contributions of this thesis relate to the features of the two data sources used (elaborated in Chapter 3) and to analytical methodology (discussed in respective chapters). This section elaborates on new evidence produced by the thesis in the larger stroke research landscape.

The CVH framework has been universally promoted as a target of prevention strategies that aim to reduce the burden of CVD and non-CVD outcomes (52, 280). However, the impact of a collective CVH metric or score would depend on associations of its component metrics with an outcome, and whether these retain their strength and expected direction or become weak or antagonistic across age and ethnicity (498). As summarised in Chapter 2, while previous research has examined the impact of CVH on composite-CVD (55), evidence on the burden specifically of stroke that could be eliminated by improving CVH among CVD free older adults and South Asians is missing. Findings from Chapter 4 answer these questions by demonstrating that the utility of the CVH model for stroke prevention in older adults may be limited, and (to my knowledge for the first time) describing the distribution of CVH and its prospective protective associations and impact on stroke among British South Asians. Both findings have implications for tailoring stroke prevention efforts in these high-risk subgroups (section 8.4 below).

Chapter 2 also points to the paucity of studies externally validating, and in particular, comparing the performance of, stroke-specific and composite-CVD risk prediction tools for estimating the absolute risk of stroke in independent prospective cohorts of older adults. Chapter 2 additionally highlights the influence competing mortality can have on risk estimation – nearly all of which has been examined in the context of composite CVD outcomes and not stroke per se. This thesis addresses these gaps by validating multiple risk tools developed using data from British and non-British adults in a good-sized sample of older BRHS men, and assessing the accuracy of stroke risk prediction while also accounting for competing non-stroke deaths. Findings from these analyses elaborated in Chapter 5 also supplement ongoing scientific debates on using age-specific CVD risk thresholds for initiating preventive interventions which take the age-driven risk of CVD into consideration (124, 499, 500), and disaggregating absolute

risks by CVD subtypes (62); and emphasize the need for exploring more age-specific markers of stroke risk.

While augmenting risk stratification by using Natriuretic Peptides has been and continues to be researched, much of this work points to the role of NT-proBNP in refining the global risk of multiple CVD event types, and mostly in Caucasian populations. In the context of methodological limitations described earlier (Chapter 2), of using a composite outcome when its components may vary in type and proportion across age and ethnic groups, evidence on how NT-proBNP specifically relates to stroke and its various manifestations i.e., TIAs, fatal and non-fatal events; and hence its contribution to stroke risk estimation and especially risk refinement in older adults without a history of clinical CVD is less well established. Further, the distribution of NT-proBNP and its anticipated role in predicting stroke in CVD- free SAs has so far not been reported.

Analyses described in Chapter 6 make several contributions in these respects: they confirm the long-term predictive ability of NT-proBNP for stroke in both older adults and SAs, and uniquely, demonstrate that this predictive power remains robust to adjustment of Troponin T – an equally popular and accessible biomarker of subclinical cardiac dysfunction, suggesting NT-proBNP may be a superior candidate for refining stroke risk in these populations. Additional findings suggest that SAs may on average be having lower levels of NT-proBNP which adds to the limited evidence base on biomarkers in this ethnic group and may have implications for further research into predisposition and management of their cardiometabolic risk.

Finally, Chapter 7 explicitly reports on both discrimination and ability of NT-proBNP to separately reclassify those with and without incident stroke events. It extends what has been previously reported regarding NT-proBNP's role in improving specificity of CVD risk prediction in Caucasian adults to increasing specificity of stroke risk prediction in older age and among middle-aged SAs.

8.4 Implications for Policy, Public Health and Clinical Practice

The urgency for preventing strokes has been recognized and asserted by many international bodies such as the World Stroke Organization (222, 501, 502), WHO

(503), and European Stroke Organization (26), which recommend a combination of population-wide and high-risk prevention strategies. Stroke has also been acknowledged as a named clinical priority alongside CVD in the 2019 NHS Long Term Plan for England (504), with focus not only on acute stroke and post stroke care but also prevention, and has a fully aligned National Stroke Programme developed by NHS England and the Stroke Association (505).

The focus of this thesis has been primary prevention of stroke in older adults and in SAs who have not experienced any cardiovascular events. While the findings have been arrived at using data from British cohorts, it is hoped they will be useful for guiding public health and policy for reducing the burden of stroke in older adults and SAs in UK and more widely.

8.4.1 Strategies Targeting CVH and LS7 Metrics in Older Adults

The CVH model brings together key cardiovascular risk factors targeted by population-wide and high-risk prevention approaches. In light of findings from this thesis, better CVH as a whole is associated with some reduction in the relative risk of experiencing a stroke in old age and should be promoted for improving wider cardiovascular health outcomes. However, considering the greatest PAF of stroke among older adults is attributable to non-ideal levels of BP while other metrics weaken in impact; enhanced focus on detection and control of hypertension is necessary to bring about a greater reduction in first ever strokes.

Population-level policies to modify CVH metrics such as tobacco use, dietary intake of salt and sugars, and promoting physical activity are present in most European countries including UK and have the potential of influencing risk factors across the life course (506). In addition, without formally adopting the CVH model, the NHS Health Check offered to those between 40-75y without a history of CVD, assesses all LS7 metrics (except diet) and provides relevant advice. But there is a paucity of evidence on the components and combinations of interventions that can bring about individual level risk factor modification in those over 55y, and hence limited guidelines for promotion of healthy behaviours in this age (507). In this respect, interventions need to be designed for the older population keeping in mind that behaviour change – whether related to lifestyle or compliance to medication will be a challenge. Determinants of behaviour change, structure and content of goals, processes that help

translate intention into action (508) and behaviour change techniques (509) effective for middle-aged adults may not be similarly useful or even applicable in older age. Experts recommend intervention development for older adults be guided by explicit behaviour change theories (for example the health belief model or COM-B which in explaining what determines behaviour change help specifically target these determinants), and reported in enough detail to be robustly examined and compared (508, 510).

Detection of hypertension in primary care interactions remains suboptimal across Europe (506). Based on survey data from 2015-2019, around 4 million adults in England - nearly 30% of those expected to have hypertension, live with undiagnosed hypertension. This includes half a million males aged 55-64y and just a slightly lower number of females aged 65-74y (511). Of those diagnosed 40% have poorly controlled BP (505).

In alignment with the NHS Long Term Plan, the National CVD Prevention System Leadership Forum had set out a goal of diagnosing 80% of those expected to have hypertension and treating 80% of those with hypertension per NICE guidelines, by 2029 (512). But work on this was affected by national lockdowns during the pandemic. The latest report of the CVDPREVENT national primary care audit (513) notes that up to 60% of adults with diagnosed hypertension were treated to target by March 2022, which is poorer than pre-pandemic levels; while nearly 3 million (40%) had either unknown or high BP. Based on the finding that high BP is a key driver of risk of strokes in older BRHS men, stronger systematic efforts are needed to detect and control hypertension in the 60y+ age group, underscoring the need for policy makers to enhance support for primary care networks in delivering a proactive older population targeted response for BP monitoring and treatment through GPs, community NHS health checks, community pharmacies and access to the BP@Home programme (514).

A key aspect of optimizing BP control in older adults is setting safe BP targets. European and North American clinical guidelines vary in their recommendations, as in their definitions of 'old' (515), and these targets may not necessarily match the cut-offs suggested for ideal or intermediate levels of BP in the CVH model. Recent NICE guidelines suggest aiming for <140/90mmHg clinic BP for those <80y; and

<150/90mmHg clinic BP for those 80y or older, irrespective of prevalent CVD or Diabetes; while making clinical judgement on factors such as multimorbidity, frailty and postural hypotension (516).

Older adults hence need individualized BP treatment, which once agreed upon should be supported by primary care embedded mechanisms for improving medication adherence such as reminders, supervision and monitoring of adverse effects that may reduce compliance or indeed offset benefit (517). Digital platforms have also been explored for the delivery of CVD risk modifying interventions and self-management. For older people it has been found that apart from computer literacy, the success of such programs depends highly on having some form of initial and ongoing in-person support, making them part of daily routine, personalising content and goal setting, and offering them not in lieu of but alongside primary care visits (518).

8.4.2 Strategies Improving the Detection and Management of AF in Older Adults

The falling contribution of CVH and LS7 metrics to stroke risk in older BRHS men, and acknowledging that the AHA definition of ideal or even intermediate BP level may not necessarily be aimed for in older adults due to reasons described above, raises further the importance of detecting and managing wider age related causes of stroke especially AF. AF is a well-established cause of cardio-embolic ischaemic strokes (73), which are generally more severe both in terms of mortality and disability (122). One in 5 strokes in the UK are due to AF. AF particularly increases the risk of IS in those that have hypertension (183).

AF is associated with palpitations and dizziness but like hypertension can remain symptomless and often intermittent, and many with AF remain undiagnosed. In the UK, as globally, national screening for AF is not recommended due to lack of evidence on the balance between harms and benefits, with detection limited to those suspected of having AF due to symptoms or a stroke/TIA, or at NHS Health Checks. This is subject to review pending results of the ongoing Screening for Atrial Fibrillation with ECG to Reduce stroke (SAFER) trial among participants aged 70y and older (519). However, the UK endorses the European Society of Cardiology recommendation on opportunistic detection of AF by pulse taking or ECG rhythm strip in people aged 65 and over (520, 521). Yet according to GP surveys, less than 10% of such patients were being screened (506).

National CVD Prevention ambitions included a target of diagnosing 85% of those expected to have AF and adequately anticoagulating 90% of those with known AF by 2029 (512). Opportunistic screening for AF during primary care interactions was affected during Covid restrictions. Guidelines suggested using vaccination centres, where a good number of 65y+ would be attending to opportunistically screen for AF and link to physician service (522). Latest figures from the British Heart Foundation indicate some success towards detection; there are now 1.5 million people with AF in the UK (523), but at least 270,000 more who remain undiagnosed (524).

Additionally, under prescribing has previously been reported in UK primary care among adults with stroke or TIA who were eligible for anticoagulation (525), with figures suggesting half of all people with known AF who suffer a stroke not having received anticoagulants before their stroke, and some evidence this is linked to age (85y+) and female sex (526). CVDPREVENT audit findings (513) suggest there has been improvement towards reaching the prescribing goal at a national level, but regional variation persists. There is also currently no data to show if anticoagulation is optimised. This is important as under or over treatment, can predispose to ischaemic and haemorrhagic events respectively, the latter being a special concern among those with frailty or a high falls risk who may need more frequent follow-up (527). Administrators and primary care networks need to be aware of the gaps in local AF services to bring about a reduction in AF-linked strokes most of which occur in older age groups.

8.4.3 Strategies Targeting CVH in South Asians

The thesis suggests that improvements in overall CVH can lead to reductions in the 20y burden of stroke among CVD free middle-aged SAs by 36% to 44% (depending on how obesity is classified). Existing population-level policies (as mentioned above) and cardiovascular screening programs such as the NHS Health Check which influence CVH are therefore, as expected, needed to prevent first ever strokes in SAs. And attention should continuously be paid to their relevance and accessibility among the ethnic group. Places of worship and community events are well known avenues for offering health checks and signposting (528, 529). The recommendation to lower the eligibility for an NHS check from 40y to 30y may also be particularly beneficial for SAs who are more likely to experience stroke events earlier (530).

It is worth stating also that the higher risk of stroke/CVD and their underlying risk factors among SAs is rightfully and amply conveyed through public health messaging and clinical interactions. There is a chance however that emphasis on how an ethnic group is disproportionately more likely to suffer ill health compared to the majority can lead to feelings of stigmatization (531). An important finding from the thesis was that in SAs there was incremental benefit of small improvements in CVH which was similar to that noted in Europeans, if not better. This positive notion should also be leveraged as part of public health/community media campaigns and clinical encounters in order to bring reassurance leading to greater engagement, and to motivate behaviour change.

Thesis findings also highlight the major contribution of BP and glucose levels to stroke risk relative to other metrics such as smoking in SAs, and policies and services addressing the health of SA communities should be planned in the context of this knowledge.

To some extent, this is already the case in England. Hypertension control in ethnic minorities, including SAs was identified as a challenge in the Department of Health 2007 Stroke Prevention strategy. But hypertension management continues to be suboptimal in SAs in 2019 (532). NHS England-NHS Improvement developed a CORE20PLUS5 approach for reduction of health inequalities which has hypertension case finding and optimal management as a clinical focus area. The 'PLUS' population groups are to be identified through local population needs assessment and are expected to include ethnic minority communities (533). However, current primary care audit figures indicate that under two-thirds of SAs hypertensives are being treated to goal (513). Although this is similar to the rate noted among the White ethnic group, keeping in view the higher PAF of stroke attributable to hypertension among SAs (67% vs 7% among Europeans), more needs to be in place for hypertension management among SAs.

Similarly, early service evaluation of the NHS Diabetes Prevention Programme, which offers behavioural interventions for weight loss/maintaining healthy weight, and achieving UK dietary and physical activity recommendations through face to face or online sessions to preventing/delay the onset of type 2 diabetes in adults with nondiabetic hyperglycaemia, indicated that although referral for and initial attendance

by Asian ethnic groups were high, they were less likely to complete the 9 month programme and had smaller reductions in weight (534). Strategies need to be adopted for promoting uptake of and retention within programmes to ensure outcomes benefit and can include having providers of similar ethnic background (535, 536) and greater efforts to co-design programs and interventions with recipient groups (537).

Analysis from the thesis notes that calculating CVH based on 23kg/m² and 27.5kg/m² to define intermediate and ideal BMI in SAs resulted in a greater burden of stroke being attributable to sub-optimal CVH. This has implications for the criteria by which SAs are offered obesity interventions. SA adults are currently referred for NHS Digital weight management program if they have a BMI >27.5kg/m² and diabetes/hypertension. The programme reports comparable early weight loss and equitable engagement from all ethnic groups (538) but more long-term follow-up of the programme may be needed to measure successful maintenance. Additionally, BMI boundaries even lower than those examined here have been suggested for initiating interventions for prevention of type 2 diabetes in SA subgroups (539). If similar further research can confirm and identify the exact BMI threshold at which SAs become more prone to a higher incidence of stroke and/or CVD then commissioners may need to reconsider the criteria for offering weight management services to SAs.

8.4.4 Strategies for Estimating Stroke Risk

European and North American cardiovascular guidelines recommend estimating the combined risk of fatal and non-fatal heart disease and stroke, based on shared risk factors and hence common interventions. However, older adults are more apprehensive about the risk of a life-changing illness like stroke than of death (68). Elders from a variety of ethnic backgrounds report worrying more about suffering a stroke and related disability than a heart attack, and most believe these risks should be reported separately (305). This is in line with recent suggestions to improve absolute stroke risk prediction for addressing risk factors more relevant to stroke (540) such as hypertension and atrial fibrillation as discussed above.

Absolute stroke risk can be estimated either by using stroke-specific risk tools or by scaling total CVD risk predicted by composite-CVD risk tools. This thesis notes that the ability of composite-CVD tools QRISK and PCE, and stroke-specific FSRP and QStroke to predict stroke risk in older men is comparable – discrimination by all is

modest at best; calibration similar except for overestimation of risk at high predicted risk by stroke-specific tools, and competing mortality influences both by generally exaggerating overestimation. This suggests that either type of tool may be useful to predict stroke if discrimination of tools can be improved, and tools re-calibrated to reflect the stroke risk of older populations for which they will be used by means of an appropriate contemporary data set that represents a more current distribution of stroke risk factors, events and treatment practices (286). Models can also be re-estimated while accounting for competing non-stroke risks to capture true stroke risk in older age.

However, there are additional points of relevance to clinical practice. Firstly, tools differ in whether they predict the risk of all strokes or IS or TIAs. Secondly, there are currently no agreed thresholds for defining the level of absolute *stroke* risk which makes CVD free individuals, whether young or old, eligible for an intervention. Thirdly, as noted in the thesis for CVD free older men not in receipt of statins, defining them as high risk based on QRISK3 and PCE recommended CVD thresholds (10% and 7.5% respectively) results in a very high (~97%) false positive rate for stroke. The consequence of estimating stroke risk as part of broader CVD risk in this manner, alluded to in Chapter 5, then relates to misclassifying older adults as being eligible for an intervention (statin) which they might not need nor benefit from (315, 461, 462). Updated NICE guidelines recommend considering statins for those with a QRISK3 score <10% if there is a chance risk may have been underestimated which would further affect specificity in older adults (32).

Similarly poor specificity has been observed even for broader CVD outcomes when evaluating the 7.5% PCE risk threshold in 66-75y participants of the Framingham Offspring Study (500), indicating the need for selecting intervention thresholds based on age (313, 500). The importance of context in applying risk tools has also been highlighted elsewhere (541, 542). Revised European guidelines on CVD prevention take this into consideration and recommend age-specific thresholds (342). The thesis noted that false positive rates of stroke could be reduced by raising intervention thresholds while retaining reasonable sensitivity and predictive values, thereby reducing the number of men incorrectly being assigned as high risk and so unnecessarily being offered pharmacological therapy, without remarkably reducing the number that are correctly assigned as high risk, but this remains to be more

comprehensively examined. More importantly, it may be necessary to ascertain thresholds appropriate for increasing age, based on cost-effective investigations for stroke specific work-up such as carotid or cardiac imaging and interventions besides statins. Until then, clinicians should be aware of the potential of misclassification and the ever-continuing need for patient discussions on risk enhancers/modifiers (discussed further in section 8.4.6) and shared decision making.

There are no dedicated stroke risk prediction equations for SAs. Composite tools developed from Caucasian populations can underestimate stroke risk in minorities who have a greater burden of stroke (540). QStroke and QRISK3 include SA ethnic groups as predictor variables but have not been validated in independent SA cohorts. Unfortunately, SABRE follow up at 10y had insufficient stroke events for the thesis to attempt any validation in SAs and this remains an opportunity for future research.

An alternative approach proposed by the World Stroke Organization is for stroke risk to be measured on a continuum instead of classifying people arbitrarily as low or high risk. They argue this is more likely to motivate individuals at all levels of risk for changing behaviour and modifying risk factors. The Stroke Riskometer, available as a copyrighted digital application, has been approved for this purpose by World Stroke Organization and WHO (502). However, it lacks robust validation among older adults and SAs (543).

8.4.5 Strategies for Improving Stroke Risk Communication

The concept of cardiovascular risk prediction is more familiar to researchers and clinicians than many for whom this risk is being predicted. In fact many GPs report challenges in using risk assessment tools due to difficulties in interpreting them, lack of clear guidelines and applicability to their patient profiles, concerns regarding patient capacity and medicalization, and time constraints (517, 544). Among UK general practices, only around 60% of eligible patients were found to receive appropriate primary prevention treatment and guideline adherence was better in younger patients compared to those 65-74y (545).

To enable shared decision making on interventions, and for these interventions to be adopted and bring benefit, it is vital that risk communication to patients is clear and informs them all that they would wish to know. This becomes even more important for older adults, in whom balancing benefits and harms of interventions is complex, and

in whom more frequent reviews of risk are recommended (70). Decision aids (546) that make percentage numerical predicted risk easier to understand as figures, and which consider varying languages and levels of literacy are one way to mitigate this.

Knowledge of stroke risk factors has been found to be low among older adults and ethnic minority groups who are most at risk (547). Organizations such as the Stroke Association, Age UK, South Asian Health Foundation may have a role in running collaborative population specific awareness campaigns similar to World Stroke Days. As part of its 2020-2025 strategy's Predictive Prevention Priority, Public Health England also aims to increase the understanding of personal health risks, especially among disadvantaged and vulnerable groups, by using digital technology combined with behavioural science for risk communication, and to offer them personalised options for preventive interventions (548). It is hoped that stroke and stroke risk factors will be included in the chronic diseases being targeted.

Additionally, although the CVH model has not been developed for risk prediction, it has the advantage of including physical activity and diet metrics – two predictors which are generally not included in formal CVD risk equations. This is likely because they are mostly based on recall and liable to self-reporting bias, less easy to standardize and difficult to ascertain reliably during time limited routine examinations. The thesis indicates that a straightforward 0-14 CVH score can capture some degree of stroke risk among middle-aged SAs (and Europeans) and may have utility as a simpler risk communication and monitoring tool, especially if incorporated into electronic health records (283). Adapting the BMI and diet metrics in CVH to ethnic groups may further increase its relevance and accuracy (278).

8.4.6 Role of NT-proBNP in Refining Stroke Risk

The Joint British Societies' consensus recommendations for the prevention of CVD (JBS3) published in 2014 did not endorse non-invasive imaging (for measuring CIMT or CAC) or novel blood biomarkers for enhancing CVD risk estimation (330). However later European Society of Cardiology (342) and AHA/American College of Cardiology (30) guidelines include a consideration for measuring CAC to inform treatment decisions when predicted risks are around decision thresholds. The predictive value of CAC for *stroke* however is less reliable (343, 549) and it is unclear how a high CAC

finding should be managed or further evaluated with respect to stroke. Imaging for CAC is also expensive and not universally available.

In comparison, NT-proBNP, already offered as a standard clinical test for diagnosis and prognosis of HF, is safer and cheaper at £15-25 per test (550, 551). The ability of NT-proBNP in improving the specificity of global CVD risk prediction has been recognized (346). Findings from this thesis verify its ability (albeit modest) to correctly downgrade stroke risk in both older men and middle-aged SAs and suggest a potential also to upgrading stroke risk more appropriately in older adults. If confirmed more widely, this may be helpful for informing prevention therapy in SAs and especially in older adults who end up being classified as high risk just by virtue of age.

Considering the greater number of non-events in the population, downgrading the risk of even a small percentage of such individuals would translate as a large number of older adults, often already experiencing polypharmacy, not having to undergo unnecessary preventive treatment. Similarly considering stroke is a lifechanging event, higher risk assignment to even a small number of individuals who may then be more justifiably offered aggressive therapeutic or procedural interventions may help avert critical health and social care burden. However, biomarkers must go through a rigorous validation cost-effectiveness analysis and regulatory clearance before being fully implementable as part of clinical or public health practice (552). The European Society of Cardiology currently states that cardiac biomarkers hold promise for CVD risk stratification pending further research (342). Allocating funds for this may be a worthwhile policy decision (553).

8.4.7 Relevance in the context of Multimorbidity

Stroke and stroke related disability contribute to a significant burden of physical and mental multimorbidity (36). Hence findings from the thesis and strategies outlined above have a direct relevance to reducing this aspect of multimorbidity among older adults and SAs. In the context of shared risk factors between stroke and related cardiovascular conditions such as CHD, peripheral arterial disease and dementia, findings from both cohorts but especially BRHS endorse the value of adopting healthier lifestyles and improving cardiovascular health *before* older age sets in to be able to maximally delay multimorbidity. More broadly, this underscores the need and application of health and intersectoral policies that take a life-course approach to

prevention (38, 554). Further, with LS7 metrics such as smoking and obesity being linked to non-cardiovascular adverse health outcomes such as cancers, such an approach is likely to bring additional benefits for preventing a range of long-term conditions across population groups.

8.5 Future Research

Stroke remains underfunded relative to other non-communicable diseases in comparison to the burden it begets (555). And research on primary prevention of stroke is still less attractive for funding agencies even in developed countries (25). However, majority of strokes are preventable, and this thesis has attempted to inform prevention strategies for two high-risk groups. Nevertheless, limitations of data and methodology and implications of findings suggest further evidence is required, especially with regards to examining CVH, stroke risk prediction and augmentation by NT-proBNP among older and SA women. Other areas identified for research are as follows.

8.5.1 Investigating associations of the updated CVH model with Stroke

In August 2022, the CVH model was updated from a collection of Life's Simple 7 to Life's Essential 8. Sleep was added as an additional metric and measured as number of hours per night; total cholesterol was replaced by non-HDL cholesterol and smoking with nicotine exposure which additionally accounts for second hand smoke. Additionally ethnicity-specific BMI criteria for obesity were introduced; and each metric score continuously as opposed to categorical poor intermediate and ideal levels, resulting in a CVH score out of 100 that allows for more intra-individual changes to be captured (280).

Both the BRHS and SABRE cohorts used in this thesis do not measure sleep at baseline to allow for calculation of an LE8 score. But others have recently started reporting on associations of the updated model with various prospective outcomes. Using National Health and Nutrition Examination Survey data in the US, Sun et al found that 2% of cardiovascular mortality among adults 30-79y was attributable to sleep health (281). There is evidence regarding change in sleeping patterns with age (556), and variation in sleep characteristics by ethnicity (557). Research additionally

points to a U-shaped association between sleep duration and risk of stroke (558, 559) but comparisons on the burden of stroke attributable to sleep duration across age and ethnicity remain to be conducted.

Using UK Biobank data (mean age of participants 56y), Li et al (560) reported that compared to the LS7 model, LE8 was more accurate in discriminating the risk of stroke, while also observing that protective associations were stronger for those 55y or younger. It would be valuable to examine how this translates as the PAF based impact of the updated metrics, and whether this can more usefully inform stroke prevention strategies in older adults and SAs.

8.5.2 Examining Newer Models Derived for Risk Prediction in Older Adults

Most risk prediction tools have little or no data from older adults and predict the 10y risk for events. SCORE2-OP is an updated version of the original SCORE CVD risk prediction tool, derived from a Norwegian cohort of adults aged ≥ 65 y which predicts the 5 and 10y risk of composite fatal and non-fatal CVD in older adults (70y plus) while accounting for competing non-CVD deaths. The model has been calibrated for four risk regions within and outside of Europe using estimated contemporary age- and sex-specific incidences and risk factor distributions (307). External validation of SCORE2-OP was conducted by the authors in multiple prospective cohorts and pooled clinical trials data, with C-indices ranging from 0.63 to 0.67. However, independent external validation for prediction of stroke in older adults has not been reported so far. Additionally, the reported discrimination is sub-optimal even for CVD and examining the added value of biomarkers such as NT-proBNP in a tool that has been derived for old age risk prediction would greatly inform its utility for improving risk classification and clinical practice.

Further, as life expectancy decreases with age, some researchers reason that even 10y may be a relatively long timeframe for estimating risk when changes in health and hence risk may be taking place over a shorter timescale, and interventions may become inappropriate or unnecessary relatively quickly. It has been suggested that short-term (4y follow-up) risk prediction (333) to inform shorter term prevention therapies may be more appropriate for older adults. While this seems to be a practical argument, it is aligned more with prediction of broad global CVD. Whether limited follow-up can provide enough event numbers to estimate the absolute risk of stroke

as a CVD subtype as argued by this thesis remains to be examined and more evidence would be needed before short-term risk assessment for older adults can be incorporated into clinical practice.

8.5.3 Using Data from Maturing South Asian Cohorts to Confirm Impact of CVH on Stroke and for Developing a Dedicated Stroke Risk Score

In SABRE, while better overall CVH was protective against stroke risk, diet and physical activity failed to show expected associations with stroke. This may be because they were affected by self-reporting bias and/or measured in a limited manner. In particular SA diet is extremely diverse and more research on diet quality and cooking methods (such as frying and high heat cooking) that result in contaminants which can catalyse atherosclerosis has already been called for (10). Further, as acknowledged earlier (section 1.3.2), SA is a broad classification of a number of heterogeneous groups who experience a range of lifestyles and social determinants of health. And while SABRE has allowed comparisons between middle aged British Europeans and first-generation migrant SAs (mostly from India), examination of the impact of CVH and individual metrics in light of this knowledge, would be necessary in other SA groups to assess their exact value for stroke prevention for SAs widely. South Asian cohorts established a few years ago are gradually accruing enough events to allow prospective analyses to be conducted (191). In parallel, the use of electronic health records in which ethnicity recording can be improved through linkage across health care settings (95) can also be explored for more comprehensive research among SA diaspora in the West. Ideally future prospective data collections should be large and granular enough to research subgroup specific outcomes and disentangle any interactions these social determinants may have with ethnicity.

Additionally, as pointed out in Chapter 2, there are no CVD/stroke risk prediction equations specifically for SAs, and validation of currently available CVD risk tools for SAs has been very limited (327). A research priority is to use data from maturing cohorts to first validate/recalibrate currently available equations, and ideally derive de novo models. Apart from confirming the added contribution of NT-proBNP, factors such as triglycerides (209) and homocysteine (128, 561) which have been implicated as increasing the risk of CVD and stroke in SAs, also need to be examined for their role in risk prediction and/or improving risk stratification and intervention decisions.

8.5.4 Investigating the Population Preventable Fractions of Stroke

This thesis estimated the fraction of stroke attributable to poor CVH using counterfactual scenarios where all older adults or all SAs would have optimal CVH. An alternative method for estimating the proportion of an outcome that would not have occurred by reducing exposure to risk factor is the population preventable fraction, in which the counterfactual scenario assumes an 'attainable' level of risk. This risk distribution is informed by studies of effects of interventions/policies or which is pre-defined, for example that observed in a different population (562). Population preventable fraction gives a more realistic assessment of the burden of an outcome that can be averted. Considering findings from this thesis, future research can examine proportion of stroke that would be preventable in older age for example by reducing (uncontrolled) hypertension or optimising anti-coagulation for AF through interventions appropriate for or known to be effective in old age. Or, among SAs by comparing interventions that can reduce sub-optimal CVH to an achievable prevalence. Population preventable fraction can hence inform the potential impact (563) of interventions and be used in health economic analysis (e.g., cost of saving quality adjusted life years) (562) to identify cost-efficient stroke prevention among both sub-groups.

8.5.5 Validating the Stroke Riskometer Algorithm

The Stroke Riskometer Application developed by an international collaboration of stroke and IT experts, endorsed by the World Stroke Organization and European Stroke Organization, is freely available for the general public (20-90y+) to estimate their 5 or 10 y risk of stroke. Its algorithm is based on the FSRP and includes additional risk factors noted by INTERSTROKE to be important for stroke. Uniquely, this means that the algorithm includes a measure of diet and PA. The app also allows for comparison of individually estimated risk with a baseline and with others of similar age and sex who are free of stroke risk factors, and suggests possible preventive action. To my knowledge, there has been only one external validation of the algorithm, by the same researchers who developed it, which concluded that there was a continuing need to improve its performance (543), and cross-cultural prospective validation in specific ethnic groups is lacking (564). Trials assessing its effectiveness in promoting positive lifestyle changes are still emerging (565, 566), however, independent

validations of the algorithm will be extremely useful in assessing if it can accurately predict stroke risk in older adults and SAs.

8.5.6 Investigating Predictive Power of NT-proBNP for Subtypes of Stroke

Chapter 2 described how age and ethnicity are related with different proportions of stroke subtypes. Evidence points to strong associations of NT-proBNP with cardioembolic stroke (77), and recently even haemorrhagic stroke in middle-aged Europeans (76). Both BRHS and SABRE were limited by a lack of classification of stroke types, and presence/absence of associations in the two population subgroups may shed helpful light on the mechanistic relationships between NT-proBNP and stroke, and potentially be useful for informing anticoagulation decisions in older adults with heart rhythm disorders.

8.5.7 Investigating the Role of Augmenting the Natriuretic Peptide System

Neprilysin is an endogenous protein that facilitates the breakdown of NPs. Sacubitril is a pro-drug that, upon activation, acts as a neprilysin blocker leading to a prolonged duration of the favourable effects of these NPs, which in turn reduces haemodynamic stress on the heart. Use of neprilysin inhibitors has been examined in trials for treatment of heart failure (567) but effectiveness in preventing stroke related outcomes is less clear.

In addition, the positive metabolic effects of NPs include increased lipolysis (358) potentially influencing insulin resistance. In relation to the thesis finding that SAs have lower average levels of NT-proBNP than Europeans, the potential use of exogenously augmenting the NP system for cardiometabolic risk protection in SAs is also worth investigating.

8.5.8 NT-proBNP Guided Stroke Prevention Interventions

Robust associations of NT-proBNP with stroke risk in older men and middle-aged SAs are in agreement with observational studies examining NT-proBNP for monitoring cardiovascular risk (568), and for guiding intensity of hypertension treatment in those without CVD (351, 484). There exists some research supporting the use of NT-proBNP guided intervention for preventing ventricular dysfunction and cardiovascular hospitalization among those without HF (569), but randomized controlled trial based evidence on hard individual outcomes such as stroke is lacking (570), especially among SAs. The high PAF of stroke due to non-ideal BP and raised FPG (Chapter 4)

in SAs, together with an especially raised risk of stroke in those with who are hypertensive or diabetic and have NT-proBNP >100pg/ml (Chapter 6) suggests that NT-proBNP based selection of SA adults for aggressive primary prevention of stroke should be distinctly examined.

Anticoagulation for rhythm disorders to prevent ischaemic strokes is already part of clinical management, but cardioembolic (often fatal) strokes can result from emboli originating in the aging heart without manifest arrhythmias (353). As yet, anticoagulation for those who have HF but are in sinus rhythm is debatable (571). In this context, Chapter 6 noted associations of NT-proBNP reflecting age related subclinical cardiac dysfunction with stroke in older BRHS men who were free of AF and HF; and encourage exploring benefits and risks of NT-proBNP guided anticoagulation for stroke prevention in older adults without these conditions.

Additionally, TIAs are a challenge to diagnose by virtue of transient symptoms and mimics like migraine and syncope. Case-control research has recorded significantly higher mean values of NT-proBNP in cardioembolic TIAs and TIAs with non-focal symptoms (572). The observation that NT-proBNP can predict TIAs over long term supports further research into its role as an aid in TIA diagnosis, and hence prompt preventive management of stroke, especially in resource poor settings.

8.5.9 Net Benefit Analyses for the Utility of NT-proBNP in Augmenting Stroke Risk Classification

Beyond measuring prediction model performance as C-indices, sensitivity/specificity or NRI when a new predictor such as NT-proBNP is added to traditional risk factors, the *clinical utility* of the (new vs the base) model should also be assessed (71). This is done through decision analytic techniques which ‘incorporate the clinical consequences of using a model’ by applying a ‘an exchange rate’ – or trade-off between misclassifying a case (false negative – which leads to morbidity or mortality) and non-case (false positive - which leads to unnecessary treatment or testing) (573). This trade-off is related to the threshold for carrying out or offering an intervention, which is itself based on ethical, health and financial costs of intervening. The net benefit of using a particular model which is the comparison of benefits and risks of decisions, can then be estimated by

$$Net\ Benefit = \frac{True\ Positive}{Total\ N} - \frac{False\ Positive}{Total\ N} \times \frac{Threshold}{1 - Threshold}$$

Further research is therefore needed to compare the net benefit between traditional and NT-proBNP based models, using data with equal representation from men and women both among older and SA populations. Because current clinical practice makes use of composite-CVD risk assessment, examining the net benefit of extending PCE, QRISK3 and SCORE2 equations with NT-proBNP for stroke risk prediction would be a logical next step.

Comparison of net benefit between NT-proBNP based models with models incorporating imaging reliant markers such as CAC, and other candidate blood biomarker such as Troponins and Lp(a), will be further needed to guide choice of biomarker measurement.

8.5.10 The Role of Artificial Intelligence and Electronic Health Records in Improving Stroke Risk Stratification.

The use of machine learning to infer stroke diagnosis and post stroke outcomes from images has already been examined (574). Evidence also indicates that machine learning models may be able to improve on traditional statistical techniques that are currently used to predict future stroke risk (575). This is because where statistical models may be limited in handling multi-dimensional data, artificial intelligence and machine learning techniques may be used to create risk prediction models that incorporate for e.g. not just blood biomarkers such as serial NT-proBNP (dynamic risk), but information from other modalities such as imaging and electrocardiography, as well as their interactions with time (575, 576).

However, before machine learning based models can be employed in routine clinical practice to guide prevention and management of stroke, robust algorithms need to be developed, validated and made available as efficient user-friendly interfaces. Optimal algorithms will however only be developed when data representative of all those patient populations for whom these algorithms will be making predictions is used to train and test them (95). The availability of electronic health records that link demographically diverse patient profiles across primary and secondary care may allow information on a wide range of clinical and non-clinical predictors and

stroke/related outcomes to be analysed as part of longitudinal health journeys by machine learning. Comparisons between existing statistical and artificial intelligence models will then have to be conducted to establish performance metrics, net benefit and improvement in clinical outcomes (575).

8.7 Concluding Statement

This doctoral research provides new evidence regarding the usefulness of the cardiovascular health model as a population-level approach to stroke prevention in CVD free older adults and middle-aged South Asians; the accuracy of individual risk assessment, and whether this could be improved using a commonly available natriuretic peptide marker of cardiac dysfunction.

The thesis shows that population-level approaches for primary prevention of stroke based on the CVH model may not be universally beneficial across adult life, and older adults need comprehensive strategies which focus on controlling high BP and on causes beyond traditional risk factors. Individual stroke risk assessment among older adults, whether by stroke-specific or composite-CVD risk prediction tools, lacks good discrimination and requires consideration of age-appropriate high-risk thresholds. Misclassification of older adults at low risk could be reduced by incorporating NT-proBNP in risk assessment tools if formal clinical utility can be established above and beyond traditional models. Use of NT-proBNP in guiding management of BP and selecting older adults for more intensive work up of stroke risk needs further examination.

For middle-aged SAs, the thesis notes the CVH model to be as useful a population-level stroke prevention approach as for Europeans, while highlighting BP, glucose levels and BMI as being key contributors and hence key factors for public health programs to focus on. As in other ethnic groups, NT-proBNP is observed to be a robust independent marker of stroke risk in SAs. Therefore, until stroke risk prediction tools can be validated and ideally developed specifically for SAs, the role of NT-proBNP in improving stroke risk prediction in SAs, in particular downgrading those classified as false positive; as well as directing risk factor management needs to be further assessed.

As older adults and SAs continue to experience a steadily increasing absolute number of stroke events, findings from this thesis can hopefully strengthen and refine primary prevention efforts, as well as inform stroke prevention research, for reducing stroke related morbidity and mortality among both groups.

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Appendix 2

Appendix 2.1: Search Terms for Literature Review

Population	Burden/Exposure/Risk Tool	Outcome
Old* Elder* Ageing Aging Ethnic* Rac* South Asia* India* Pakistan* Bangladesh* Punjab*	Incidence Prevalence Risk factor* Impact life* simple 7 LS7 cardiovascular health American Heart Association AHA bnp pro-brain natriuretic peptide natriuretic Natriuretic peptide NT-proBNP ntprobnp Risk QRISK* QSTROKE Framingham Pooled cohort equations PCE score	cardiovascular acute cerebrovascular accident cerebrovascular cerebral small vessel disease/or “intracranial embolism or thrombosis”/ or intracranial hemorrhages stroke TIA transient ischemic attack perform* validat* predict*

Appendix 3

Appendix 3.1: BRHS baseline 1978-80 Q1 Recruitment Questionnaire

1			
Serial Number			1
Card Number			9
Date of Screening			11
Time of Screening			17

1. <u>GENERAL</u>			
What is your date of birth?	Day		21
	Month		23
	Year	19	25
Where were you born?	Town		
	County		
	Country		

1.2	How many years have you lived within 10 miles of this town? If you have moved to this area <u>within the last five years</u> , where did you move from?		27
		years	

1.3	What is your marital status?		
	Single	1	
	Married	2	
	Widowed	3	29
	Other	4	

1.4	How many children do you have?		
	<5 yrs		30
	5-10 yrs.		32
	11-16 yrs.		34
	> 16 yrs.		36

2 <u>YOUR FATHER</u>			
2.1	Where was your Father born?		
	Town		
	County		
	Country		
2.2	Is your father alive? (Y/N)		38
2.3	How old is he now? / How old was he when he died?		39
		years	

2.4	If your father has died, what were you told was the cause of his death?			
	Heart trouble	1		41
	High blood pressure	2		
	Stroke	3		
	Respiratory disease	4		
	Cancer of lung	5		
	Other cancer	6		
	Accident or injury	7		
	Other	8		
	Don't know	9		
3	<u>YOUR MOTHER</u>			
3.1	Where was your mother born?			
	Town			
	County			
	Country			
3.2	Is your mother alive? (Y/N)			42
3.3	How old is she now? / How old was she when she died?		years	43
3.4	If your mother has died, what were you told was the cause of her death?			
	Heart trouble	1		45
	High blood pressure	2		
	Stroke	3		
	Respiratory disease	4		
	Cancer of breast	5		
	Other cancer	6		
	Accident or injury	7		
	Other	8		
	Don't know	9		
4.	<u>OCCUPATION</u>			
4.1	What is your present job?			
	If employed go to question 4.4			
4.2	If you are unemployed, for how long has this been?			
	<8weeks	1		46
	8wk.-5mo.	2		
	6mo. -1yr.	3		
	> 1 year	4		

APPENDIX 4

4.3	Is this because of ill health? (Y/N)	☐	47
4.4	What kind of work have you done for the longest period of time?		
4.5	What business or industry is this?		
4.6	How many years have you done this kind of work?		years 48
4.7	Are / were you:		
	SELF-EMPLOYED with 25 or more employees	1	
	with less than 25 employees	2	
	without employees	3	
	MANAGER of 25 or more people	4	☐ 50
	of less than 25 people	5	
	FOREMAN	6	
	ORDINARY EMPLOYEE	7	
	ARMED SERVICES	8	
5	<u>SEVERE CHEST PAIN</u>		
5.1	Have you <u>ever</u> had a <u>severe</u> pain in your chest lasting for half an hour or more? (Y/N) <u>If NO, go to question 6.</u>	☐	51
5.2	Where did you get this severe pain? (Show chart.)	 	52
5.3	Did you see a doctor because of this pain? (Y/N)	☐	55
6	<u>CHEST PAIN</u>		
6.1	Do you ever have any pain or discomfort in your chest? (Y/N) <u>If NO, go to question 7.</u>	☐	56
6.2	When last did you get the pain?		
	Within 1 month	1	
	1-5 months ago	2	☐ 57
	6-12 months ago	3	
	Over 1 year ago	4	
	Occasionally	5	

6.3	How often do you get it?	Daily	1		58
		Weekly	2		
		Monthly	3		
		Once only	4		
		Occasionally	5		
6.4	Where do you get this pain or discomfort? (Show chart.)				59
6.5	When you walk at an ordinary pace on the level, does this produce the pain? (Y/N)				62
6.6	When you walk uphill or hurry, does this produce the pain? (Y/N)				63
6.7	When you get any pain or discomfort in your chest on walking, what do you do?	Stop	1		64
		Slow down	2		
		Continue at the same pace	3		
6.8	Does the pain or discomfort in your chest go away if you stand still? (Y/N)				65
6.9	How long does it take to go away?	10 minutes or less	1		66
		more than 10 minutes	2		
7.0	<u>PHLEGM, COUGH AND BREATHING</u>				
7.1	Do you usually bring up phlegm (spit) from your chest first thing in the morning in the winter? (Y/N)				67
	<u>If NO, go to question 7.4</u>				
7.2	Do you bring up phlegm like this on most days for as much as 3 months in the winter each year? (Y/N)				68
7.3	In the past 3 years have you ever had a period of increased cough and phlegm lasting 3 weeks or more?	Yes, once	1		66
		Yes, twice or more	2		
		Never	3		
7.4	Does your chest sound wheezy or whistling on most days (or nights)? (Y/N)				70

7.5	Does the weather affect your breathing? And if so, at what season of the year is it most affected?		
	Not affected 1	☐	71
	Winter 2		
	Summer 3		
	Both 4		
8	<u>BREATHLESSNESS</u>		
8.1	Do you get short of breath walking with people your own age on level ground? (Y/N)	☐	72
8.2	On walking up hills or stairs, do you get more breathless than people you on age? (Y/N)	☐	73
8.3	Do you ever have to stop walking because of breathlessness? (Y/N)	☐	74
		S.E.G.	☐ ☐ 75
		Social class	☐ 77
		Activity score	☐ 78

APPENDIX 4

6

Serial Number

Card Number

0	2

9		<u>LEG PAIN</u>		
9.1	Do you ever get pain in your calf muscles on walking at an ordinary pace, on the level? (Y/N)		☐	11
9.2	Do you get pain in your calf muscles when you walk uphill or hurry? (Y/N)		☐	12
10		<u>MEDICAL HISTORY</u>		
10.1	Have you ever been told by a doctor that you have, or have had, any of the following?			
	Angina	(Y/N)	☐	13
	Heart attack	(Y/N)	☐	14
	Coronary thrombosis	(Y/N)	☐	15
	Myocardial infarction	(Y/N)	☐	16
	Other heart trouble	(Y/N)	☐	17
	High blood pressure	(Y/N)	☐	18
	Stroke	(Y/N)	☐	19
	Diabetes	(Y/N)	☐	20
	Peptic ulcer	(Y/N)	☐	21
	Gout	(Y/N)	☐	22
	Gall bladder disease	(Y/N)	☐	23
	Thyroid disease	(Y/N)	☐	24
	Arthritis	(Y/N)	☐	25
	Bronchitis	(Y/N)	☐	26
	Asthma	(Y/N)	☐	27
	Other condition (s)			
	including surgery.....	(Y/N)	☐	28
10.2	Are you on any regular medical treatment from a doctor for any condition? (Y/N)		☐	29
<u>If NO, go to question 10.3</u>				
Do you know if the pills / medicines /injections are:-				
	Tranquillizers	Y/N	☐	30
	Pain killers	Y/N	☐	31
	Antihypertensive drugs	Y/N	☐	32
	Anti coagulants	Y/N	☐	33
	Lipid lowering drugs	Y/N	☐	34

APPENDIX 4

	Oral antidiabetics	Y/N	☐	35
	Injection of insulin	Y/N	☐	36
	Any others	Y/N	☐	37
	Don't know	Y/N	☐	38
10.3	Have you taken any of these in the last 48 hours?			
	Tranquillizers	Y/N	☐	39
	Pain killers	Y/N	☐	40
	Antihypertensive drugs	Y/N	☐	41
	Anti coagulants	Y/N	☐	42
	Lipid lowering drugs	Y/N	☐	43
	Oral antidiabetics	Y/N	☐	44
	Injection of insulin	Y/N	☐	45
	Any others	Y/N	☐	46
	Don't know	Y/N	☐	47
11	<u>DIET & ALCOHOL</u>			
11.1	How many times during an average week would you have the following foods?			
	Meat (including beef, lamb, pork, bacon in any form)		☐	48
	Chicken		☐	50
	Fish		☐	52
	Eggs - how many eggs do you eat in a week		☐	54
	Cheese - how often do you eat cheese, including cheese dishes?		☐	56
	Breakfast cereals - how often do you eat these (porridge included)? State kind		☐	58
11.2	What kinds of bread do you eat ?			
	White	Y/N	☐	60
	Brown	Y/N	☐	61
	Wholemeal	Y/N	☐	62
	Other	Y/N	☐	63
11.3	Spreading fats: What kinds do you use at home?			
	Butter	Y/N	☐	64
	Margarine	Y/N	☐	65
	(State kind or brand name.)			
11.4	Do you take sugar?			
	In tea	Y/N	☐	66
	In coffee	Y/N	☐	67
	In other drinks	Y/N	☐	68

11.5 Do you use milk?				
	On cereals	Y/N	☐	69
	In tea	Y/N	☐	70
	In coffee	Y/N	☐	71
	As a milk drink	Y/N	☐	72
11.6 (i)	Would you describe your present alcohol intake as:			
	None	1		
	On special occasions only	2		
	Once or twice a month	3	☐	73
	Weekends	4		
	Daily / most days	5		
	<u>If NONE, go to question 12</u>			
(ii)	What type of drink do you usually take?			
	Beer	1		
	Spirits	2		
	Wine/sherry	3	☐	74
	Mixed beer & spirits	4		
	Mixed beer, spirits, wine and sherry	5		
(iii)	How much do you usually take?			
	2 drinks a day or less	1		
	3-6 drinks a day	2		
	more than 6 drinks a day	3	☐	75
(One drink is a single whisky, gin or brandy, a glass of wine, sherry or port or half a pint of beer.)				

Serial Number

Card Number

0	3

12 <u>SMOKING</u>			
12.1	(i) Do you smoke at present?		
	Yes, regularly	1	
	No	2	11
	Occasionally	3	
	<u>If NO, go to question 12.6</u>		
	(ii) How old were you when you started?		12
			years
	(iii) Have you ever given up smoking? (Y/N)		14
	(iv) If yes, what is the maximum time for which you have given up smoking?		15
			years
12.2	(i) Do you smoke cigarettes now?		
	Yes regularly	1	
	No	2	17
	Occasionally (<1 day)	3	
	<u>If NO, or OCCASIONALLY go to question 12.3</u>		
	(ii) How many cigarettes do you usually smoke a day?		18
	(iii) If hand rolled, how much tobacco do you use a week? (ozs.)		20
			ozs.
	<u>Now proceed to 12.4</u>		
12.3	(i) Were you previously a regular cigarette smoker? (Y/N)		22
	(ii) If Yes, how many cigarettes did you usually smoke a day?		23
	(iii) At what age did you change to a pipe and / or cigars?		25
			years
12.4	(i) Do you smoke a pipe now?		
	Yes regularly	1	
	No	2	27
	Occasionally	3	
	<u>If NO or OCCASIONALLY go to question 12</u>		
	(ii) If YES, how many ozs. a week do you smoke?		20
			ozs.
12.5	(i) Do you smoke a pipe now?		
	Yes regularly	1	
	No	2	30
	Occasionally	3	
	(ii) If YES, how many cigars do you smoke a day?		31
			Large
			Small
	<u>If you smoke ANYTHING currently, go to question 13.</u>		

12.6	(i)	Have you ever smoked for a more than 1 month ? (Y/N)	☐	35
		How much did you <u>usually</u> smoke		
		Cigarettes (per day)	☐	36
		Pipe (ozs) (per week)	☐	38
		Cigars (per day)	☐	40
			☐	42
			Large	
			Small	
		<u>If NO, go to question 13.</u>		
	(ii)	At what age did you start smoking?		44
			years	
	(iii)	At what age did you finally stop smoking?		46
			years	
	(iv)	What was the maximum time between these two ages for which you gave up smoking?		48
			years	
13	<u>EXERCISE</u>			
13.1	(i)	Do you usually walk or cycle in the course of your journeys to or from work each day?		
		No	1	
		Walk	2	☐
		Cycle	3	50
		If YES, how many minutes do these journeys take?		
			mins	51
	(ii)	Apart from your journeys to or from work, do you usually walk or cycle on weekdays?		
		No	1	
		Walk	2	☐
		Cycle	3	50
		If YES, how many minutes do you walk/cycle each day?		
			mins	51
	(iii)	Would you say that in your occupation you are physically :		
		Very active	1	
		Fairly active	2	
		Average	3	☐
		Fairly inactive	4	56
		Very inactive	5	
13.2		On average, a man of your age spends 4 hours on most weekends on some of the following activities: walking, gardening, household chores, DIY projects. Compared to such a man, how physically active do you consider yourself?		
		Very active	1	
		Fairly active	2	
		Average	3	☐
		Fairly inactive	4	57
		Very inactive	5	

13.3	Apart from these activities, do you take active physical exercise, e.g. running, digging, swimming, tennis, golf, sailing, etc.			
	No	1		
	Occasionally	2		58
	Frequently	3		
	<u>If NO or Occasionally – stop here.</u>			
13.4	Please state type of activity.....			
13.5	How many years have you been involved in this activity?		 years	59
13.6	How many times a month (on average) do you undertake these activities?			
	Winter			61
	Summer			63
	Administrator			65
	Coder			66

Appendix 3.2: BRHS Q1 Physical Exam Data Collection Form

British Regional Heart Study (BRHS) **APPENDIX 5**
1978-80 Baseline physical examination data collection form

Physical and Physiological Measurements

			Serial Number								
			Card Number	11							
			Units	Obs Measurement							
	Height	mms.									11
	Weight	1/10 kgms.									16
(1)	Blood pressure	S ₁ mmHg									20
		D _s									23
(2)	Blood pressure	S ₁ mmHg									26
		D _s									29
(1)	FVC	cl									32
	FEV1	cl									35
(2)	FVC	cl									38
	FEV1	cl									41
	Pulse Rate	per min									44

Appendices

Appendix 3.3: List of morbidity events obtained from BRHS Participating Practices.

BRHS - Major morbidity events recorded from the GP Record Review.

Event	Year when data collection of events commenced*	BRHS Event Code
Myocardial Infarction (MI)	1978	1
Angina	1978	2
Stroke	1978	3
Transient Ischemic Attack (TIA)	1978	4
Coronary Artery Bypass Graft (CABG)	1983	5
Percutaneous Transluminal Coronary Angioplasty, (PTCA)	1983	7
Diabetes	1988	6
Heart Failure (HF)	1996	D
Cancer	1996	8
Peripheral Vascular Disease (PVD)	1998	A
Deep Vein Thrombosis (DVT)	2000	B
Pulmonary Embolism (PE)	2000	C
Abdominal Aortic Aneurysm	2000	X
Atrial Fibrillation	2014	G
Dementia	2014	
Dementia - Type not known		H0
Dementia - Vascular		H1
Dementia - Alzheimers		H2
Dementia - Mixed Typed		H3
Dementia - Lewy Body		H4
Dementia - Parkinsons Disease		H5
Dementia - Alcohol Related		H6
Dementia - Other Type		H8
COVID-19	2020	Z
Frailty	2020	

*This is the year when data collection commenced and continued prospectively – events that occurred prior to this year were collected retrospectively.

Appendices

Appendix 3.4: BRHS Sample GP Record Review Form

BRHS (men) Record Review 2018 1

Serial No: _____
 Name: _____
 Address: _____
 DOB: _____
 NHS No: _____

New address:

Please tick if address is correct ☐

THE QUESTIONS ON THIS PAGE RELATE TO THE PERIOD FROM 1ST JANUARY 2017 TO DATE

		YES	NO	
1	Is the above patient still registered with you?	☐	☐	
2	Has he consulted you since 1st January 2017?	☐	☐	
3	Was any consultation for a new episode of:	YES	NO	(day, month, year)
	Myocardial Infarction (MI) Heart attack, Coronary thrombosis	☐	☐	Date:
	Acute Coronary Syndrome	☐	☐	Date:
	Angina Exertional or stress related chest pain	☐	☐	Date:*
	Stroke Cerebrovascular accident (CVA), cerebral thrombosis, haemorrhage, embolism	☐	☐	Date:
	Transient Ischaemic Attack (TIA) Cerebrovascular disturbance (<24 hours); leaving no residual damage	☐	☐	Date:*
	Diabetes (NIDDM Type 2 / IDDM Type 1)	☐	☐	Date:*
	Heart Failure Congestive Cardiac Failure - (CCF) or Left Ventricular Failure - (LVF)	☐	☐	Date:
	Other Cardiovascular disease:			
	Peripheral Arterial Disease (PAD, PVD) Intermittent claudication, lower limb ischaemia	☐	☐	Date:*
	Aortic Aneurysm rupture, dissection	☐	☐	Date:*
	Deep Vein Thrombosis (DVT) blood clot in the leg	☐	☐	Date:
	Pulmonary Embolism (PE) blood clot in the lung	☐	☐	Date:
	* If Yes, please send a copy of the hospital letter or discharge summary			
		YES	NO	
4	Has he been referred to a Consultant for any new cardiovascular condition?	☐	☐	Date:*
	Diagnosis :			
5	Have any of the following procedures taken place:	YES	NO	
	Coronary Artery Bypass Graft (CABG)	☐	☐	Date:*
	Coronary Angioplasty (PTCA) Percutaneous coronary angioplasty, balloon treatment. Insertion of stents ☐	☐	☐	Date:*
6	Has he had a Cancer diagnosis?	☐	☐	Date:*
	Site:			
7	Has there been a diagnosis of:	YES	NO	
	Atrial Fibrillation	☐	☐	Date:*
	Dementia	☐	☐	Date:*
	If yes, please give details of the type of dementia:-			
	Vascular dementia	☐		
	Alzheimer's disease	☐		
	Other, please give details	☐		*
	Dementia type not known	☐		

Appendices

Appendix 3.5: BRHS Stroke Validation Form

VALIDATION FORM: STROKE

Study No:	
Name:	
Address:	
DOB:	
NHS:	

Dear Doctor,

Thank you for supplying information on the above patient who took part in the British Regional Heart Study. We note that he has had a major CVA event recently and would be most grateful if you could complete the following brief enquiry to provide documentation for our record, OR send us a photocopy of the hospital letter or discharge summary. This information is critical for the validation of our case criteria.

RE: STROKE		Date of Event		
1.	Did signs/symptoms last for longer than 24 hours?	Yes ☐ 1	No ☐ 2	Don't Know ☐ 3
2.	Did he have definite hemiparesis or hemiplegia? (weakness affecting one side on the body)	☐ 1	☐ 2	☐ 3
2.1	If No, how did he present?			
3.	Did he have a CT/MRI scan?	Yes ☐	No ☐	Don't Know ☐
3.1	If Yes, what was the CT/MRI Scan result?			
	Ischaemic stroke	☐ 1		
	Haemorrhagic stroke	☐ 2		
	Normal scan	☐ 3		
	Other pathology, not a stroke	☐ 4		
	Results unavailable / Not known	☐ 5		
4.	What was the final diagnosis?			
	Ischaemic stroke	☐ 1		
	Haemorrhagic stroke	☐ 2		
	Subarachnoid haemorrhage	☐ 3		
	Stroke of uncertain pathological type	☐ 4		
	Not a stroke at all	☐ 5		
	Possible stroke	☐ 6		
	Transient Ischaemic Attack	☐ 7		
	Aneurysm/ Arteriovenous malformation	☐ 8		
	Vascular Dementia	☐ 9		
	Chronic Cerebrovascular Disease	☐ 10		
	Subdural Haematoma	☐ 11		
5.	Was he admitted to hospital?	Yes ☐	No ☐	Don't Know ☐

We are extremely grateful for the co-operation we have received from so many GPs and hope to provide valuable information for the treatment and prevention of strokes in the future.

Yours sincerely



Prof Peter H Whincup
Professor of cardiovascular Epidemiology

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UCL Medical School, Royal Free Campus, Rowland Hill Street, London NW3 2PF.
Tel: 020 7830 2335 Fax: 020 7794 1224 Email: l.lennon@ucl.ac.uk

BRHS STROKE CONFIRMATION: CODING SCHEDULE

Q2.1	<u>Other presentations</u>	
	One sided weakness	1
	One sided visual loss (homonymous hemianopia)	2
	One sided sensory loss	3
	Dysphasia	4
	Weakness/inco-ordination (non specific)	5
	Visual symptoms (non specific)	6
	Sensory symptoms (non specific)	7
	Dizziness/ Vertigo	8
	Confusion/collapse/Seizure	9
	Headache	10
	Cognitive decline/ Dementia	11
	Other	12

Appendix 3.6: BRHS Q20 Nurse Administered Main Questionnaire

BRITISH REGIONAL HEART STUDY
20 YEAR FOLLOW-UP SURVEY

Thank you for your help.

Stroke		Yes	No	Year of first diagnosis
3.0	Have you ever been told by a doctor that you have had a stroke ?	☐	☐	19
(a)	If Yes, did the symptoms last for more than 24 hours ?	☐	☐	

Appendices

Cancer

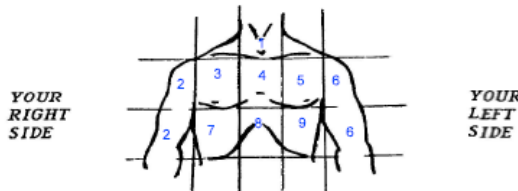
- 4.0 Have you **ever** been told by a doctor that you have or have had Cancer? Yes ☐ No ☐ q20q4_0
- If Yes, please give the following information:-**
- (a) Cancer Site q20q4_0a Year first diagnosed 19 q20q4_0a_y

Diabetes

Please answer all the questions

- 5.0 Have any of your close 'blood' relatives (your parents, brothers or sisters) **ever** had diabetes? Yes ☐ No ☐ q20q5_0
- If Yes, please list any of these relatives who have had diabetes and if possible their age when they were first diagnosed:**
- (a) Mother q20q5_a_y
- (b) Father q20q5_b_y
- (c) Brothers q20q5_c q20q5_c_y ☐ ☐ ☐
- (d) Sisters q20q5_d q20q5_d_y ☐ ☐ ☐
- 5.1 Have you **ever** been told by a doctor that you have (or have had) diabetes? Yes ☐ No ☐ q20q5_1
- (a) **If Yes, in what year was your diabetes first diagnosed?** 19 q20q5_1a

Chest pain

- 6.0 Do you ever have any pain or discomfort in your chest? q20q6_0
- Yes ☐
- No ☐ → If No, go to Question 7.0 on the next page
- 6.1 Do you know the cause of the pain? Yes ☐ No ☐ q20q6_1
- (a) **If Yes, please state:** q20q6_1a
- (b) Where do you get this pain or discomfort?
- Please mark X on the appropriate places
- 
- q20q6_1b_1
q20q6_1b_2
q20q6_1b_3
- Codes 4 5 8 are given priority ☐ ☐ ☐
- (c) When you walk at an ordinary pace on the level does this produce the chest pain?
- Yes ☐ q20q6_1c
- No ☐
- Unable to walk on level ☐
- (d) When you walk uphill or hurry does this produce the chest pain?
- Yes ☐ q20q6_1d
- No ☐
- Unable to walk on level ☐

Appendices

Chest pain continued

(e) When you get any pain or discomfort in your chest on walking, what do you do?

- Yes ☐_1
 No ☐_2
 Continue at the same pace ☐_3

q20q6_1e

(f) Does the pain or discomfort in your chest go away if you stand still? Yes ☐_1 No ☐_2

q20q6_1f

(g) How long does it take to go away? 10 minutes or less ☐_1
 More than 10 minutes ☐_2

q20q6_1g

(h) Overall is the chest pain
 Becoming more frequent ☐_1
 Staying about the same ☐_2
 Becoming less frequent ☐_3

q20q6_1h

Previous Chest Pain

7.0 Have you previously had chest pain, which has stopped because of an operation?

- Yes ☐_1 No ☐_2

q20q7_0

(a) If Yes, please give details:

OFFICE USE
 q20q7_0a ☐

Severe chest pain

8.0 Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

Yes ☐_1 No ☐_2 → If No, go to question 9.0 on the next page

q20q8_0

(a) If Yes, what year did this happen? 19_____

q20q8_0a

(b) Did you see a doctor because of this pain? Yes ☐_1 No ☐_2

q20q8_0b

(c) If Yes, what were you told was the cause _____

OFFICE USE
 q20q8_0c

Leg pain

9.0 Do you get pain or discomfort in your leg (or legs) when you walk? q20q9_0

Yes ☐_1
 No ☐_2
 Unable to walk ☐_3

→ If No or Unable to walk, go to question 10.0, on the next page

9.1 Do you know the cause of the pain? q20q9_1

(a) If Yes, please state: -

Yes ☐_1 No ☐_2

OFFICE USE

q20q9_1a ☐

(b) Does this pain ever begin when you are standing still or sitting? Yes ☐_1 No ☐_2

q20q9_1b

(c) Do you get the pain if you walk uphill or hurry?

Yes ☐_1
 No ☐_2
 Unable to walk ☐_3

q20q9_1c

(d) Do you get the pain walking at an ordinary pace on the level?

Yes ☐_1
 No ☐_2
 Unable to walk ☐_3

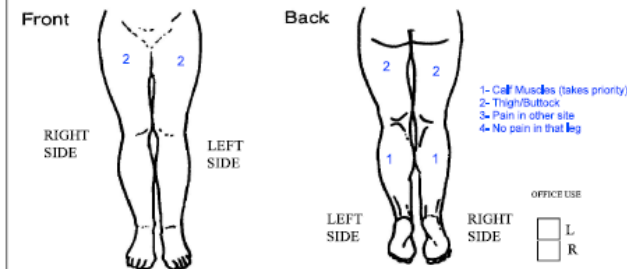
q20q9_1d

(e) What happens to the pain if you stand still?

Usually continues more than 10 minutes ☐_1
 Usually disappears in 10 minutes or less ☐_2

q20q9_1e

(f) Please mark on the diagram below where you get the pain.



q20q9_1f_l

q20q9_1f_r

Appendices

Smoking

10.0 Have you **ever** smoked cigarettes regularly (at least 1 a day) ?

Yes ☐_1
No ☐_2 → If **No**, go to question 10.3 below

q20q10_0

10.1 Do you smoke cigarettes at present?

Yes ☐_1
No ☐_2

q20q10_1

(a) If **Yes**, how many cigarettes do you smoke a day at present ?

q20q10_1a_d

(If hand-rolled, how much tobacco do you use a week ?

oz / q20q10_1a_oz

grams) q20q10_1a_gr

(b) If **No**, at what age did you give up ?

years q20q10_1b

10.2 Have you changed your cigarette smoking habits over the last three years ?

No ☐_1
Yes, increased ☐_2
Yes, decreased ☐_3
Yes, given up ☐_4

q20q10_2

Pipe & Cigar Smoking

10.3 Have you **ever** regularly smoked a pipe ?

Yes ☐ No ☐

q20q10_3

(a) If **Yes**, do you currently smoke a pipe ?

Yes ☐ No ☐

q20q10_3a

(b) If **Yes**, how much tobacco do you smoke per week?

oz / q20q10_3b_oz
 grams q20q10_3b_gr

10.4 Have you **ever** regularly smoked cigars ?

Yes ☐_1
No ☐_2 → If **No**, go to question 10.5 below

q20q10_4

(a) If **Yes**, do you currently smoke cigars ? Yes ☐ No ☐

q20q10_4a

(b) If **Yes**, how many cigars do you smoke per week ?

q20q10_4b

Other exposure to Cigarette smoke

10.5 Does your wife / partner smoke cigarettes ?

Yes ☐_1 → Number per day
Ex -Smoker ☐_2
No ☐_3
Does not apply ☐_4

q20q10_5

q20q10_5a

10.6 For about how many hours each day are you exposed to other people's cigarette smoke ?

(a) at home (hours)

q20q10_6a

(b) outside the home (hours)

q20q10_6b

(c) Tick here if rarely exposed to cigarette smoke ☐_1

q20q10_6c

Appendices

Alcohol			
11.0	Would you describe your present alcohol intake as	☐ Daily/most days ☐ Weekends only ☐ Occasionally (once or twice a month) ☐ Special occasions only ☐ None	q20q11_0
One drink is HALF a pint of beer /cider, a SINGLE whisky, gin, etc. or ONE GLASS of wine or sherry			
11.1	How much do you usually drink on the days when you drink alcohol ?	☐ More than 6 drinks ☐ 3-6 drinks ☐ 1-2 drinks ☐ None	q20q11_1
11.2	How many alcoholic drinks do you have during an average week ?		q20q11_2
11.3	What type of drink do you usually take?	☐ Beers, Lagers ☐ Wines, Sherry ☐ Spirits ☐ Variety of Beers, Wines or Spirits ☐ Low alcohol drinks	q20q11_3
(a)	Do you drink	Yes ☐ No ☐ If Yes, glasses per week	q20q11_3a_w q20q11_3a_wx
	red wine ?	☐ Yes ☐ No ☐ If Yes, glasses per week	q20q11_3a_r q20q11_3a_rx
11.4	Is the alcohol which you drink usually taken (tick whichever applies) :-	☐ before meals ☐ with meals ☐ after meals ☐ separate from meals	q20q11_4_1 q20q11_4_2 q20q11_4_3 q20q11_4_4
11.5	Have you changed your alcohol intake in the last three years?	☐ No ☐ Yes, increased ☐ Yes, cut down ☐ Yes, given up	q20q11_5
11.6	If you have CUT DOWN or GIVEN UP Was this due to (tick which ever apply):-	☐ Personal choice ☐ Doctor's advice ☐ Illness or ill health ☐ Health precaution ☐ Being on medication ☐ Financial reasons ☐ Other	q20q11_6_1 q20q11_6_2 q20q11_6_3 q20q11_6_4 q20q11_6_5 q20q11_6_6 q20q11_6_7

Physical Activity			
12.0	Do you make regular journeys every day or most days either walking or cycling ?	☐ No ☐ Walk ☐ Cycle ☐ Both	q20q12_0
12.1	How long do you spend on all forms of walking in an average week ?	hours	q20q12_1
12.2	Which of the following best describes your usual walking pace	☐ Slow ☐ Steady average ☐ Fairly brisk ☐ Fast (at least 4 mph)	q20q12_2
12.3	How long do you spend cycling in an average week ?	hours	q20q12_3
12.4	Compared with a man who spends four hours on most weekends on activities such as: walking, gardening, household chores, DIY projects, how physically active would you consider yourself?	☐ Much more active ☐ More active ☐ Similar ☐ Less active ☐ Much less active	q20q12_4
12.5	Do you take active physical exercise such as running, swimming, dancing, golf, tennis, squash, jogging, bowls, cycling, hiking, etc.?	☐ No ☐ Occasionally (less than once a month) ☐ Frequently (once a month or more)	q20q12_5
(a)	If you ticked frequently please state type of activities :		OFFICE USE q20q12_5a
(b)	How many years have you been engaged in these sort of physical activities ?		q20q12_5b
(c)	How many times a month (on average) do you take part in these activities (give overall total)?	In winter In summer	q20q12_5c_w q20q12_5c_s

Appendices

Your Health Overall

Please indicate which statements best describe your health **TODAY**
(Do not tick **more than one** box in each group)

13.0 General Health:- Excellent ☐_1 q20q13_0
Good ☐_2
Fair ☐_3
Poor ☐_4

13.1 Pain / Discomfort:- I have no pain or discomfort ☐_1 q20q13_1
I have moderate pain or discomfort ☐_2
I have extreme pain or discomfort ☐_3

13.2 Usual Activities (e.g. work, study, housework, family or leisure activities):-
I have no problems with performing my usual activities ☐_1 q20q13_2
I have some problems with performing my usual activities ☐_2
I am unable to perform my usual activities ☐_3

13.3 Self Care:- I have no problems with washing and dressing ☐_1 q20q13_3
I have some problems with washing and dressing myself ☐_2
I am unable to wash or dress myself ☐_3

13.4 Mobility:- I have no problems in walking about ☐_1 q20q13_4
I have some problems in walking about ☐_2
I am confined to a chair / wheelchair ☐_3

13.5 Anxiety /Depression:-
I am not anxious or depressed ☐_1 q20q13_5
I am moderately anxious and /or depressed ☐_2
I am extremely anxious and /or depressed ☐_3

13.6 Your Memory:- compared to five years ago, is your memory
improved ☐_1
the same ☐_2 q20q13_6
almost as good ☐_3
worse ☐_4
much worse ☐_5

13.7 Health Scale

We have drawn a health scale (rather like a thermometer) on which perfect health is 100 and very poor health is 0. Please put a cross (X) on the scale to reflect how good or bad your health is today.

Worst Imaginable Health State 0 10 20 30 40 50 60 70 80 90 100 Best Imaginable Health State q20q13_7 OFFICE USE

Disability

14.0 Do you have any long-standing illness, disability or infirmity ? Yes No
☐ ☐ q20q14_0

('long-standing' means anything which has troubled you over a period of time or is likely to do so)

If Yes, Yes No
(a) Does this illness or disability limit your activities in any way? ☐ ☐ q20q14_0a
(b) Do you receive a disability allowance ? ☐ ☐ q20q14_0b

14.1 Do you currently have difficulty carrying out any of the following activities on your own as a result of a long term health problem?

	Yes	No	Date started	Cause of problem	OFFICE USE
(a) Difficulty going up / down stairs	☐ q20q14_1a	☐ q20q14_1a_y	19	q20q14_1a_c	
(b) Difficulty bending down / straightening up	☐ q20q14_1b	☐ q20q14_1b_y	19	q20q14_1b_c	
(c) Falling or having great difficulty keeping balance	☐ q20q14_1c	☐ q20q14_1c_y	19	q20q14_1c_c	
(d) Difficulty walking for a quarter of a mile on the level	☐ q20q14_1d	☐ q20q14_1d_y	19	q20q14_1d_c	

14.2 Is your present state of health causing problems with any of the following ?

	Yes	No	Cause of problem	OFFICE USE
(a) Job at work (paid employment)	☐ q20q14_2a	☐ q20q14_2a_c		
(b) Household chores	☐ q20q14_2b	☐ q20q14_2b_c		
(c) Social life	☐ q20q14_2c	☐ q20q14_2c_c		
(d) Interests and hobbies	☐ q20q14_2d	☐ q20q14_2d_c		
(e) Holidays and outings	☐ q20q14_2e	☐ q20q14_2e_c		
(f) Family relationships	☐ q20q14_2f	☐ q20q14_2f_c		

Appendices

Contact with relatives and friends

15.0 How often do you see or speak to :-

	Every week ₁	Every month ₂	Every few months ₃	Every Year ₄	Rarely or Never ₅	Does not apply ₆
Your Children						q20q15_0_1
Brothers / Sisters						q20q15_0_2
Friends						q20q15_0_3
Neighbours						q20q15_0_4

15.1 Is the amount of contact you have with each of these:-

	Too little ₁	About right ₂	Too much ₃	Does not apply ₄
Your Children				q20q15_1_1
Brothers / Sisters				q20q15_1_2
Friends				q20q15_1_3
Neighbours				q20q15_1_4

Present Circumstances

16.0 Are you at present :- Please give year

single ☐ ₁

married ☐ ₂ → 19 _____ q20q16_0

widowed ☐ ₃ → 19 _____ q20q16_0_y

divorced or separated ☐ ₄ → 19 _____

other ☐ ₅

16.1 Are you at present :-

living alone ☐ ₁ q20q16_1

living with a partner or spouse ☐ ₂

living with other family member(s) ☐ ₃

living with other people ☐ ₄

16.2 Your accommodation

Are you :- an owner occupier ☐ ₁ q20q16_2

renting from the local authority ☐ ₂

renting privately ☐ ₃ OFFICE USE

other (please give details) _____ ☐ ₄ q20q16_2x

Present Circumstances continued

16.3 Do you have a car available for your own use ? Yes ☐ No ☐ q20q16_3

16.4 Do you have a pet ? ☐ ₁ ☐ ₂ q20q16_4

(a) If Yes, what kind of pet do you own :- _____ q20q16_4a OFFICE USE

16.5 Heating

Please tick the fuels you use to heat your home:-

q20q16_5_1 Natural gas ☐ ₁ Oil ☐ ₁ Wood ☐ ₁ q20q16_5_3

q20q16_5_4 Calor gas ☐ ₁ Coal ☐ ₁ q20q16_5_5 OFFICE USE

q20q16_5_6 Electricity ☐ ₁ Other ☐ ₁ please specify _____ q20q16_5_7 q20q16_5_8

16.6 Does your home have:-

Central heating ☐ ₁ Yes ☐ ₂ No ☐ ₂ q20q16_6_1

Open fires ☐ ₁ ☐ ₂ q20q16_6_2

Double Glazing ☐ ₁ ☐ ₂ In part ☐ ₃ q20q16_6_3

16.7 Please tick the fuels you use for cooking:-

Natural gas ☐ ₁ q20q16_7_1

Electricity ☐ ₁ q20q16_7_2 OFFICE USE

Other ☐ ₁ (Please specify) _____ q20q16_7_3 q20q16_7_4

Work and Retirement

17.0 At present are you :-

retired ☐ ₁ age at retirement q20q17_0_y

employed, full time ☐ ₂

employed, part time ☐ ₃

unemployed, seeking work ☐ ₄

unemployed, not seeking work ☐ ₅

(a) If you are retired, did you retire because of:-

normal retiring age ☐ ₁ q20q17_0a

early retirement, voluntary ☐ ₂

early retirement, compulsory ☐ ₃

retirement, medical grounds ☐ ₄

other reasons ☐ ₅

17.1 Please give details of your current occupation or the last job you held before retiring: -

(a) What kind of work do you / did you do _____ OFFICE USE

(b) Type of business or industry _____ q20q17_1b

(c) How many years have you done or did you do that kind of work ? _____ q20q17_1c

Medications / treatments

Appendices

18.0 Are you on any regular medication ?

Yes ☐

q20q18_0

No ☐ → If No, go to question 18.3 on the next page

For Research Nurse use only	
Actual medications	☐ _1
Prescription Card (repeat)	☐ _2 q20q18_0m
Other list	☐ _3
No formal documentation	☐ _4

18.2 Which medications (including tablets, medicines, inhalers, sprays, injections) you are taking ? Please list medications below:

Medication	Dose	Frequency	Reason for taking	BNF CODE	ICD CODE
q20q18_2_bnf12_1 q20q18_2_bnf13_1 q20q18_2_bnf14_1 q20q18_2_bnf15_1			q20q18_2_icd1		
q20q18_2_bnf12_2 q20q18_2_bnf13_2 q20q18_2_bnf14_2 q20q18_2_bnf15_2			q20q18_2_icd2		
q20q18_2_bnf12_3 q20q18_2_bnf13_3 q20q18_2_bnf14_3 q20q18_2_bnf15_3			q20q18_2_icd3		
q20q18_2_bnf12_4 q20q18_2_bnf13_4 q20q18_2_bnf14_4 q20q18_2_bnf15_4			q20q18_2_icd4		
q20q18_2_bnf12_5 q20q18_2_bnf13_5 q20q18_2_bnf14_5 q20q18_2_bnf15_5			q20q18_2_icd5		
q20q18_2_bnf12_6 q20q18_2_bnf13_6 q20q18_2_bnf14_6 q20q18_2_bnf15_6			q20q18_2_icd6		
q20q18_2_bnf12_7 q20q18_2_bnf13_7 q20q18_2_bnf14_7 q20q18_2_bnf15_7			q20q18_2_icd7		
q20q18_2_bnf12_8 q20q18_2_bnf13_8 q20q18_2_bnf14_8 q20q18_2_bnf15_8			q20q18_2_icd8		
q20q18_2_bnf12_9 q20q18_2_bnf13_9 q20q18_2_bnf14_9 q20q18_2_bnf15_9			q20q18_2_icd9		
q20q18_2_bnf12_10 q20q18_2_bnf13_10 q20q18_2_bnf14_10 q20q18_2_bnf15_10			q20q18_2_icd10		

Aspirin

18.3 Do you take aspirin regularly ? ☐ Yes ☐ No ☐ → If No, go to question 18.3(b) below

(a) If Yes, year started 19 q20q18_3a_y

Dose mg q20q18_3a_mg

Frequency / week q20q18_3a_f

Reason for use q20q18_3a_r

On Prescription Yes ☐ No ☐ q20q18_3a_op

18.3 (b) If No, have you taken aspirin regularly in the past ? ☐ Yes ☐ No ☐ q20q18_3b

If Yes, year started 19 q20q18_3b_y

year stopped 19 q20q18_3b_y2

Reason for taking q20q18_3b_r

On Prescription Yes ☐ No ☐ q20q18_3b_op

Warfarin

18.4 Have you taken warfarin regularly at any time ? ☐ Yes ☐ No ☐ q20q18_4

If Yes, year started 19 q20q18_4_y

Duration in months q20q18_4_m

Reason for taking q20q18_4_r

GTN

18.5 Have you ever taken GTN tablets under the tongue (or spray) to relieve pain in the chest ?

Yes ☐ No ☐ q20q18_5

(a) If Yes, when was the last time you used them ? mths ago q20q18_5a

Appendices

Vitamins & Minerals

18.6 Do you regularly take any vitamin or mineral tablets? ☐ Yes ☐ No [q20q18_6](#)

(a) If Yes, please give details :-

Name of vitamin / mineral ☐	Daily Dose ☐	Year Started ☐
q20q18_6a_1	q20q18_6a_2	19 q20q18_6a_3
q20q18_6a_4	q20q18_6a_5	19 q20q18_6a_6
q20q18_6a_7	q20q18_6a_8	19 q20q18_6a_9
q20q18_6a_10	q20q18_6a_11	19 q20q18_6a_12

Blood Cholesterol Test

19.0 Have you ever had your blood cholesterol measured? ☐ Yes ☐ No [q20q19_0](#)

(a) If Yes, were you told that the result was

High	☐	q20q19_0a
Normal	☐	
Low	☐	
Not told	☐	

(b) If High, have you been advised to take any particular action? (please give details)

Diet ☐ [q20q19_0b_di](#)
 Drugs ☐ [q20q19_0b_dr](#)

Eating and drinking

20.0 What time did you last have something to eat or drink other than water?

hours ☐ If yesterday please tick ☐ [q20q20_0h](#) [q20q20_0m](#) [q20q20_0y](#)

21.0 Consent to follow up studies

An important part of this study is to observe the future health of the people taking part. We are therefore seeking your permission to receive specific information related to heart disease and stroke, particularly from the records held by your general practitioner. All these details would be treated in **absolute confidence** by the Research Team.

Do you agree to us following your future health through your health records?

☐ Agreed ☐ Not Agreed
[q20q21_0_1](#)

We will arrange to have your blood sample checked for cholesterol and other factors which are important for heart disease risk. The results of these tests will be sent back to your doctor in the next four to five weeks. If any of the results give cause for concern, you will be asked to make an appointment with your doctor.

Do you agree to us passing the test results to your doctor?

☐ Agreed ☐ Not Agreed
[q20q21_0_2](#)

Part of your blood sample will be frozen and kept for special scientific studies of factors affecting heart disease risk, which may help us to understand how to prevent heart disease in the future. Among the factors we may need to study will be the way in which genetic factors affect heart disease risk.

Would you allow us to use your sample in this way?

☐ Agreed ☐ Not Agreed
[q20q21_0_3](#)

I agree to allow the Research Team to continue to study my health in accordance with the criteria above. I understand that any details recorded will be treated in complete confidence.

Signed: [q20sig](#)

Date: [q20date1](#) [q20_date2](#) [q20_date3](#)

Appendices

Appendix 3.7: BRHS Q20 Physical Examination Data Collection Form

APPENDIX 4 - 20 year follow-up Physical examination data collection form

British Regional Heart Study Datasheet 1998-2000

Serial: Batch:
 Name:
 DOB:

Station 1: MEASUREMENTS Observer

Height: (cm)

Current weight estimate: st/lb

Weight change in the last 3 years
☐ No = 1, Gain = 2
☐ Loss = 3, Fluct = 4

Arm Circ. (R) (cm)

Triceps Skinfold (R) 1 (mm)

Triceps Skinfold (R) 2 (mm)

Waist Circumference 1 (cm)

Waist Circumference 2 (cm)

☐ Waist circ. Inadequate = 1

Blood Pressure (R arm)

SITTING				STANDING			
SBP1				SBP2			
DBP1				DBP2			
MAP1				MAP2			
PULSE1				PULSE2			

Cuff Inst.

A/jc ☐ 1 = yes

Temp. (C)

Dementia ☐ 1 = Yes

READINGS INADEQUATE? ☐

Actual Weight kg

Was loss intentional?
☐ Yes = 1, No = 2

Posture=2

Ever weighed more than present? ☐ Yes = 1
 No = 2
 If Yes, Maximum weight ever st/lb DK = 3

Reason for change
☐ Personal choice = 1,
☐ Doctor's advice = 2,
☐ Illness = 3, Change in smoking = 4, Other = 5

Subscapular skinfold (R) 1 (mm)

Subscapular skinfold (R) 2 (mm)

Hip Circumference 1 (cm)

Hip Circumference 2 (cm)

☐ Hip circ. Inadequate = 1

28.0 to 35 cm inclusive → Adult Cuff = 1
 <28.0cm → Small Adult= 2; >35 cm → Large Adult Cuff = 3

Faintness on standing ☐ 1 = Yes

Ethnicity ☐

Cau = 1, A/C = 2, Asian = 3,
 Orien = 4, Other = 5

Breathless = Yes ☐ 1

Appendices

SPIROMETRY Instr

No. Readings BTV%
 FVC
 FEV .5
 FEV1
 PEF
 FEF25-75
 FEF75-85
 FEF25
 FEF50
 FEF75

Readings inadequate ? Inad=1

Spirometer Output

Station 2

Observer

LEFT SIDE

Ankle oedma

Yes= 1, No= 2

Leg ulcer

Sole = 1, Ankle =2, Shin= 3

Pulses

Dorsalis Pedis

Yes= 1, No= 2

Post Tibial

Yes= 1, No= 2

Pacemaker

Yes= 1, No= 2

Impedance

RIGHT SIDE

Ankle oedma

Yes= 1, No= 2

Leg ulcer

Sole = 1, Ankle =2, Shin= 3

Pulses

Dorsalis Pedis

Yes= 1, No= 2

Post Tibial

Yes= 1, No= 2

ECG

Yes= 1, No= 2

BLOOD SAMPLING

Success

No=0, Part =1, All =2

Failure

Refusal = 1,
No sample =2

Time .

Station 3 BLOOD ALIQUOTTING

Observer

All tubes Filled?

Yes= 1, No= 2

Tube
missing(=1)

A B C D E

F G H I J

K

L M N O P

Q R

Appendices

Appendix 3.8: BRHS Q20 Physical Activity and Food Frequency Self-administered Questionnaire

PART I: PHYSICAL ACTIVITY

These questions are designed to find out how physically active you are in everyday life, both inside and outside your home. Please try to answer all questions, describing your usual activities **OVER THE LAST YEAR**.

Getting About

- 1.0 Which of the following forms of transport do you use most often? (tick only one box)
- | | | |
|--------------------|---|------------|
| Car | 1 | |
| Public transport | 2 | q20pa_q1_0 |
| Walking or Cycling | 3 | |

Walking

- 1.1 How many miles do you walk in total in an average week? q20pa_q1_1 miles / week
- 1.2 How many journeys of at least a mile do you walk each week? q20pa_q1_2 journeys
(Please write '0' if none)

2.0 Household Activities

About how many hours each week do you usually spend on the following household activities? (please tick one box for each question)

	None 1	Less than 1 hour a week 2	1 to 3 hours a week 3	3 to 6 hours a week 4	6 to 10 hours a week 5	More than 10 hours a week 6
Light Activities (eg preparing food, cooking, washing up, dusting) q20pa_q2_0la						
Moderate Activities (eg cleaning, sweeping, hoovering, washing floors, shopping) q20pa_q2_0ma						
Heavy Activities (eg scrubbing floors, walking with heavy shopping) q20pa_q2_0ha						

3.0 Climbing Stairs

How many flights of stairs do you climb up each day? (a flight of stairs = 10-15 stairs)

	None 1	1 to 5 flights 2	6 to 10 flights 3	11 to 15 flights 4	More than 15 flights 5
On a weekday q20pa_q3_0wky					
On a weekend day q20pa_q3_0wkd					

4.0 Other Activities in the past year

Please indicate how often you did these activities **during the past year**.
If you didn't do a particular activity at all, simply write 'X' in the first column.

	How many times each month? □□	How many months of the year? □□	Average time on each occasion? Hours □□ Minute □□
Walking on specific journeys (eg to shops, errands)	q20pa_q4_0walk_tmonth	q20pa_q4_0walk_myear	q20pa_q4_0walk_hooc q20pa_q4_0walk_moooc
Rambling / Hiking	q20pa_q4_0ramb_tmonth	q20pa_q4_0ramb_myear	q20pa_q4_0ramb_hooc q20pa_q4_0ramb_moooc
Cycling	q20pa_q4_0cycle_tmonth	q20pa_q4_0cycle_myear	q20pa_q4_0cycle_hooc q20pa_q4_0cycle_moooc
Light gardening (eg watering the lawn/garden)	q20pa_q4_0lgarden_tmonth	q20pa_q4_0lgarden_myear	q20pa_q4_0lgarden_hooc q20pa_q4_0lgarden_moooc
Moderate gardening (eg planting, cutting grass)	q20pa_q4_0mgarden_tmonth	q20pa_q4_0mgarden_myear	q20pa_q4_0mgarden_hooc q20pa_q4_0mgarden_moooc
Heavy gardening (eg digging, shovelling)	q20pa_q4_0hgarden_tmonth	q20pa_q4_0hgarden_myear	q20pa_q4_0hgarden_hooc q20pa_q4_0hgarden_moooc
DIY (eg home / car maintenance, carpentry)	q20pa_q4_0DIY_tmonth	q20pa_q4_0DIY_myear	q20pa_q4_0DIY_hooc q20pa_q4_0DIY_moooc
Swimming	q20pa_q4_0swim_tmonth	q20pa_q4_0swim_myear	q20pa_q4_0swim_hooc q20pa_q4_0swim_moooc
Jogging	q20pa_q4_0jog_tmonth	q20pa_q4_0jog_myear	q20pa_q4_0jog_hooc q20pa_q4_0jog_moooc
Exercises (stretching, bending, keep fit, etc)	q20pa_q4_0exer_tmonth	q20pa_q4_0exer_myear	q20pa_q4_0exer_hooc q20pa_q4_0exer_moooc
Dancing	q20pa_q4_0dance_tmonth	q20pa_q4_0dance_myear	q20pa_q4_0dance_hooc q20pa_q4_0dance_moooc
Bowling (indoor, lawn, tenpin)	q20pa_q4_0bowl_tmonth	q20pa_q4_0bowl_myear	q20pa_q4_0bowl_hooc q20pa_q4_0bowl_moooc
Golf	q20pa_q4_0golf_tmonth	q20pa_q4_0golf_myear	q20pa_q4_0golf_hooc q20pa_q4_0golf_moooc
Tennis / Badminton	q20pa_q4_0tennis_tmonth	q20pa_q4_0tennis_myear	q20pa_q4_0tennis_hooc q20pa_q4_0tennis_moooc
Fishing	q20pa_q4_0fish_tmonth	q20pa_q4_0fish_myear	q20pa_q4_0fish_hooc q20pa_q4_0fish_moooc
Other exercises (please specify)	q20pa_q4_0oth1_tmonth	q20pa_q4_0oth1_myear	q20pa_q4_0oth1_hooc q20pa_q4_0oth1_moooc
	q20pa_q4_0oth2_tmonth	q20pa_q4_0oth2_myear	q20pa_q4_0oth2_hooc q20pa_q4_0oth2_moooc

OFFICE USE:

q20pa_q4_0
oth1_off
use_box
q20pa_q4_0
oth2_off
use_box

- 5.0 Did you do any of these activities vigorously enough to cause sweating, breathlessness or fast heartbeat? Yes No
□ □ q20pa_q5_0

- 5.1 If Yes, for about how many minutes did you do such vigorous activities each week? (mins) q20pa_q5_1

- 5.2 Compared with your level of activity three years ago, are you doing more □ 1 q20pa_q5_2
about the same □ 2
less □ 3

- 5.3 If less, please give the reason q20pa_q5_3 OFFICE USE

□

Appendices

PART II: YOUR DIET

1. Are you on any special diet (eg vegetarian, low fat, diabetic)? Yes ☐ No ☐ q20pa_q5_4
OFFICE USE
 If Yes, please give details q20pa_q5_4ifyes ☐

How to fill in the diet questionnaire

The following questions are mostly about how often you **USUALLY** eat different sorts of food each week.

If you usually eat a food **every day**, ring **7** days a week

If you usually eat a food on **three days a week**, ring **3**, and so on

For foods which you eat **less than once a week** :-

Ring **M** if you eat it **at least** once a month

Ring **R** if you eat it **less than** once a month, or if you **never** eat it at all

Please ring **one** answer for each of the foods listed. Remember to circle **R** if you never eat a food.

Example

	Number of days each week							Monthly	Rarely/ Never
Food eaten every day (7 days a week)	☐	6	5	4	3	2	1	M	R
Food eaten on three days a week	7	6	5	4	☐	2	1	M	R
Food eaten less often than once a week but at least once a month	7	6	5	4	3	2	1	☒ M	R
Food eaten never or less than once a month	7	6	5	4	3	2	1	M	☐

Please ring the correct number or letter for every food item (one circle only per line)

		Number of days each week							Monthly	Rarely/ Never
2. Meat										
q20di_q2a	(a) Beef (including minced beef, beef burgers)	7	6	5	4	3	2	1	M	R
q20di_q2b	(b) Lamb	7	6	5	4	3	2	1	M	R
q20di_q2c	(c) Pork, bacon, ham, salami	7	6	5	4	3	2	1	M	R
q20di_q2d	(d) Chicken, turkey, other poultry	7	6	5	4	3	2	1	M	R
q20di_q2e	(e) Tinned meat (all types, corned beef, etc)	7	6	5	4	3	2	1	M	R
q20di_q2f	(f) Pork Sausages	7	6	5	4	3	2	1	M	R
q20di_q2g	(g) Beef Sausages	7	6	5	4	3	2	1	M	R
q20di_q2h	(h) Meat Pie, Pasties	7	6	5	4	3	2	1	M	R
q20di_q2i	(i) Liver, kidney, heart	7	6	5	4	3	2	1	M	R
3. Fish										
q20di_q3a	(a) White fish (cod, haddock, hake, plaice, fish fingers, etc)	7	6	5	4	3	2	1	M	R
q20di_q3b	(b) Kippers, herrings, pilchards, tuna, sardines, salmon, mackerel (including tinned)	7	6	5	4	3	2	1	M	R
q20di_q3c	(c) Shellfish	7	6	5	4	3	2	1	M	R
4. Vegetables (fresh, tinned, dried, frozen)										
q20di_q4a	(a) Potatoes: boiled, baked, mashed	7	6	5	4	3	2	1	M	R
q20di_q4bi	(b) Potatoes									
q20di_q4bii	(i) chips or fried (from shop)	7	6	5	4	3	2	1	M	R
q20di_q4biii	(ii) chips, fried or (cooked at home)	7	6	5	4	3	2	1	M	R
	(iii) roast potatoes	7	6	5	4	3	2	1	M	R
q20di_q4c	(c) Green vegetables, salads	7	6	5	4	3	2	1	M	R
q20di_q4d	(d) Carrots	7	6	5	4	3	2	1	M	R
q20di_q4e	(e) Parsnips, swedes, turnips, beetroot, and other root vegetables	7	6	5	4	3	2	1	M	R
q20di_q4f	(f) Baked or butter beans, lentils, peas, chickpeas, sweetcorn	7	6	5	4	3	2	1	M	R
q20di_q4g	(g) Onions (cooked, raw, pickled)	7	6	5	4	3	2	1	M	R
q20di_q4h	(h) Garlic	7	6	5	4	3	2	1	M	R
q20di_q4i	(i) Spaghetti and other pasta	7	6	5	4	3	2	1	M	R
q20di_q4j	(j) Rice (all types except pudding rice)	7	6	5	4	3	2	1	M	R
q20di_q4k	(k) Tomatoes (fresh, tinned, pureed)	7	6	5	4	3	2	1	M	R
How often do you eat fresh vegetables in :										
q20di_q4l	(l) summer	7	6	5	4	3	2	1	M	R
q20di_q4m	(m) winter	7	6	5	4	3	2	1	M	R

Please remember to circle **R** if you never eat a food

Appendices

5. **Fresh fruit**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
(a) summer	7	6	5	4	3	2	1	M	R
(b) winter	7	6	5	4	3	2	1	M	R
(c) Number of apples eaten a week	_____								
(d) Number of pears eaten a week	_____								
(e) Number of oranges or grapefruit eaten a week	_____								
(f) Number of bananas eaten a week	_____								
(g) Number of other fruits eaten a week (please give name and quantity)	_____								

Name	Quantity	Name	Quantity
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

6. **Cheese**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
Full- fat cheese (eg Cheddar, Leicester, Stilton, Urie, soft cheeses)	7	6	5	4	3	2	1	M	R
Low-fat cheese (eg Edam, Cottage cheese, reduced fat cheeses)	7	6	5	4	3	2	1	M	R

7. **Bread**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
(a) White bread	7	6	5	4	3	2	1	M	R
(b) Brown bread	7	6	5	4	3	2	1	M	R
(c) Wholemeal	7	6	5	4	3	2	1	M	R
(d) Bread rolls	7	6	5	4	3	2	1	M	R
(e) Crispbread (Ryvita, cream crackers, etc)	7	6	5	4	3	2	1	M	R

please give name of crispbread etc.....

(f) Further details about your bread

	How many slices or rolls a day ?	Are the slices thick, medium or thin? Circle your answer.
(i) White Bread	_____	thick ₁ medium ₂ thin ₃
(ii) Brown Bread	_____	thick medium thin
(iii) Wholemeal Bread	_____	thick medium thin
(iv) Bread Rolls	_____	large medium small

Please remember to circle ☉ if you never eat a food

8. **Breakfast Cereals**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
(a) Grapenuts, Porridge, Ready Brek, Special K, Sugar Puffs, Rice Crispies	7	6	5	4	3	2	1	M	R
(b) Cornflakes, Muesli, Shredded Wheat, Sultana Bran, Weetabix	7	6	5	4	3	2	1	M	R
(c) Bran Flakes, Puffed wheat	7	6	5	4	3	2	1	M	R
(d) All Bran, Wheat Bran	7	6	5	4	3	2	1	M	R
(e) Another Cereal	7	6	5	4	3	2	1	M	R

please give name

9. **Biscuits, puddings and sweets**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
(a) Digestive biscuits, plain biscuits	7	6	5	4	3	2	1	M	R
(b) Sweet biscuits, sponge cakes, scones, buns	7	6	5	4	3	2	1	M	R
(c) Ice cream, sweet yoghurts, trifle	7	6	5	4	3	2	1	M	R
(d) Fruit cake, fruit bread, plum pudding	7	6	5	4	3	2	1	M	R
(e) Fruit tart, jam tart, fruit crumble	7	6	5	4	3	2	1	M	R
(f) Milk puddings (rice, tapioca)	7	6	5	4	3	2	1	M	R
(g) Tinned fruit, jellies	7	6	5	4	3	2	1	M	R
(h) Sweet sauces (chocolate, custard)	7	6	5	4	3	2	1	M	R
(i) Chocolate, chocolate bars, sweets (all types)	7	6	5	4	3	2	1	M	R

10. **Eggs**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
(a) Eggs (boiled, poached, fried, scrambled)	7	6	5	4	3	2	1	M	R
(b) Eggs in baked dishes (eg flans, quiches, soufflés, egg custard, etc)	7	6	5	4	3	2	1	M	R

11. **Other foods**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
(a) Soups (all kinds, home-made, tinned, packet)	7	6	5	4	3	2	1	M	R
(b) Nuts, nut butter (eg salted or unsalted peanuts)	7	6	5	4	3	2	1	M	R
(c) Savoury snacks (eg potato crisps, corn chips, crackers)	7	6	5	4	3	2	1	M	R
(d) Chutney, brown sauce, tomato sauce	7	6	5	4	3	2	1	M	R
(e) Sweet spreads (eg jam, honey, marmalade, chocolate spread)	7	6	5	4	3	2	1	M	R

12. **Drinks and Juices (non-alcoholic)**

Number of days each week

	7	6	5	4	3	2	1	Monthly	Rarely/ Never
(a) Natural fruit juices (including tomato juice)	7	6	5	4	3	2	1	M	R
(b) Fizzy drinks and Non-diet squashes	7	6	5	4	3	2	1	M	R
(c) Low calorie (diet) squashes and fizzy drinks	7	6	5	4	3	2	1	M	R

Please remember to circle ☉ if you never eat a food

Appendices

13. Milk

- q20di_q13a (a) Roughly how much milk do you drink a day in tea, coffee, milky drinks or cereals? (Tick only one box)
- 1 ☐ none at all
 2 ☐ half pint or less
 3 ☐ between half and one pint
 4 ☐ more than one pint

- q20di_q13b (b) What kind of milk do you usually use? (Tick only one box)
- 1 ☐ full fat milk, fresh or dried
 2 ☐ semi-skimmed milk, fresh or dried
 3 ☐ fully skimmed milk, fresh or dried
 4 ☐ other kinds of milk, eg condensed, evaporated

14. Fats

- (a) What do you usually spread on bread? OFFICE USE
- q20di_q14a_butter 1 ☐ butter Give brand name
 q20di_q14a_ffmarg 1 ☐ full-fat soft margarine Give brand name
 q20di_q14a_lfmarg 1 ☐ low-fat soft margarine Give brand name
 q20di_q14a_hmarg 1 ☐ hard margarine Give brand name
- q20di_q14b (b) How do you normally spread the fat?
- 1 ☐ thinly 2 ☐ average 3 ☐ thickly

- (c) How often do you eat home-fried food (including chips), cooked with :-
- | | Number of days each week | | | | | | | 0 | 8 |
|---|--------------------------|---|---|---|---|---|---|---------|---------------|
| | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Monthly | Rarely/ Never |
| q20di_q14c_lard Lard, dripping, solid vegetable oil | | | | | | | | M | R |
| Give brand name and type | | | | | | | | | |
| q20di_q14c_oil Liquid vegetable oil | | | | | | | | M | R |
| Give brand name and type | | | | | | | | | |

15. Salt

- q20di_q15a (a) How much salt is added to your food, on cooking?
- 1 ☐ a lot 2 ☐ a little 3 ☐ none
- q20di_q15b (b) How much salt is added to your food on your plate?
- 1 ☐ a lot 2 ☐ a little 3 ☐ none

Please remember to circle ® if you never eat a food

16. Your household

How many people normally eat in your household?

Number of adults (including yourself) q20di_q16num_ad Number of children 1 to 4 years old q20di_q16num_ch1to4
 Number of children 5 to 16 years old q20di_q16num_ch5to16 Number of babies under 1 year old q20di_q16num_chupto1

17. How much of the following foods does **your household** use on average **each week** (including cooking and baking)? If you live on your own, please give the amounts which you yourself eat a week.

	If rarely or never used tick here						
Butter	q20di_q17butt_rare ☐	q20di_q17butt_lbs	q20di_q17butt_ozs	or	q20di_q17butt_gr	grams	
Margarine (all types)	q20di_q17marg_rare ☐	q20di_q17marg_lbs	q20di_q17marg_ozs	or	q20di_q17marg_gr	grams	
Lard and solid vegetable oil	q20di_q17lavo_rare ☐	q20di_q17lavo_lbs	q20di_q17lavo_ozs	or	q20di_q17lavo_gr	grams	
Liquid vegetable oil (eg Sunflower, Corn, Groundnut oil)	q20di_q17lvo_rare ☐	q20di_q17lvo_ozs	or	q20di_q17lvo_ml	ml		
Olive Oil	q20di_q17oo_rare ☐	q20di_q17oo_ozs	or	q20di_q17oo_ml	ml		
Cream	q20di_q17cream_rare ☐	q20di_q17cream_ozs	or	q20di_q17cream_ml	ml		
Full-fat cheese (eg Cheddar, Leicester, Stilton, Brie, and soft cheeses)	q20di_q17fchee_rare ☐	q20di_q17fchee_lbs	q20di_q17fchee_ozs	or	q20di_q17fchee_gr	grams	
Low-fat cheese (eg reduced fat cheddar, reduced fat soft cheeses, Edam)	q20di_q17lchee_rare ☐	q20di_q17lchee_lbs	q20di_q17lchee_ozs	or	q20di_q17lchee_gr	grams	
Sugar	q20di_q17sug_rare ☐	q20di_q17sug_lbs	q20di_q17sug_ozs	or	q20di_q17sug_gr	grams	

18. Hot drinks

Coffee

- (a) How many cups of coffee do you have a day? q20di_q18a cups a day
- Is this ☐ ground coffee ☐ instant coffee q20di_q18a_type
- Is it decaffeinated? ☐ Yes ☐ No q20di_q18a_decaf
- (b) How many teaspoons of sugar do you take in each cup? q20di_q18b teaspoons (Do not count artificial sweeteners)

Tea

- (c) How many cups of tea do you have a day? q20di_q18c cups a day
- (d) How many teaspoons of sugar do you take in each cup? q20di_q18d teaspoons (Do not count artificial sweeteners)

Other Hot Drinks

- (e) How many cups of other hot drinks (eg drinking hot chocolate, malted milk, Horlicks) do you have a day? q20di_q18e cups a day

19. Alcoholic drinks

Appendices

- (a) Have you ever consumed alcoholic drinks ? ☐₁ ☐₂ q20di_q19a
- (b) Do you take alcoholic drinks at present ? ☐₁ ☐₂ ☐ q20di_q19b
- (c) Think back carefully over the last seven days.
Please write the number of alcoholic drinks you have consumed on each day during the past week. It may help if you try to remember where you were and who you were with on each day.

For each day, write in how much you have drunk:

- (i) the number of pints of non-alcoholic beer, lager, etc
(ii) the number of pints of low-alcohol beer, lager, etc
(iii) the number of pints of beer, lager, shandy, cider, stout, etc
(iv) the number of single glasses of whisky, vodka, gin, rum, etc
(v) the number of single glasses of wine, sherry, martini, port, etc

	(i) Pints of Non-alcoholic Beer ☐	(ii) Pints of Low-alcohol Beer ☐	(iii) Pints of Beer, Lager, Shandy ☐	(iv) Single glasses of Spirits ☐	(v) Single glasses of Wine ☐
Monday	q20di_q19c_M_i	q20di_q19c_M_ii	q20di_q19c_M_iii	q20di_q19c_M_iv	q20di_q19c_M_v
Tuesday	q20di_q19c_Tu_i	q20di_q19c_Tu_ii	q20di_q19c_Tu_iii	q20di_q19c_Tu_iv	q20di_q19c_Tu_v
Wednesday	q20di_q19c_W_i	q20di_q19c_W_ii	q20di_q19c_W_iii	q20di_q19c_W_iv	q20di_q19c_W_v
Thursday	q20di_q19c_Th_i	q20di_q19c_Th_ii	q20di_q19c_Th_iii	q20di_q19c_Th_iv	q20di_q19c_Th_v
Friday	q20di_q19c_F_i	q20di_q19c_F_ii	q20di_q19c_F_iii	q20di_q19c_F_iv	q20di_q19c_F_v
Saturday	q20di_q19c_Sa_i	q20di_q19c_Sa_ii	q20di_q19c_Sa_iii	q20di_q19c_Sa_iv	q20di_q19c_Sa_v
Sunday	q20di_q19c_Su_i	q20di_q19c_Su_ii	q20di_q19c_Su_iii	q20di_q19c_Su_iv	q20di_q19c_Su_v

- (d) Would you say last week was fairly typical of what you usually have to drink in one week ? ☐₁ ☐₂ q20di_q19d
- (e) If last week was not typical, would you normally drink more or less in a week ? ☐₁ ☐₂ q20di_q19e

20. Birth Weight

Recent research has suggested that circumstances around the time of birth, and particularly birthweight, may influence the heart and circulation many years later.

If you can tell us about your birthweight and the birthweight (s) of your children (asking other family members if necessary) this would be very helpful :-

- (a) Your birth weight: q20di_q20a_bwt_lb lb q20di_q20a_bwt_oz oz q20di_q20a_bwt_dk Not known ☐₁
- (b) The birthweight of your children:-
- First Child q20di_q20b_bwt_ch1_lb lb q20di_q20b_bwt_ch1_oz oz q20di_q20b_sex_ch1 ☐₁ q20di_q20b_sex_ch1 ☐₂ q20di_q20b_sex_ch1 ☐₃ q20di_q20b_sex_ch1 ☐₄ q20di_q20b_sex_ch1 ☐₅ q20di_q20b_sex_ch1 ☐₆ q20di_q20b_sex_ch1 ☐₇ q20di_q20b_sex_ch1 ☐₈ q20di_q20b_sex_ch1 ☐₉ q20di_q20b_sex_ch1 ☐₁₀ q20di_q20b_sex_ch1 ☐₁₁ q20di_q20b_sex_ch1 ☐₁₂ q20di_q20b_sex_ch1 ☐₁₃ q20di_q20b_sex_ch1 ☐₁₄ q20di_q20b_sex_ch1 ☐₁₅ q20di_q20b_sex_ch1 ☐₁₆ q20di_q20b_sex_ch1 ☐₁₇ q20di_q20b_sex_ch1 ☐₁₈ q20di_q20b_sex_ch1 ☐₁₉ q20di_q20b_sex_ch1 ☐₂₀ q20di_q20b_sex_ch1 ☐₂₁ q20di_q20b_sex_ch1 ☐₂₂ q20di_q20b_sex_ch1 ☐₂₃ q20di_q20b_sex_ch1 ☐₂₄ q20di_q20b_sex_ch1 ☐₂₅ q20di_q20b_sex_ch1 ☐₂₆ q20di_q20b_sex_ch1 ☐₂₇ q20di_q20b_sex_ch1 ☐₂₈ q20di_q20b_sex_ch1 ☐₂₉ q20di_q20b_sex_ch1 ☐₃₀ q20di_q20b_sex_ch1 ☐₃₁ q20di_q20b_sex_ch1 ☐₃₂ q20di_q20b_sex_ch1 ☐₃₃ q20di_q20b_sex_ch1 ☐₃₄ q20di_q20b_sex_ch1 ☐₃₅ q20di_q20b_sex_ch1 ☐₃₆ q20di_q20b_sex_ch1 ☐₃₇ q20di_q20b_sex_ch1 ☐₃₈ q20di_q20b_sex_ch1 ☐₃₉ q20di_q20b_sex_ch1 ☐₄₀ q20di_q20b_sex_ch1 ☐₄₁ 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Appendices

Appendix 3.9: Baseline Questionnaire used for recruitment to the Southall arm of the SABRE study 1988-90

Serial Number		1 - 6	
General Instructions			
Please read these notes before filling in the rest of the questionnaire			
Please answer all the questions, except where the instructions indicate otherwise. For the answers to some questions you may need to ask others in your household but please try to answer as many questions as possible on your own.			
The answer to most questions can be indicated by ticking one of the boxes.			
Example			
Have you ever smoked cigarettes regularly?			
1.	☒ Yes		
2.	☐ No		
Where the answer requires you to write numbers, a box is used.			
Example			
(b) How many manufactured cigarettes a day do you usually smoke?			
enter number:	20		
Where the answer requires you to write a few words, dotted lines are given. Please use block letters			
Example			
What is your usual occupation? <u>PAINTER AND DECORATOR</u>			
3			
SECTION 1. HEALTH		FOR OFFICE USE ONLY	
1.1 Compared with others your age, would you say your health over the last 12 months has been			
1.	☐ Very good		
2.	☐ Good		
3.	☐ Average		
4.	☒ Poor	4	7
5.	☐ Very poor		
1.2 (a) Have you ever been told that you had high blood pressure?			
1.	☒ Yes		
2.	☐ No	1	8
If No, go to Question 1.3			
If Yes:			
(b) were you started on treatment for high blood pressure?			
1.	☐ Yes, but not on drug treatment now.		
2.	☐ Yes, still continuing drug treatment	3	9
3.	☒ No		
1.3 (a) Have you ever been told that you had diabetes?			
1.	☐ Yes		
2.	☒ No	2	10
If No, go to Question 1.4			
If Yes:			
(b) were you started on treatment for diabetes?			
1.	☐ Yes, but not on treatment now.		
2.	☐ Yes, still continuing on diet		
3.	☐ Yes, now treated with tablets		
4.	☐ Yes, now treated with insulin		
5.	☐ No		11
4			

Appendices

1.4 (a) Have you ever been told by a doctor that you had heart trouble?

1. ☒ Yes
2. ☐ No

If No, go to Question 1.5

If Yes:

(b) When was the first time (give year)?

19 87

(c) What did the doctor say it was?

1. ☐ Heart attack
2. ☒ Angina
3. ☐ Heart failure
4. ☐ High blood pressure
5. ☐ Valve disease
6. ☐ Hole in the heart
7. ☐ Other-Please specify: _____

1.5 Have you ever been told by a doctor that you had any of the following:

Please tick either Yes or No for each illness or condition:

	Yes	No
(a) Asthma	1. ☐	2. ☒
(b) An ulcer (stomach or duodenal)	1. ☒	2. ☐
(c) A stroke	1. ☐	2. ☒
(d) Arthritis	1. ☐	2. ☒
(e) Kidney stones	1. ☐	2. ☒

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USE ONLY

1 12

8 7
13 - 14

2 15

2 16

1 17

2 18

2 19

2 20

5

1.6 Please list any serious illnesses not yet mentioned that you have had in the last 12 months

Backaches, pain in

legs and feet. Ulcers on ankles.

Migraine.

1.7 Please list any other serious illnesses you had before 12 months ago.

Illness Year of onset

_____ 19

_____ 19

1.8 Please list any major operations you have had, and the year of each operation.

Operation Year

_____ 19

_____ 19

1.9 In the last twelve months how many times have you been off work for illness lasting a week or more?

Enter total number of weeks: 52

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21 - 22

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25 - 26

27 - 28

29 - 30

31 - 32

33 - 34

35 - 36

37 - 38

39 - 40

41 - 42

6

Appendices

1.10 Are you taking any medicines at the moment, either prescribed by a doctor or something you buy yourself?

1. ☒ Yes
2. ☐ No If No, go to Question 1.11

If Yes:

Please list the names of all the drugs you are taking below.

You need not include creams or ointments that you are using on your skin or eyes.

Please bring the bottles with you when you come for your examination.

Zantac, Paracetamol
Propranolol and Nitroglycerin Spray

FOR OFFICE USE

Beta-blocker
Thiazide
Other diuretic
Calcium antagonist
Sympatholytic
Other vasodilator
Nitrate
ACE antagonist
Sulphonylurea
Biguanide
Lipid-lowering
Glucocorticoid
Hypnotic/tranquillizer
Other

FOR OFFICE
USE ONLY

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1.11 (a) Have you ever had any pain or discomfort in your chest?

1. ☒ Yes
2. ☐ No If No, go to Question 1.12

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If Yes:

(b) Do you get this pain or discomfort when you walk uphill or hurry?

1. ☐ Yes
2. ☐ No
3. ☒ Never walk uphill or hurry

(c) Do you get it when you walk at an ordinary pace on the level?

1. ☐ Yes
2. ☒ No

(d) What do you do if you get it while you are walking?

1. ☒ Stop
2. ☐ Slow down
3. ☐ Carry on at the same pace

(e) Does it go away when you stop?

1. ☒ Yes
2. ☐ No If No, go to Question 1.12

If Yes:

(f) How soon does it go away?

1. ☒ More than 10 minutes
2. ☐ 10 minutes or less

(g) Where do you get this pain or discomfort?

(Mark the place(s) with 'X' on the diagram)

RIGHT

LEFT



FRONT VIEW

8

FOR OFFICE
USE ONLY

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Appendices

1.12 (a) In winter, do you usually bring up phlegm from your chest first thing in the morning?

1. ☒ Yes
2. ☒ No

If No, go to Question 1.13

If Yes,

(b) For how many months of the year does this usually happen?

1. ☐ Less than three months
2. ☒ Three months or more

1.13 (a) Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

1. ☒ Yes
2. ☐ No

If No, go to Question 1.14

If Yes,

(b) Are you short of breath when walking with other people of your own age on level ground?

1. ☒ Yes
2. ☐ No

(c) Are you troubled by breathlessness when lying down at night?

1. ☒ Yes
2. ☐ No

1.14 Do you suffer from swollen ankles?

1. ☒ Yes
2. ☐ No

1.15 Do you have difficulty in falling asleep?

1. ☒ Yes
2. ☒ No

FOR OFFICE
USE ONLY

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1.16 Do you usually wake up too early?

1. ☐ Yes
2. ☒ No

1.17 Do you still feel tired when you wake up in the morning?

1. ☒ Yes
2. ☐ No

1.18 How often do you snore at night? (If you are not sure, please ask someone who is likely to know)

1. ☐ Never snore
2. ☐ Occasionally snore
3. ☐ Often snore
4. ☒ Almost always snore.

FOR OFFICE
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SECTION 2. DIET

2.1 On how many of the last seven days did you eat each of the following foods?

In each row, please tick one of the four choices given: even if the food is something you never eat, remember to tick the appropriate box.

	Not at all in last 7 days	On one day only	2 or 3 days in last 7	On most days
Animal products				
(a) Eggs	1. ☐	2. ☐	3. ☒	4. ☐
(b) Milk, butter or cheese	1. ☐	2. ☐	3. ☐	4. ☒
(c) Fish or other seafood	1. ☐	2. ☒	3. ☐	4. ☐
(d) Chicken	1. ☐	2. ☐	3. ☒	4. ☐
(e) Lamb	1. ☐	2. ☒	3. ☐	4. ☐
(f) Beef (including hamburgers)	1. ☒	2. ☐	3. ☐	4. ☐
(g) Pork, ham or bacon	1. ☒	2. ☐	3. ☐	4. ☐
Fruit and vegetables				
(h) Fresh green vegetables	1. ☐	2. ☐	3. ☒	4. ☐
(i) Fresh fruit	1. ☐	2. ☐	3. ☒	4. ☐
(j) Fruit juices	1. ☐	2. ☐	3. ☐	4. ☒
Sweets and baked confectionery				
(k) Jam, jellies, preserves, syrup or honey	1. ☒	2. ☐	3. ☐	4. ☐
(l) Cakes or sweet buns	1. ☐	2. ☐	3. ☒	4. ☐
(m) Sweet biscuits	1. ☐	2. ☐	3. ☐	4. ☒
(n) Sweet rolls, flans, tarts or other sweet pastry	1. ☒	2. ☐	3. ☐	4. ☐
(o) Fudge, sweetmeats or mithai	1. ☒	2. ☐	3. ☐	4. ☐
(p) Chocolate, toffee, boiled sweets, or mints	1. ☐	2. ☐	3. ☐	4. ☒
(q) Sweetened desserts or puddings: e.g. flavoured yogurt, cheesecake, rice pudding, halva	1. ☐	2. ☒	3. ☐	4. ☐
(r) Carbonated soft drinks: e.g. Coca-Cola, lemonade	1. ☒	2. ☐	3. ☐	4. ☐

FOR OFFICE
USE ONLY

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	08 - 09

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2.2 How many teaspoons of sugar do you usually add

(a) to a cup of coffee? number of teaspoons:

(b) to a cup of tea? number of teaspoons:

2.3 In total, how many teaspoons of sugar do you usually use each day in drinks like tea and coffee or on food at table (e.g. breakfast cereal)?

1. ☐ None
2. ☐ 1-2 teaspoons
3. ☐ 3-5 teaspoons
4. ☒ 6-10 teaspoons
5. ☐ 11-20 teaspoons
6. ☐ More than 20 teaspoons

Please fill out the next question with the help of the person who is responsible for buying and preparing your food at home.

2.4 Which of the following kinds of fat or oil do you use at home, either in cooking or on your food?

Please tick either Yes or No for each kind of fat or oil

	Yes	No
(a) Corn oil, soya oil, or sunflower oil	1. ☒	2. ☐
(b) Olive oil	1. ☐	2. ☒
(c) Peanut oil or groundnut oil	1. ☐	2. ☒
(d) Mixed or unspecified vegetable oil	1. ☐	2. ☒
(e) Lard or dripping (e.g. Blue Leaf lard)	1. ☐	2. ☒
(f) Creamed coconut	1. ☐	2. ☒
(g) Hard vegetable lard or margarine (e.g. Trex, Krona, Stork)	1. ☐	2. ☒
(h) Soft polyunsaturated margarine (e.g. Flora, Blue Leaf sunflower)	1. ☐	2. ☒
(i) Butter	1. ☒	2. ☐
(j) Other mixed spreads containing butter (e.g. Shape, Half Fat Anchor, Meadowcup, Willows)	1. ☐	2. ☒
(k) Pure ghee (clarified butter)	1. ☐	2. ☒
(l) Vegetable ghee	1. ☒	2. ☐

FOR OFFICE
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Appendices

2.5 (a) Are you following any kind of special diet different from what you usually eat: for instance to lose weight or for medical reasons?

1. ☐ Yes
2. ☒ No

If No, go to Question 2.6

If Yes:

(b) Which of the following best describes the diet you are on?

1. ☐ Slimming diet
2. ☐ Diabetic diet
3. ☐ Cholesterol-lowering diet
4. ☐ Fasting or abstaining for religious reasons
(e.g. Lent or Ramadan)
5. ☐ Other kind of special diet-

Please specify: _____

2.6 Which of the following do you think best describes your weight?

1. ☐ Underweight
2. ☐ About the right weight
3. ☒ A little overweight
4. ☐ Very overweight

FOR OFFICE
USE ONLY

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SECTION 3: SMOKING HABITS

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3.1 (a) Do you smoke cigarettes?

1. ☒ Yes
2. ☐ No

If No, go to Question 3.2

If Yes:

(b) Which kinds of cigarettes do you smoke?

Please tick either Yes or No for each of the kinds listed:

- (i) filter-tipped (manufactured) cigarettes? 1. ☒ Yes 2. ☐ No
(ii) manufactured cigarettes without filters? 1. ☐ Yes 2. ☒ No
(iii) hand-rolled cigarettes? 1. ☐ Yes 2. ☒ No

(c) How many manufactured cigarettes a day do you usually smoke?

enter number: 15

(d) How many hand-rolled cigarettes a day do you usually smoke?

enter number:

(e) How many ounces of tobacco do you use per week for hand-rolled cigarettes?

enter number:

Please go to Question 3.3

3.2 (a) Have you ever smoked cigarettes regularly?

1. ☐ Yes
2. ☐ No

If No, go to Question 3.4

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Appendices

If Yes:

(b) About how many manufactured cigarettes did you smoke in a day when you smoked them regularly?

enter number:

(c) About how many hand-rolled cigarettes did you smoke in a day when you smoked them regularly?

enter number:

(d) And about how many ounces of tobacco did you use per week for handrolled cigarettes?

enter number:

(e) How old were you when you stopped smoking cigarettes regularly?

enter age:

X 3.3 How old were you when you started to smoke cigarettes regularly?

enter age:

3.4 (a) Do you smoke cigars ?

1. ☐ Yes

2. ☒ No

If No, go to Question 3.5

If you do smoke cigars:

(b) How many cigars per week?

enter number:

FOR OFFICE
USE ONLY

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3.5 (a) Do you smoke a pipe?

1. ☐ Yes

2. ☒ No

If No, go to Section 4

If you do smoke a pipe:

(b) How many ounces of pipe tobacco do you smoke per week?

enter number:

FOR OFFICE
USE ONLY

5:

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5:

SECTION 4. DRINKING HABITS

4.1 (a) In the past 12 months have you taken an alcoholic drink:

1. ☐ Twice a day or more
2. ☐ Almost daily
3. ☐ Once or twice a week
4. ☐ Once or twice a month
5. ☐ On special occasions only
6. ☒ Not at all

If you have ever taken alcohol:

(b) Comparing now with 5 years ago would you say that you are:

1. ☐ Drinking about the same now as 5 years ago
2. ☐ Drinking more now than 5 years ago
3. ☐ Drinking less now than 5 years ago

If you have given up drinking or you are drinking less,

(c) What was the reason?

1. ☐ Illness/doctor's advice
2. ☐ Concerned about health
3. ☐ Too expensive
4. ☐ Other reason - Please specify: _____

IF YOU NEVER DRINK ALCOHOL PLEASE GO TO SECTION 5.

4.2 Which of the following best describes the amount you drink?

1. ☐ Hardly drink at all
2. ☐ Drink a little
3. ☐ Drink a moderate amount
4. ☐ Drink quite a lot
5. ☐ Drink heavily

FOR OFFICE
USE ONLY

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4.3 (a) How often have you had a drink of beer or cider during the last 12 months?

1. ☐ Most days
2. ☐ Three or four times per week
3. ☐ Once or twice a week
4. ☐ Once or twice a month
5. ☐ Once or twice in 6 months
6. ☐ Once or twice a year
7. ☐ Not at all in the last 12 months

If not at all in the last 12 months, go to Question 4.4

(b) When you have had a drink of beer or cider in the last 12 months, how many pints have you usually drunk on any one occasion?

1. ☐ 1/2-1 pint
2. ☐ 1-2 pints
3. ☐ 3-4 pints
4. ☐ 5 pints or more

4.4 (a) How often have you had a drink of wine during the last 12 months?

1. ☐ Most days
2. ☐ Three or four times per week
3. ☐ Once or twice a week
4. ☐ Once or twice a month
5. ☐ Once or twice in 6 months
6. ☐ Once or twice a year
7. ☐ Not at all in the last 12 months

If not at all in the last 12 months, go to Question 4.5

(b) When you have had a drink of wine in the last 12 months, how many glasses have you usually drunk on any one occasion? (1 bottle of wine contains 6 glasses).

1. ☐ 1-2 glasses
2. ☐ 3-4 glasses
3. ☐ 5 glasses or more

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FOR OFFICE USE ONLY

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4.5 (a) How often have you had a drink of fortified wine - sherry, vermouth, port, cinza-
no or duobornet - during the last 12 months?

If not at all in the last 12 months, go to Question 4.6

1. ☐ Most days
2. ☐ Three or four times per week
3. ☐ Once or twice a week
4. ☐ Once or twice a month
5. ☐ Once or twice in 6 months
6. ☐ Once or twice a year
7. ☐ Not at all in the last 12 months

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(b) When you have had a drink of fortified wine in the last 12 months, how many
glasses (equivalent to sherry glasses) have you usually drunk on any one occasion?

1. ☐ 1-2 glasses
2. ☐ 3-4 glasses
3. ☐ 5 glasses or more

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4.6 (a) How often have you had a drink of spirits - gin, whisky, rum, brandy or vodka -
during the last 12 months?

If not at all in the last 12 months, go to Section 5

1. ☐ Most days
2. ☐ Three or four times per week
3. ☐ Once or twice a week
4. ☐ Once or twice a month
5. ☐ Once or twice in 6 months
6. ☐ Once or twice a year
7. ☐ Not at all in the last 12 months

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(b) When you have had a drink of spirits in the last 12 months, how many measures
have you usually drunk on any one occasion? (Please remember that a drink poured
at home could be equivalent to two or three pub measures).

1. ☐ 1-2 measures
2. ☐ 3-4 measures
3. ☐ 5 measures or more

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USE ONLY

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SECTION 5. EXERCISE

5.1 Which of the answers below best describe your activity at work?

Please tick one of the boxes in answer to each question.

- Never Seldom Sometimes Often Always
- (a) Do you sit 1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☒
- (b) Do you stand 1. ☐ 2. ☐ 3. ☒ 4. ☐ 5. ☐
- (c) Do you walk 1. ☐ 2. ☐ 3. ☒ 4. ☐ 5. ☐
- (d) Do you lift heavy loads 1. ☐ 2. ☒ 3. ☐ 4. ☐ 5. ☐

5.2 While travelling to and from work, or in your spare time:

(a) How many miles do you walk on an average weekday?

1. ☒ Less than 1 mile
2. ☐ 1 to 3 miles
3. ☐ 4 miles or more

(b) How many miles do you walk in an average weekend?

1. ☒ Less than 1 mile
2. ☐ 1 to 3 miles
3. ☐ 4 miles or more

5.3 (a) Do you ride a bicycle regularly?

1. ☐ Yes
2. ☒ No If No, go to Question 5.4

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USE ONLY

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If Yes,

(b) How many miles do you cycle on an average weekday?

1. ☐ Less than 2 miles
2. ☐ 2 to 6 miles
3. ☐ 7 miles or more

(c) How many miles do you cycle in an average weekend?

1. ☐ Less than 2 miles
2. ☐ 2 to 6 miles
3. ☐ 7 miles or more

5.4 (a) Do you play any sport (or other recreational exercise such as swimming or dancing)?

1. ☐ Yes
2. ☒ No If No, go to Question 5.6

If Yes,

(b) Which sport do you play most frequently?

01. ☐ Bowling	06. ☐ Dancing (disco/aerobic)
02. ☐ Football or rugby	07. ☐ Cricket
03. ☐ Golf	08. ☐ Badminton
04. ☐ Swimming	09. ☐ Tennis
05. ☐ Jogging	10. ☐ Squash

Other sport - please specify: _____

(c) How many hours a week do you play it?

1. ☐ Less than 1 hour/week
2. ☐ 1 to 2 hours/week
3. ☐ 3-4 hours/week
4. ☐ 5 hours/week or more

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	02

Appendices

(d) How many months a year?

1. ☐ Less than 1 month in a year
2. ☐ 1 to 3 months/year
3. ☐ 4 to 6 months/year
4. ☐ More than 6 months of the year

5.5 (a) Do you play a second sport?

1. ☐ Yes
2. ☐ No

If No, go to Question 5.6

If Yes,

(b) Which sport is it?

01. ☐ Bowling	06. ☐ Dancing (disco/aerobic)
02. ☐ Football or rugby	07. ☐ Cricket
03. ☐ Golf	08. ☐ Badminton
04. ☐ Swimming	09. ☐ Tennis
05. ☐ Jogging	10. ☐ Squash

Other sport - please specify: _____

(c) How many hours a week do you play it?

1. ☐ Less than 1 hour/week
2. ☐ 1 to 2 hours/week
3. ☐ 3-4 hours/week
4. ☐ 5 hours/week or more

(d) How many months a year?

1. ☐ Less than 1 month in a year
2. ☐ 1 to 3 months/year
3. ☐ 4 to 6 months/year
4. ☐ More than 6 months of the year

FOR OFFICE
USE ONLY

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5.6 (a) Do you undertake in your spare time any other strenuous activities, such as the following:-

Digging
Pushing a hand lawn mower
Sawing wood with a handsaw
Lifting heavy loads

1. ☐ Yes
2. ☒ No

If No, go to Question 5.7

If Yes:

(b) How many hours a week do you spend in activities like these?

enter number of hours:

5.7 For how many hours in an average week do you watch television or video?

1. ☐ Less than 1 hour a week
2. ☐ 1-3 hours a week
3. ☐ 4-8 hours a week
4. ☒ 9-15 hours a week
5. ☐ 16 hours a week or more

5.8 Either at work or in leisure time:

(a) At least once a week do you engage in any regular activity similar to brisk walking, jogging, cycling, etc long enough to work up a sweat?

1. ☐ Yes
2. ☒ No

If Yes:

(b) How many times per week?

Enter number of times:

FOR OFFICE
USE ONLY

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☐ 2 13

☐ 14 - 15

Appendices

5.9 (a) Is your activity limited by any disability?

1. ☒ Yes
2. ☐ No

If Yes,

(b) Which of these most limits your activity?

1. ☒ Old injury
2. ☐ Arthritis
3. ☒ Back pain
4. ☒ Foot problems such as bunions or corns
5. ☒ Chest trouble such as asthma or bronchitis
6. ☒ Heart trouble
7. ☒ Other disability -

Please specify: Perforated ear drum (left)
Muscular pains

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SECTION 6. WORK CHARACTERISTICS

6.1 (a) What is your usual occupation?

Please give the exact title of your job: PRINTER (LINO TYPE)

(b) What kind of work do you do in this job?

Your main activity: NO WORK

(c) How many years' training (beyond leaving school at age 16) are required by your job?

1. ☐ Less than 1 year
2. ☐ At least 1 year but less than 3 years
3. ☒ At least 3 years but less than 5 years
4. ☐ 5 years or more

(d) Does your job require any special qualifications, training or apprenticeship?

1. ☐ No special training
2. ☒ Apprenticeship
3. ☐ Certificate, diploma or professional qualification -

Please specify: Composites

(e) Do you have to supervise other workers?

1. ☐ Yes
2. ☒ No

(f) Do you have to do the same thing over and over again?

1. ☒ Yes
2. ☐ No

(g) Do you have to ask permission if you need about half an hour during working hours to attend to your own affairs?

1. ☒ Yes
2. ☐ No

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Appendices

6.2 Are you employed at present?

1. ☐ Yes
 2. ☒ No If No, which one of the following reasons applies?
1. ☐ Waiting to take up a job already accepted
 2. ☐ Unemployed and seeking work
 3. ☐ Prevented by temporary sickness from seeking work
 4. ☒ Permanently sick or disabled
 5. ☐ Retired
 6. ☐ A full-time student
 7. ☐ Not working for any other reason

6.3 On average how many hours do you work per week?

Number of hours

FOR OFFICE
USE ONLY

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SECTION 7. GENERAL BACKGROUND INFORMATION

7.1 (a) What country were you born in?

01. ☐ England	13. ☐ Barbados
02. ☐ Wales	14. ☐ Trinidad
03. ☐ Scotland	15. ☐ Guyana
04. ☐ Northern Ireland	16. ☒ Kenya
05. ☐ Eire	17. ☐ Uganda
06. ☐ France	18. ☐ South Africa
07. ☐ Italy	19. ☐ India
08. ☐ Spain	20. ☐ Pakistan
09. ☐ Poland	21. ☐ Bangladesh
10. ☐ Cyprus	22. ☐ Sri Lanka
11. ☐ Malta	23. ☐ China
12. ☐ Jamaica	24. ☐ Hongkong

If none of the above, please write the name of the country below :-

Name of country: _____

(b) Where were your family living at the time you were born?

Name of place: NARCEI

Name of county or province: KENYA

(c) Was this in an urban area (a town or built-up suburb) or a rural area (a village or farming district)?

1. ☒ Urban area
 2. ☐ Rural area

7.2 (a) Were both your parents born in the same country as you were?

1. ☐ Yes If Yes, go to Question 7.3
 2. ☒ No

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Appendices

If No,

(b) What country was your father born in?

Name of country: PAKISTAN

(c) What country was your mother born in?

Name of country: PAKISTAN

7.3 At what age did you start school?

enter age: 5

7.4 At what age did you finish your full-time education?

enter age: 16

7.5 Please indicate your marital status. (tick one box)

1. ☒ Married (or equivalent)
2. ☐ Single
3. ☐ Widowed
4. ☐ Divorced
5. ☐ Separated

7.6 Is your home owned by you or your family, or rented?

1. ☒ Owned (with or without a mortgage)
2. ☐ Rented from the local council
3. ☐ Rented from a private landlord

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USE ONLY

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7.7 What is your religion?

01. ☐ Church of England	05. ☐ Hindu
02. ☐ Roman Catholic	06. ☐ Jain
03. ☐ Other Christian denomination	07. ☐ Sikh
04. ☐ Jewish	08. ☒ Muslim

09. ☐ Other religion - Please specify: _____

10. ☐ None If None, please go to Question 7.10

7.8 How often do you attend a church, synagogue, gurdhwara, temple or mosque for religious observance?

1. ☐ Daily
2. ☐ Three times a week or more
3. ☒ At least once a week
4. ☐ At least once a month
5. ☐ At least once a year
6. ☐ Never, or only for weddings and funerals

7.9 How often do you make religious observance at home?

1. ☒ Daily
2. ☐ Three times a week or more
3. ☐ At least once a week
4. ☐ At least once a month
5. ☐ Less than once a year
6. ☐ Never

The next few questions (7.10 to 7.15) ask about your family's circumstances at the time when you were twelve years old:

7.10 (a) What was your father's main job at the time you were twelve years old (or his last job if he died before this time)?

Title of job: TAILOR

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USE ONLY

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Appendices

(b) What kind of work did he do in this job?

Main activity: Cushion & Pillow covers, etc.

(c) Did this job require any special qualifications or training?

1. ☒ No special training
2. ☐ Apprenticeship
3. ☐ Certificate, diploma, degree or professional qualification
Please specify: _____

(d) Did he have to supervise other workers?

1. ☐ Yes
2. ☒ No

(e) Was he self-employed (running his own business) or working for an employer?

1. ☒ Working for employer
2. ☐ Self-employed

If he was self-employed:

(f) Did he employ anyone else apart from his own family?

1. ☐ Yes
2. ☐ No

7.13 At the time you were twelve years old was your family home:

1. ☒ Owned (with or without a mortgage) by your family
2. ☐ Rented from the local council
3. ☐ Rented from a private landlord

7.14 Did your family own any land, or property apart from their own house?

1. ☐ Owned land or houses rented to others
2. ☐ Owned land for their own cultivation only
3. ☒ Owned no land

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7.15 How many people lived in the family home at this time?

enter number: 13

7.16 How many rooms (bedrooms or living rooms) did the family home have at this time?

enter number: 5

7.17 Did your family home have:

1. ☒ Running water with a bath or shower
2. ☐ Running water but no bath or shower
3. ☐ No running water

If you were born overseas please answer the last question. (7.18.) If you were born in Britain please go straight to the instructions on page 35.

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USE ONLY

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7.18 (a) At what age did you come to England to live? (Do not count student visits, or visits to relatives and friends.)

Enter age: 42

(b) In the 10 years before you came to England, which country did you live in for the most time?

02. ☐ Wales	13. ☐ Barbados
03. ☐ Scotland	14. ☐ Trinidad
04. ☐ Northern Ireland	15. ☐ Guyana
05. ☐ Eire	16. ☒ Kenya
06. ☐ France	17. ☐ Uganda
07. ☐ Italy	18. ☐ South Africa
08. ☐ Spain	19. ☐ India
09. ☐ Poland	20. ☐ Pakistan
10. ☐ Cyprus	21. ☐ Bangladesh
11. ☐ Malta	22. ☐ Sri Lanka
12. ☐ Jamaica	23. ☐ China
	24. ☐ Hongkong

If none of the above, please write the name of the country below:

(c) What language did you first speak as a child?

Enter this language: Uganda

If this first language was not English:

(d) Which one language do you usually speak at home with your spouse?

1. ☐ English
2. ☒ First language
3. ☐ Other language
4. ☐ No spouse

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2 64

(e) Which one language do you usually speak at home with your children?

1. ☐ English
2. ☒ First language
3. ☐ Other language
4. ☐ No children at home

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2 65

Appendix 4

Appendix 4.1: No of Ideal LS7 Metrics in participants free of stroke and heart disease

British Regional Heart Study

Number of ideal LS7 metrics	Q1 n=7112 (%)	Q20 excluding diet n=3177 (%)	Q20 including diet n=3177 (%)
0	8.9	2.6	2.4
1	27.6	18.0	14.4
2	32.6	34.2	29.6
3	21.2	30.9	31.9
4	7.7	11.7	15.6
5	1.8	2.4	5.2
6	0.2	0.3	0.9
7	-	-	0.1
Total	100	100	100

Southall and Brent Re-Visited Study

Number of ideal LS7 metrics	European n=1860 (%)	South Asian n=1352 (%)
0	3	1
1	14	10
2	25	22
3	26	29
4	20	22
5	8	11
6	3	4
7	<1	<1
Total	100	100

Appendices

Appendix 4.2: Risk of stroke in middle-aged (Q1) and older (Q20) BRHS men free of prevalent stroke and heart disease.

	Q1 1978-1980 ¹				Q20 1998-2000 ²			
	Events/N	Rate/1000PY [95% CI]	HR [95% CI]		Events/N	Rate/1000PY [95% CI]	HR [95% CI]	
			Model 1 N=7112	Model 2 N=7097			Model 1 N=3177	Model 2 N=3135
BMI								
Poor	43/564	4.44 [3.29-5.99]	1	1	46/502	6.71 [5.02-8.95]	1	1
Intermediate	202/3260	3.47 [3.03-3.99]	0.75 [0.54-1.04]	0.77 [0.55-1.07]	202/1673	8.54 [7.44-9.81]	1.20 [0.87-1.65]	1.21 [0.88-1.68]
Ideal	176/3228	2.98 [2.57-3.45]	0.69 [0.49-0.96]	0.73 [0.52-1.01]	115/1002	8.50 [7.08-10.2]	1.15 [0.82-1.62]	1.17 [0.83-1.65]
P for trend			0.03	0.06			0.43	0.38
BP								
Poor	301/4109	4.21 [3.76-4.71]	1	1	264/2138	9.19 [8.15-10.4]	1	1
Intermediate	103/2371	2.35 [1.93-2.85]	0.64 [0.51-0.80]	0.65 [0.52, 0.81]	83/835	6.85 [5.52-8.49]	0.82 [0.64-1.06]	0.81 [0.63-1.04]
Ideal	17/632	1.47 [0.91-2.36]	0.40 [0.25-0.65]	0.42 [0.26-0.68]	16/204	5.00 [3.06-8.15]	0.60 [0.36-1.00]	0.60 [0.36-0.99]
P for trend			<0.001	<0.001			0.051	0.046
Glucose								
Poor	46/579	4.60 [3.44-6.13]	1	1	35/289	10.1 [7.22-14.0]	1	1
Intermediate	127/1930	3.73 [3.13-4.43]	0.87 [0.62-1.22]	0.89 [0.63-1.24]	164/1368	8.77 [7.53-10.2]	0.85 [0.59-1.22]	0.83 [0.57-1.19]
Ideal	248/4603	2.99 [2.64-3.39]	0.72 [0.53-0.99]	0.75 [0.54-1.02]	164/1520	7.50 [6.44-8.74]	0.76 [0.53-1.09]	0.74 [0.51-1.06]
P for trend			0.04	0.07			0.14	0.10
Cholesterol								
Poor	206/3457	3.35 [2.92-3.84]	1	1	146/1270	8.12 [6.90-9.54]	1	1
Intermediate	160/2590	3.45 [2.95-4.02]	1.04 [0.85-1.28]	1.03 [0.84-1.26]	136/1252	7.79 [6.59-9.21]	0.93 [0.74-1.18]	0.93 [0.73-1.17]
Ideal	55/1065	2.90 [2.23-3.78]	0.89 [0.66-1.19]	0.86 [0.64-1.16]	81/655	9.43 [7.58-11.7]	1.12 [0.85-1.47]	1.14 [0.87-1.50]
P for trend			0.43	0.32			0.41	0.35
PA								
Poor	46/597	4.56 [3.42-6.09]	1	1	31/318	9.08 [6.39-12.9]	1	1
Intermediate	246/3800	3.68 [3.24-4.17]	0.77 [0.56-1.06]	0.79 [0.57-1.08]	165/1324	9.21 [7.90-10.7]	0.96 [0.65-1.41]	0.97 [0.65-1.43]
Ideal	129/2715	2.58 [2.17-3.08]	0.59 [0.42-0.83]	0.64 [0.45-0.89]	167/1535	7.36 [6.32-8.56]	0.79 [0.54-1.16]	0.82 [0.55-1.21]
P for trend			0.003	0.009			0.23	0.32
Smoking								
Poor	211/2915	4.25 [3.72-4.87]	1	1	42/406	8.63 [6.37-11.7]	1	1
Intermediate	142/2470	3.17 [2.69-3.74]	0.67 [0.54-0.83]	0.70 [0.56-0.86]	6/88	5.42 [2.44-12.1]	0.69 [0.29-1.63]	0.70 [0.30-1.65]
Ideal	68/1727	2.09 [1.65-2.65]	0.53 [0.40-0.70]	0.58 [0.44-0.77]	315/2683	8.28 [7.41-9.24]	0.84 [0.61-1.16]	0.85 [0.62-1.18]
P for trend			<0.001	<0.001			0.28	0.34

Appendices

	Q1 1978-1980 ¹				Q20 1998-2000 ²			
	Events/N	Rate/1000PY [95% CI]	HR [95% CI]		Events/N	Rate/1000PY [95% CI]	HR [95% CI]	
			Model 1 N=7112	Model 2 N=7097			Model 1 N=3177	Model 2 N=3135
EDI								
Poor	...	...	...	...	132/1214	8.32 [7.01-9.87]	1	1
Intermediate	...	...	...	...	140/1188	8.44 [7.15-9.96]	1.03 [0.81-1.30]	1.06 [0.83-1.35]
Ideal	...	...	...	...	91/775	7.86 [6.40-9.65]	0.96 [0.73-1.26]	0.99 [0.75-1.31]
P for trend			...	...			0.77	0.96

Model 1 adjusted for age. Model 2 adjusted additionally for social class and alcohol intake at Q1/Q20.

¹Followed from Q1 to Q20; ²Followed from Q20 to June 2018.

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; EDI, Elderly Diet Index; PA, Physical Activity

Appendices

Appendix 4.3: Risk of stroke in middle-aged European and South Asian SABRE participants free of prevalent stroke and CHD.

	Europeans				South Asians			
	Events/N	Rate/1000PY [95% CI]	HR [95% CI] Model 1 N=1860	Model 2 N=1785	Events/N	Rate/1000PY [95% CI]	HR [95% CI] Model 1 N=1352	Model 2 N=1269
BMI								
Poor	21/267	4.37 [2.85-6.70]	1	1	18/170	5.74 [3.62-9.12]	1	1
Intermediate	62/805	4.12 [3.21-5.29]	0.85 [0.52-1.40]	0.99 [0.59-1.65]	65/644	5.29 [4.15-6.75]	0.96 [0.56-1.63]	1.03 [0.58-1.80]
Ideal	63/788	4.30 [3.36-5.50]	0.98 [0.60-1.60]	1.07 [0.64-1.79]	48/538	4.67 [3.52-6.20]	0.82 [0.47-1.42]	0.84 [0.47-1.52]
P for trend			0.93	0.80			0.47	0.57
BP								
Poor	38/346	6.29 [4.58-8.65]	1	1	54/355	8.47 [6.49-11.1]	1	1
Intermediate	61/775	4.22 [3.28-5.42]	0.70 [0.46-1.04]	0.72 [0.48-1.10]	64/561	6.03 [4.72-7.71]	0.76 [0.53-1.10]	0.78 [0.53-1.14]
Ideal	47/739	3.35 [2.52-4.46]	0.67 [0.44-1.04]	0.73 [0.47-1.13]	13/436	1.49 [0.87-2.57]	0.21 [0.12-0.39]	0.23 [0.12-0.43]
P for trend			0.07	0.17			<0.001	<0.001
Glucose								
Poor	13/88	9.00 [5.22-15.5]	1	1	39/205	11.2 [8.17-15.3]	1	1
Intermediate	51/582	4.76 [3.62-6.26]	0.61 [0.33-1.12]	0.61 [0.33-1.12]	35/406	4.44 [3.19-6.18]	0.43 [0.27-0.69]	0.40 [0.25-0.64]
Ideal	82/1190	3.67 [2.96-4.56]	0.49 [0.27-0.89]	0.52 [0.29-0.93]	57/741	3.98 [3.07-5.16]	0.39 [0.26-0.59]	0.37 [0.24-0.57]
P for trend			0.02	0.03			<0.001	<0.001
Cholesterol								
Poor	65/782	4.49 [3.52-5.73]	1	1	56/493	6.08 [4.68-7.90]	1	1
Intermediate	62/659	5.07 [3.95-6.50]	1.26 [0.88-1.79]	1.27 [0.89-1.81]	47/511	4.77 [3.59-6.35]	0.82 [0.56-1.21]	0.87 [0.58-1.31]
Ideal	19/419	2.46 [1.55-3.82]	0.70 [0.42-1.17]	0.71 [0.42-1.19]	28/348	4.22 [2.91-6.11]	0.76 [0.48-1.19]	0.84 [0.52-1.34]
P for trend			0.18	0.20			0.23	0.46
PA								
Poor	24/371	3.60 [2.41-5.37]	1	1	44/405	5.90 [4.39-7.93]	1	1
Intermediate	77/946	4.36 [3.49-5.46]	1.35 [0.85-2.15]	1.54 [0.94-2.52]	62/697	4.62 [3.60-5.92]	0.99 [0.66-1.48]	0.82 [0.53-1.25]
Ideal	45/543	4.42 [3.30-5.92]	1.53 [0.92-2.56]	1.72 [1.00-2.95]	25/250	5.19 [3.51-7.68]	1.16 [0.69-1.95]	1.04 [0.61-1.77]
P for trend			0.10	0.05			0.57	0.89
Smoking								
Poor	60/606	5.59 [4.34-7.19]	1	1	!	5.45 [3.43-8.64]	1	1
Intermediate	50/659	4.06 [3.08-5.35]	0.58 [0.40-0.85]	0.60 [0.40-0.88]	!	4.73 [2.54-8.79]	0.79 [0.36-1.70]	0.99 [0.44-2.22]
Ideal	36/595	3.15 [2.27-4.36]	0.49 [0.32-0.74]	0.56 [0.36-0.85]	103/1062	5.08 [4.19-6.16]	0.85 [0.51-1.41]	1.03 [0.59-1.80]
P for trend			<0.001	0.007			0.53	0.92

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	Europeans				South Asians			
	Events/N	Rate/1000PY [95% CI]	HR [95% CI]		Events/N	Rate/1000PY [95% CI]	HR [95% CI]	
			Model 1 N=1860	Model 2 N=1785			Model 1 N=1352	Model 2 N=1269
FFV intake								
Poor	17/139	6.89 [4.29-11.1]	1	1	!	2.57 [0.83-7.96]	1	1
Intermediate	59/689	4.64 [3.60-5.99]	0.70 [0.41-1.21]	0.81 [0.46-1.43]	!	5.63 [4.26-7.42]	2.05 [0.64-6.59]	2.05 [0.63-6.63]
Ideal	70/1032	3.62 [2.87-4.58]	0.50 [0.30-0.85]	0.59 [0.34-1.04]	78/820	4.99 [3.99-6.22]	1.61 [0.51-5.12]	1.67 [0.52-5.37]
P for trend			0.01	0.07			0.42	0.39

Model 1 adjusted for age and sex. Model 2 adjusted additionally for social class and alcohol intake. Median follow-up 20y.

! small numbers not disclosed.

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; FFV, Fresh Fruit and Vegetable; PA, Physical Activity

Appendices

Appendix 4.4: Risk of events in older BRHS men free of CVD – comparison with sensitivity analyses

	Risk of Stroke in men free of stroke and MI (Main)	Risk of Stroke in men free of stroke, MI, <i>HF</i> and <i>AF</i>	Risk of MI in men free of stroke and MI	Composite Risk of Stroke and MI in men free of stroke and MI
No. events/N Rate/1000PY [95%CI]	363/3177 8.24 [7.44-9.14]	344/3011 8.13 [7.31-9.03]	485/3177 10.97 [10.03-11.99]	808/3177 18.47 [17.24-19.79]
HR [95%CI] CVH Score CVH Status[§]	0.95 [0.90, 1.01]	0.95 [0.90-1.01]	0.86 [0.82-0.90]	0.89 [0.86-0.93]
Poor	1	1	1	1
Average	0.73 [0.46, 1.15]	0.71 [0.44-1.13]	0.66 [0.46-0.95]	0.68 [0.51-0.91]
Optimal	0.68 [0.41, 1.13]	0.68 [0.41-1.14]	0.37 [0.24-0.58]	0.48 [0.34-0.67]
P for trend	0.14	0.15	<0.001	<0.001
PAF (%) [95% CI]	6.4 [-16.8-25.0]	4.9 [-19.1-24.0]	40.5 [23.2-54.0]	27.3 [13.5-39.0]
CVH Trajectories				
Low-Low	1	1	1	1
Low-High	0.60 [0.44-0.83]	0.63 [0.46-0.88]	0.70 [0.55-0.90]	0.65 [0.54-0.80]
High-Low	0.83 [0.60-1.15]	0.92 [0.66-1.29]	0.67 [0.50-0.90]	0.73 [0.58-0.91]
High-High	0.86 [0.66-1.12]	0.87 [0.65-1.16]	0.47 [0.35-0.62]	0.60 [0.49-0.73]

Incidence rates are unadjusted. HR adjusted for social class, age and alcohol intake.

CVH, Cardiovascular Health

[§]Poor: 0-4, Average: 5-9, Optimal: 10-14.

PAF (Population attributable fraction) calculated using punafcc package for Stata, evaluating the scenario where all participants had optimal CVH, adjusted for age, sex, social class and alcohol intake. Negative values of PAF correspond to 95% CI for respective HR crossing 1.

CVH trajectories exclude diet.

Appendices

Appendix 4.5: Comparison of older BRHS men with complete and missing data, free of prevalent CVD at Q20 (n=3798).

Variable	Complete cases n=3135	Missing sample n=663	P value
Stroke Events	358	88	0.18
Rate/1000PY [95%CI]	8.2 [7.4-9.1]	11.2 [9.1-13.8]	
Age	68.3 (5.4)	69.8 (5.7)	<0.001
SBP	149.7 (23.7)	150.4 (25.5) n=648	0.49
DBP	85.6 (11.0)	85.0 (11.6) n=648	0.21
BMI	26.8 (3.6)	27.4 (4.2) n=648	<0.001
Glucose	5.97 (1.68)	6.21 (2.46) n=483	0.01
Cholesterol	6.05 (1.07)	5.91 (1.09) n=483	0.01
Physical Activity		n=530	
Poor	10	14	0.001
Intermediate	42	46	
Ideal	48	40	
Smoking		n=657	
Poor	13	15	0.37
Intermediate	3	3	
Ideal	85	83	
Diet		n=377	
Poor	38	45	0.02
Intermediate	37	34	
Ideal	25	21	
Q20 CVH score (0-14)	7.71 (2)	7.02 (2) n=42	0.03
Q20 CVH score excl. diet (0-12)	6.85 (2)	6.72 (2) n=287	0.26
Q1 CVH score (0-12)	6.66 (2) n=3089	6.33 (2) n=645	<0.001
Q1 CVH Status[§]	n=3089	n=645	
Poor	11	18	<0.001
Average	72	69	
Optimal	16	13	

Values are mean (sd) or %. Compared using t-tests or chi square tests.

Abbreviations: BMI, Body Mass Index; BRHS, British Regional Heart Study; CI, Confidence Intervals; CVD, cardiovascular disease; CVH, cardiovascular health; DBP, Diastolic Blood Pressure; PY, person years; SBP, Systolic Blood Pressure.

[§]Inadequate: 0-4, Average: 5-8, Optimal: 9-12.

Appendices

Appendix 4.6: Hazard ratios [95% CI] of stroke among men free of prevalent CVD at Q20, assigned poor level for missing LS7 in sensitivity sample.

Variable	Sensitivity Sample
Stroke Events/Total	446/3798
Rate /1000PY [95%CI]	8.7 [7.9, 9.5]
Q20 CVH score, mean (sd), range 0-14	7.43 (2)
Hazard Ratio per unit increase in CVH score*	0.96 [0.91, 1.00]
Hazard Ratios per CVH Status* [§]	
Poor	1
Average	0.85 [0.60-1.22]
Optimal	0.78 [0.51-1.19]
P for trend	0.25
PAF for suboptimal CVH (%)	8.26 [-14.3-26.3]
Hazard ratios CVH Trajectories**	
LL	1
LH	0.63 [0.47, 0.86]
HL	0.87 [0.65, 1.17]
HH	0.86 [0.66, 1.11]

Abbreviations: CI, Confidence Intervals; CVD, cardiovascular disease; CVH, cardiovascular health; PY, person years; Q20, 20year follow up; Trajectories LL, Low-Low; LH, Low-High; HL, High-Low; HH, High-High.

*N=3732 Reduced due to missing social class and alcohol intake (n=66). ** N=3668 Exclusive of diet, based on CVH score at Q1 and Q20. [§]Inadequate: 0-4, Average: 5-9, Optimal: 10-14

Appendices

Appendix 4.7: Risk of stroke, CHD and composite events in European and South Asian SABRE participants free of CVD

	Europeans			South Asians		
No. events/N Rate/1000PY [95%CI]	Stroke 146/1860 4.23 [3.60-4.98]	CHD 426/1856 13.1 [11.9-14.4]	CVD 509/1851 15.9 [14.6-17.4]	Stroke 131/1352 5.10 [4.30-6.05]	CHD 494/1353 21.4 [19.6-23.4]	CVD 543/1344 24.0 [22.1-26.2]
HR [95%CI]						
CVH Score	0.91 [0.83-0.99]	0.84 [0.80-0.88]	0.85 [0.81-0.89]	0.84 [0.77-0.92]	0.83 [0.80-0.87]	0.84 [0.80-0.88]
CVH Status ^s						
Poor	1	1	1	1	1	1
Average	0.65 [0.30-1.41]	0.56 [0.36-0.88]	0.62 [0.41-0.95]	0.75 [0.30-1.87]	0.42 [0.27-0.64]	0.47 [0.31-0.73]
Optimal	0.49 [0.21-1.11]	0.26 [0.16-0.43]	0.32 [0.20-0.51]	0.41 [0.15-1.07]	0.23 [0.15-0.37]	0.27 [0.17-0.42]
P for trend	0.09	<0.001	<0.001	0.07	<0.001	<0.001
PAF (%)	20.8	44.9	36.0	35.7	33.9	33.1
[95%CI]	[-7.03-41.4]	[32.6-54.9]	[28.1-49.2]	[11.3-53.4]	[23.6-42.8]	[23.4-41.7]
HR [95%CI]				0.86 [0.78-0.94]	0.83 [0.80-0.87]	0.84 [0.81-0.88]
CVH Score ABMI~						
CVH Status ABMI~						
Poor				1	1	1
Average				0.56 [0.28-1.13]	0.41 [0.29-0.59]	0.44 [0.31-0.63]
Optimal				0.28 [0.12-0.63]	0.25 [0.17-0.37]	0.26 [0.18-0.38]
P for trend				0.002	<0.001	<0.001
PAF~ (%)				44.4	34.9	35.2
[95%CI]				[16.4-63.0]	[22.7-45.1]	[23.8-45.0]

Incidence rates are unadjusted. HR adjusted for age sex social class, and alcohol intake. CVH categories Poor: 0-4, Average: 5-9, Optimal: 10-14

PAF (Population attributable fraction) calculated using punafcc package for Stata, evaluating the scenario where all participants had optimal CVH, adjusted for age, sex, social class and alcohol intake. Negative values of PAF correspond to 95% CI for respective HR crossing 1.

~ABMI: Asian BMI Cut-offs applied 23kg/m² for overweight and 27.5 kg/m² for obesity.

Appendices

Appendix 4.8: Comparison of CVH status between middle-aged European and South Asian participants of the SABRE study, with Asian obesity thresholds applied.

Using Asian BMI cut-offs: 23kg/m ² for overweight and 27.5 kg/m ² for obesity			
	European n=1860	South Asian n=1352	
BMI*			
Poor	14	13	
Intermediate	43	48	
Ideal	42	40	
ABMI~**			
Poor	14	31	
Intermediate	43	51	
Ideal	42	18	
CVH Status ABMI~			
Poor	3	4	
Average	64	66	
Optimal	33	30	
		Without incident stroke (N=1221)	With incident stroke (N=131)
CVH Status ABMI~**			
Poor		4	!
Average		65	!
Optimal		31	15

CVH: cardiovascular health; ~ Asian BMI cut-offs applied. *p 0.04 **p <0.001

Appendices

Appendix 4.9: Comparison of SABRE participants with complete and missing data, free of prevalent CVD

Variable	Europeans			South Asians		
	Complete cases n=1785	Missing sample n=89	P value	Complete cases n=1269	Missing sample n=107	P value
No. Stroke Events	142	!	0.23	120	16	0.07
Rate/1000PY [95%CI]	4.29 [3.64-5.05]	2.44 [0.92-6.50]		4.96 [4.15-5.93]	8.10 [4.96-13.2]	
Age	52.7 (7)	53.7 (7)	0.20	50.6 (7)	51.5 (7)	0.23
SBP	123 (17)	121 (16), n=88	0.51	125 (18)	125 (18)	0.93
DBP	77 (11)	76 (10), n=88	0.26	80 (11)	80 (9)	0.53
BMI	26.1 (4)	26.7 (5), n=88	0.19	26.1 (4)	26.8 (4), n=106	0.05
Glucose	5 [5, 6]	5 [5, 6], n=81	0.74	5 [5, 6]	5 [5, 6], n=97	0.96
Cholesterol	6.1 (1.2)	6.2 (1.2), n=82	0.29	5.9 (1.1)	6.0 (1.2), n=102	0.32
Social Class Manual	60	75, n=72	0.01	75	79, n=66	0.51
Units of Alcohol/wk	8 [1, 20]	2 [0.1, 12], n=27	0.05	1 [0, 12]	0 [0, 0], n=55	<0.001
Physical Activity	10 [7, 15]	10 [5, 14]	0.07	9 [4, 13]	7 [2, 12]	0.004
Smoking		n=88			n=103	
Poor	32	38		13	!	
Intermediate	36	30	0.45	9	!	0.61
Ideal	32	33		78	80	
Diet		n=88			n=94	
Poor	7	14		5	!	0.42
Intermediate	37	35	0.08	35	!	
Ideal	56	51		61	60	
CVH score (0-14)	8.5 (2)	8.1 (2), n=75	0.10	8.7 (2)	8.5 (2), n=83	0.37

Values are mean (sd) and %. Compared using t-tests/K-wallis or Chi square/Fischer's exact tests.

Abbreviations: BMI, Body Mass Index; BRHS, British Regional Heart Study; CI, Confidence Intervals; CVD, cardiovascular disease; CVH, cardiovascular health; DBP, Diastolic Blood Pressure; PY, person years; Q20, 20year follow up; SBP, Systolic Blood Pressure.

Appendix 5

Appendix 5.1:TRIOPD Checklist

Section/Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	185
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Summary 185
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	186-187
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	187
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	188
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	188
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	188, section 3.2
	5b	Describe eligibility criteria for participants.	Tables 5.1 and 5.2
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	188, Tables 5.1 and 5.2
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Tables 5.1 and 5.2
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	189
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	191, Appendix 5.2A-E
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	189
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	190-191
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	Provide details on how risk groups were created, if done.	190

Appendices

Section/Topic		Checklist Item	Page
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	196, Tables 5.1 & 5.2, Appendix 5.3-6
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	192-194, Appendix 5.3-6
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	192-194, Appendix 5.2A-E Appendix 5.3-6
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Appendix 5.3-6
Model performance	16	Report performance measures (with CIs) for the prediction model.	192-195, Table 5.3, Figures 5.1-5.4
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	199-200
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	193, 196-199
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	196-200
Implications	20	Discuss the potential clinical use of the model and implications for future research.	198-199, 287-289, sections 8.4.4-5
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Section 3.2
Funding	22	Give the source of funding and the role of the funders for the present study.	Acknowledgements

Appendices

Appendix 5.2: Missing data comparisons

P values are for T-tests for continuous and Chi-square tests for categorical variables

(A) FSRP – missingness is 6% overall among those free of stroke and TIA (n=3981), 3% due to missing data for Diabetes and ≤1% for all other predictors.

	Men with complete data		Men with missing data		P for difference
Stats	N	Mean (SD) or %	N	Mean (SD) or %	
Manual Social Class	3755	51	218	58	0.05
Age	3762	68.5 (5.5)	219	69.1 (5.5)	0.1222
SBP	3762	141 (24)	202	140 (21)	0.5525
Bp meds	3762	32	168	34	0.517
Smoking	3762	13	212	15	0.43
Prev. CVD	3762	26	219	20	0.037
Prev. AF	3762	4	219	<5	0.911
Prev. LVH	3762	2	208	<5	0.183
Prev. DM	3762	11	83	13	0.562
Incident Stroke/TIA	3762	10	219	10	0.878

(B) QSTROKE – missingness is 12% overall among those free of stroke TIA warfarin use and not having a haemorrhagic stroke (n=3844), 5% due to missing data for CKD and chol:HDL ratio, 3% for Diabetes and ≤1% for all other predictors.

	Men with complete data		Men with missing data		P for difference
Stats	N	Mean (SD) or %	N	Mean (SD) or %	
Manual Social Class	3369	50	467	56	0.019
Age	3376	68.4 (5.5)	468	69.0 (5.4)	0.041
BMI	3376	26.8 (3.6)	452	27.5 (4.3)	0.0004
Chol:HDL	3376	4.78 (1.4)	258	4.70 (1.5)	0.3964
SBP	3376	141 (24)	451	140 (24)	0.382
Smoking	3376	13	461	12	0.451
Prev. AF	3376	3	468	3	0.898
Prev. HF	3376	2	468	3	0.299
Prev. CHD	3376	21	468	23	0.304
Prev. RA	3376	<0.5	417	<5	0.772
Prev. CKD	3376	11	282	11	0.89
BP meds	3376	30	417	37	0.006
Prev. DM	3376	11	338	12	0.524
Family h/o CHD	3376	5	419	7	0.263
Incident Stroke/TIA	3376	9	468	9	0.947

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(C) QRISK3 – missingness is 12% overall among those free of stroke TIA CHD statin use and not having a haemorrhagic stroke (n=3025), 5% due to missing data for CKD cholesterol and HDL, 3% for Diabetes and ≤1% for all other predictors.

	Men with complete data		Men with missing data		P for difference
Stats	N	Mean (SD) or %	N	Mean (SD) or %	
Manual Social Class	2662	50	355	53	0.10
Age	2669	68.1 (5.4)	356	68.8 (5.6)	0.0311
BMI	2669	26.7 (3.6)	348	27.2 (4.2)	0.0139
Chol:HDL	2669	4.8 (1.4)	207	4.7 (1.5)	0.2649
SBP	2669	142 (24)	345	141 (23)	0.501
Smoking	2669	13	352	12	0.444
Prev. AF	2669	3	356	4	0.669
Prev. RA	2669	<0.5	307	<5	0.821
Prev. CKD	2669	9	222	9	0.934
BP meds	2669	22	307	24	0.266
Prev. DM	2669	10	249	11	0.628
Family h/o CHD	2669	5	317	5	0.971
Corticosteroid use	2669	<0.5	307	<5	0.557
Antipsychotic use	2669	<0.5	307	<5	0.894
Migraine	2669	<0.5	307	<5	0.239
Impotence	2669	<0.5	307	<5	0.631
Incident Stroke/TIA	2669	9	356	8	0.73

(D) PCE – missingness is 10% overall among those free of stroke and PCE criteria of CVD and AF (n=3397), 5% due to missing data for cholesterol and HDL, 3% for Diabetes and ≤1% for all other predictors.

	Men with complete data		Men with missing data		P for difference
Stats	N	Mean (SD) or %	N	Mean (SD) or %	
Manual Social Class	3040	51	349	53	0.61
Age	3047	68.3 (5.4)	350	68.9 (5.6)	0.0634
SBP	3047	142 (24)	335	142 (23)	0.747
Chol	3047	234 (40)	197	239 (45)	0.105
HDL	3047	51.5 (13)	176	53.7 (15)	0.0354
Bp meds	3047	25	301	30	0.073
Smoking	3047	13	345	14	0.65
Prev. DM	3047	11	235	10	0.828
Incident Stroke	3047	6	350	5	0.648

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(E) Common CVD free sample used for comparing FSRP, QSTROKE and QRSIK3 - missingness is 12% overall for predictors of all 3 scores, 5% due to missing data for CKD, cholesterol and HDL, 3% for Diabetes and $\leq 1\%$ for all other predictors.

	Men with complete data		Men with missing data		P for difference
Stats	N	Mean (SD) or %	N	Mean (SD) or %	
Manual Social Class	2434	49	338	53	0.11
Age	2441	67.9 (5.3)	339	68.7 (5.5)	0.0087
BMI	2441	26.9 (3.5)	331	27.2 (4.1)	0.0124
Chol:HDL	2441	4.8 (1.4)	198	4.7 (1.5)	0.382
SBP	2441	142 (24)	328	141 (23)	0.906
Smoking	2441	13	335	13	0.867
Prev. LVH	2441	1	331	<5	0.343
Prev. RA	2441	0.41	295	<5	0.856
Prev. CKD	2441	9	212	9	0.874
BP meds	2441	20	295	24	0.142
Prev. DM	2441	10	236	11	0.478
Family h/o CHD	2441	5	306	5	0.936
Corticosteroid use	2441	<0.5	295	<5	0.623
Antipsychotic use	2441	<0.5	295	<5	0.975
Migraine	2441	<0.5	295	<5	0.975
Impotence	2441	<0.5	295	<5	0.728
Incident Stroke/TIA	2441	8	339	8	0.884

Appendix 5.3: Baseline and performance characteristics in the Framingham and BRHS samples

	BRHS		FSRP Men free of stroke
	Men free of stroke and TIA		
	Main Validation	Adjusted for Competing Risks	
Sample Size		3762	2732
Composite Events		366 [`]	213
All Strokes		221	162
TIA's		147	51
Competing Events	NA	900	-
Age (y)		68.5 (5.5), 58-81	65.4, 55-84
Systolic BP (mmHg)		141 (24.3), 73-233	139.3
BP medication		31.6	16.1
Diabetes		11.2	10.6
Smoking		12.8	33.8
Cardiovascular disease		26	22.2
Atrial Fibrillation		3.8	2.8
Left Ventricular Hypertrophy		1.7	3.5
Mean Prognostic Index [range]		5.85 [4.2-8.9]	5.68
Slope of Centred Prognostic Index	0.66 [^]	0.55 [^]	NA
[95% CI]	[0.52-0.80]	[0.41-0.68]	
Harrell's C	0.6346	0.6155	NA
[95% CI]	[0.6068-0.6624]	[0.5876-0.6434]	
10y Pred. Probability (%)			
Mean [Range]		13.7 [2.28-91.2]	NA
Median [Q1, Q3]		10.6 [6.88, 17.0]	
Mean Calibration	1.24	1.40	NA
Cut-off for high risk* (%)	10.97	9.73	-
Sensitivity (%)	67	71	-
Specificity (%)	54	47	-
Observed risk in those classified as high risk* (%)	15.5	12.5	-

[`]2 men had both TIA and Stroke on the same day. [^]P for slope=1, <0.001. *KM failure function for main analysis and cumulative incidence function for competing risks adjustment. Continuous variables show mean (sd), range. The FSRP publication does not provide a measure of SD. Categorical variables show %.

Appendix 5.4: Baseline and performance characteristics in QResearch-QStroke and BRHS samples

	BRHS		QStroke`
	Men free of stroke, TIA, anticoagulant use		Men free of stroke, TIA, anticoagulant use
	Main Validation	Adjusted for Competing Risks	
Sample Size		3376	1748108
Ischaemic Stroke or TIA events		307	38074
Competing events	NA	784	-
Age (y)		68 (5.5), 58-81	45 (15.4), 25-84
Townsend Score		Excluded	-0.1 (3.5)
Body Mass Index (kg/m ²)		26.8 (3.6), 14-48	26.0 (4.6)
Systolic BP (mmHg)		141 (24.2), 73-233	130 (19.9)
Total Cholesterol: HDL Cholesterol		4.8 (1.4), 2-12	4.1 (1.3)
Ethnicity	99 White/not recorded		94 White/not recorded
	Excluded		
Atrial Fibrillation		2.7	0.4
Premature CHD in family		5.4	12.0
Type 1 Diabetes		Excluded	0.3
Type 2 Diabetes		11 (any diabetes)	2.2
Rheumatoid Arthritis		0.4	0.6
Chronic Kidney Disease		11.1	0.2
Hypertension Treatment		30.3	6.7
CHD		21	2.8
Heart Failure		2.2	0.5
Valvular Heart Disease		Excluded	0.4
Non-smoker		30	50
Ex-smoker		57	17
Light smoker		4	7
Moderate smoker		5	8
Heavy smoker		4	6
Current smoker		13	25
Slope of Centred Prognostic Index [95% CI]	0.88^ [0.69-1.08]	0.71^ [0.53-0.90]	
Harrell's C [95% CI]	0.6431 [0.6136-0.6726]	0.6199 [0.5904-0.6495]	0.866
10y Predicted Probability (%)			
Mean [Range]		11.8 [2.2-58.0]	NA
Median [Q1, Q3]		10.3 [6.8, 15.3]	
Mean Calibration	1.16	1.30	NA
Cut-off for high risk* (%)	10.18	9.09	-
Sensitivity (%)	71	76	-
Specificity (%)	52	43	-
Observed risk in those classified as high risk* (%)	14.6	11.8	-

`Baseline characteristics given for total sample – men (49%) & women. ^P for slope=1, 0.25 for main analysis and 0.002 for competing risks analysis. *KM failure function for main analysis and cumulative incidence function for competing risks adjustment. Continuous variables show mean (sd), range. Categorical variables show %.

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Appendix 5.5: Baseline and performance characteristics in the QResearch-QRISK3 and BRHS samples.

	BRHS Men free of CHD Stroke TIA & Statin use		QRISK3 Men free of CVD & Statin use
	Main Validation	Adjusted for Competing Risks	
Sample Size		2669	3869847
Ischaemic Stroke or TIA events		232	133097 ALL
Competing events	-	570	
Age (y)	68 (5.4), 58-81		42.6 (14), 25-84
Townsend Score	Excluded		0.5 (3.3)
BMI (kg/m²)	26.7 (3.6), 14-48		25.9 (4.2)
Systolic BP (mmHg)	142 (24), 81-233		129.2 (16.3)
SBP Variability	-		9.9 (6.8)
Total Cholesterol: HDL Cholesterol	4.8 (1.4), 2-12		4.4 (1.4)
Ethnicity	99 White/not recorded		89 White/ not recorded
	Excluded		
Atrial Fibrillation	3.2		0.5
Premature CHD in family	5		9
Type 1 Diabetes	Excluded		0.3
Type 2 Diabetes	10.3		1.5
Rheumatoid Arthritis	<0.5		0.5
Chronic Kidney Disease	9.3		0.3
Hypertension Treatment	21.7		4.2
Migraine	<0.5		2.7
Corticosteroid use	<0.5		1.5
Atypical antipsychotic use	<0.5		0.5
SLE	0		<0
Severe Mental Illness	0		4.3
Erectile dysfunction/treatment	<0.5		2.3
Non-smoker	32		38
Ex-smoker	56		15
Light smoker	4		13
Moderate smoker	5		7
Heavy smoker	4		5
Slope of Centred Prognostic Index	0.82 [^]	0.69 [^]	-
[95% CI]	[0.58-1.06]	[0.47-0.92]	
Harrell's C	0.6317	0.6148	0.858
[95% CI]	[0.5970-0.6664]	[0.5800-0.6496]	
10y Pred. Probability (%)			NA
Mean [Range]	9.91 [2.1-29.9]		
Median [Q1, Q3]	9.15 [6.4, 12.5]		
Mean Calibration	1.03	1.14	NA
Cut-off for high risk* (%)	9.59	8.7	-
Sensitivity (%)	63	70	-
Specificity (%)	56	48	-
Observed risk in those classified as high risk* (%)	13.7	11.3	-

[^]P for slope=1, 0.14 for main analysis and 0.007 for competing risks analysis. *KM failure function for main analysis and cumulative incidence function for competing risks adjustment. Continuous variables show mean (sd), range. Categorical variables show %.

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Appendix 5.6: Baseline and performance characteristics in the PCE and BRHS samples.

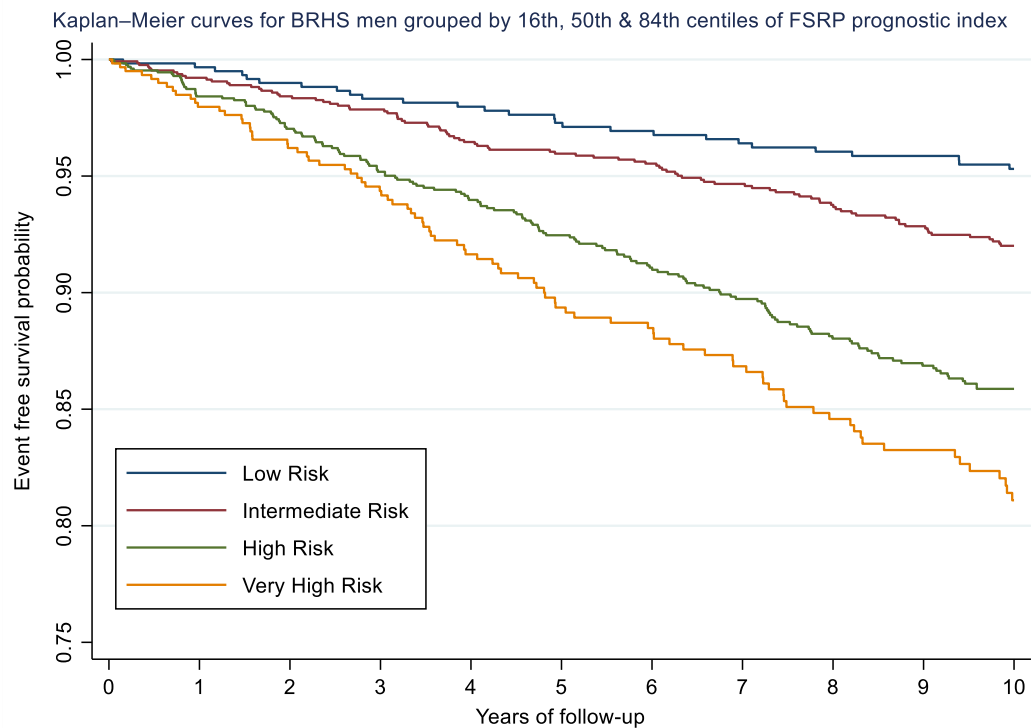
	BRHS Men free of Stroke, MI, HF & AF		Men from PCE Cohorts free of Stroke, MI, HF & AF
	Main Validation	Adjusted for competing risks	
Sample Size	3047		9098 White Men
Events	Strokes (TIAs not included) 184		All CVD: 1259
Competing events	NA		-
Age (y)	68 (5.4), 58-81		56.1
Untreated SBP (mmHg)	140 (24), 81-233		120
Treated SBP (mmHg)	150 (23), 83-232		136
Systolic BP (mmHg)	142 (24), 81-233		-
Total Chol (mg/dl)	234 (40), 116-448		210.7
HDL Chol (mg/dl)	52 (13), 19-127		44.4
BP meds	25.2		16.8
Diabetes	10.7		8.75
Smoking	13.3		25.4
Mean Prognostic Index [range]	62.24 [60.38-64.26]		61.18
Slope of Centred Prognostic Index [95% CI]	0.92 [^] [0.68-1.16]	0.79 [^] [0.56-1.02]	
Harrell's C [95% CI]	0.6606 [0.6215-0.6997]	0.6422 [0.6028-0.6816]	0.7443
10y Pred. Probability (%)			NA
Mean [Range]	7.60 [1.2-25.7]		
Median [Q1, Q3]	6.74 [4.6, 9.6]		
Mean Calibration	1.12	1.26	NA
Cut-off for high risk* (%)	6.77	6.04	-
Sensitivity (%)	73	76	-
Specificity (%)	52	43	-
Observed risk in those classified as high risk* (%)	10.3	7.9	-

[^]P for slope=1, 0.50 for main analysis and 0.07 for competing risks analysis. *KM failure function for main analysis and cumulative incidence function for competing risks adjustment. Continuous variables show mean (sd), range. Categorical variables show %.

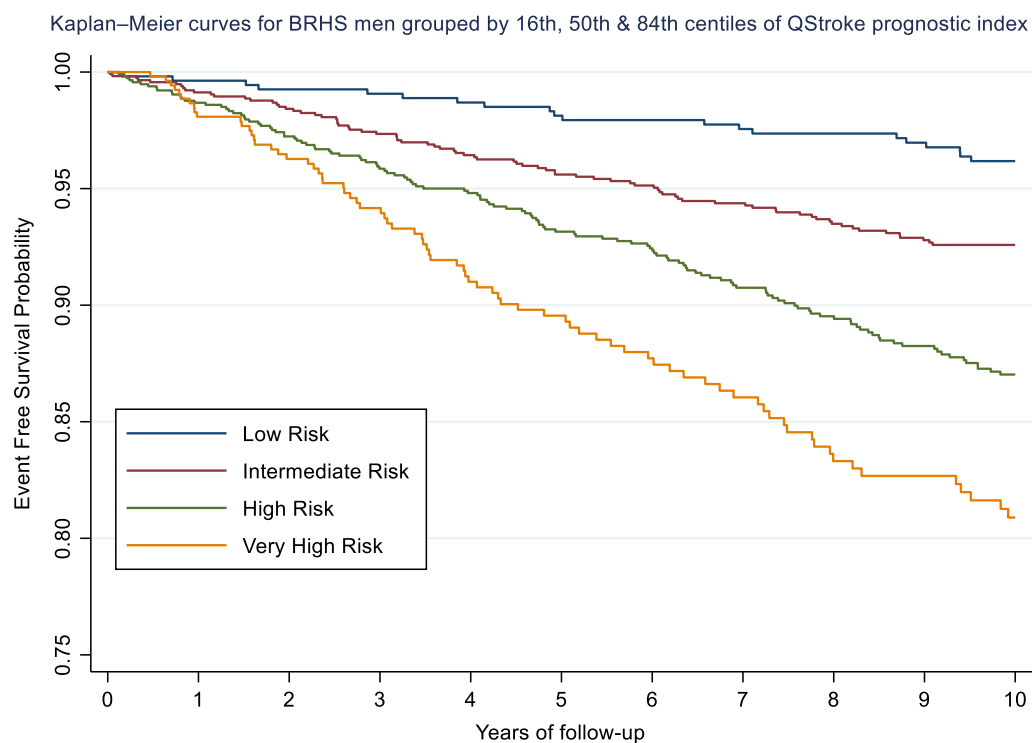
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Appendix 5.7: Stroke free survival in risk groups based on 4 categories of the prognostic index (A) FSRP (B) QStroke, (C) QRISK3 & (D) PCE

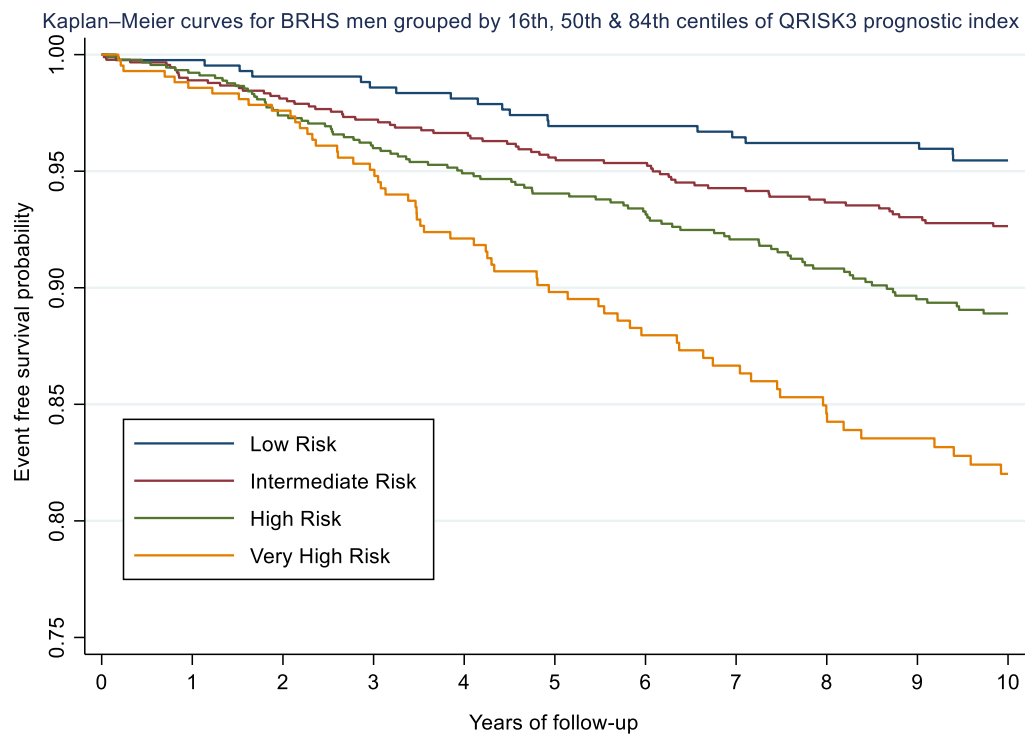
(A)



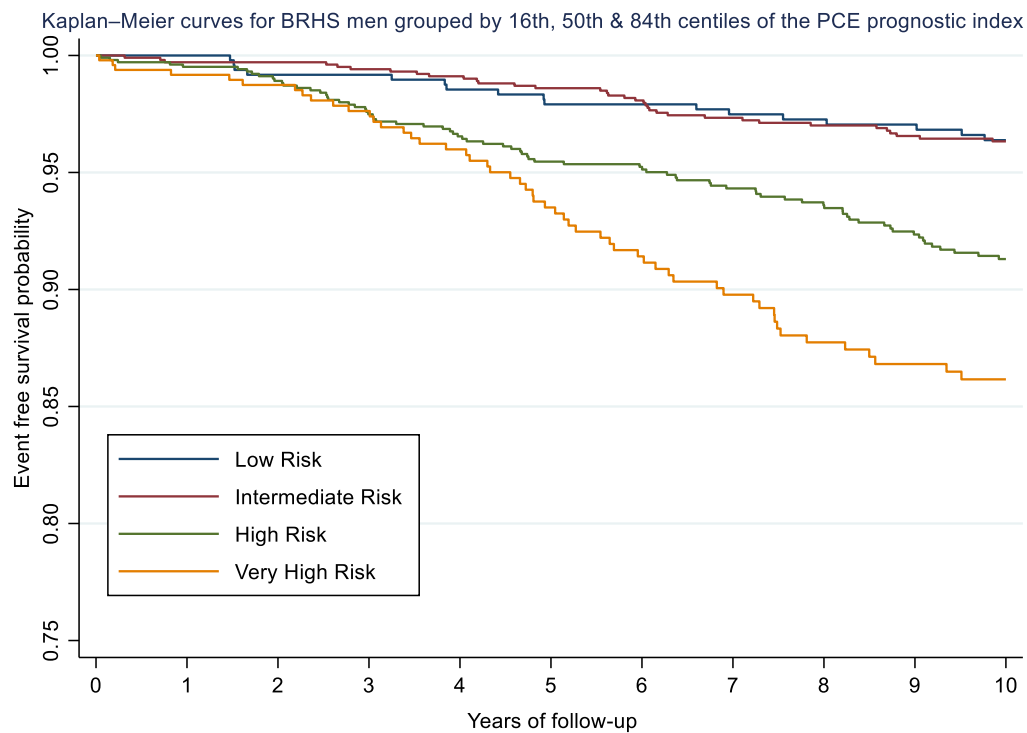
(B)



(C)



(D)



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Appendix 5.8: Comparing different cut-offs of composite-CVD risk tools for capture of stroke outcomes.

Cut-off for high risk (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
QRISK3 (n=232 events/2669 men)				
10	99	3	8.8	97
15	93	17	9.5	95
20	83	35	10.7	95
25	67	52	11.3	94
30	55	68	13.0	94
PCE (n=184 events/3047 men)				
7.5	99.5	2	6.1	98
10	96	8	6.2	96
15	88	24	6.9	97
20	78	43	7.9	97
25	67	59	9.11	96

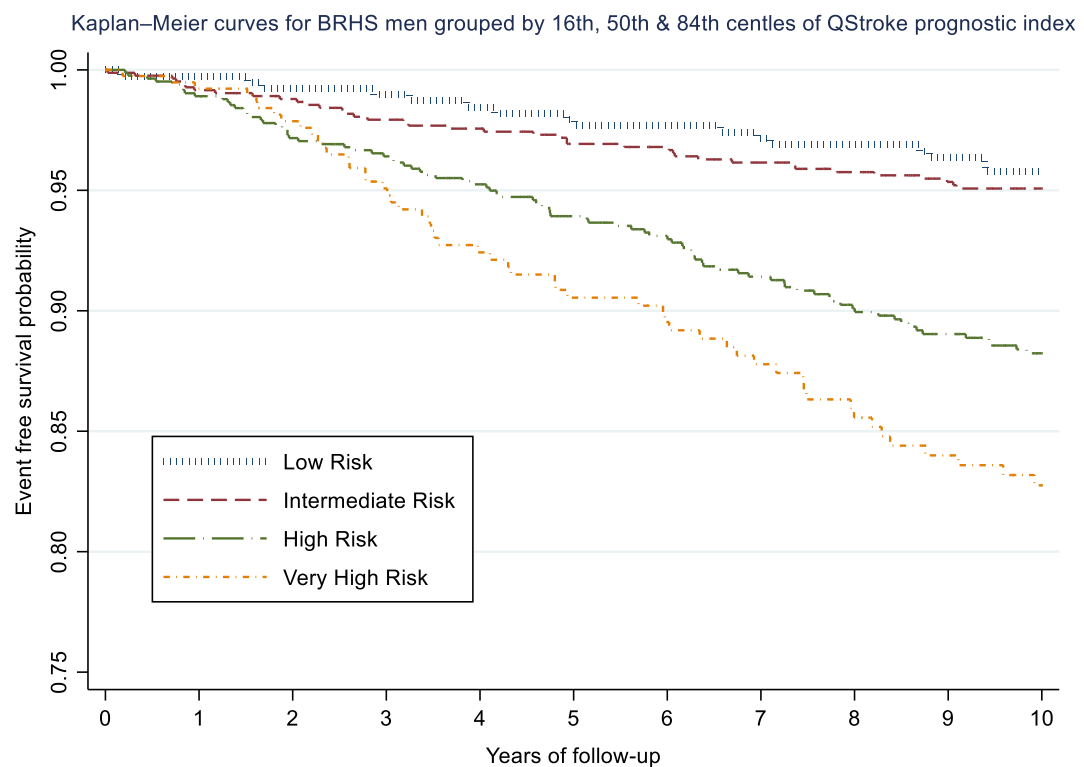
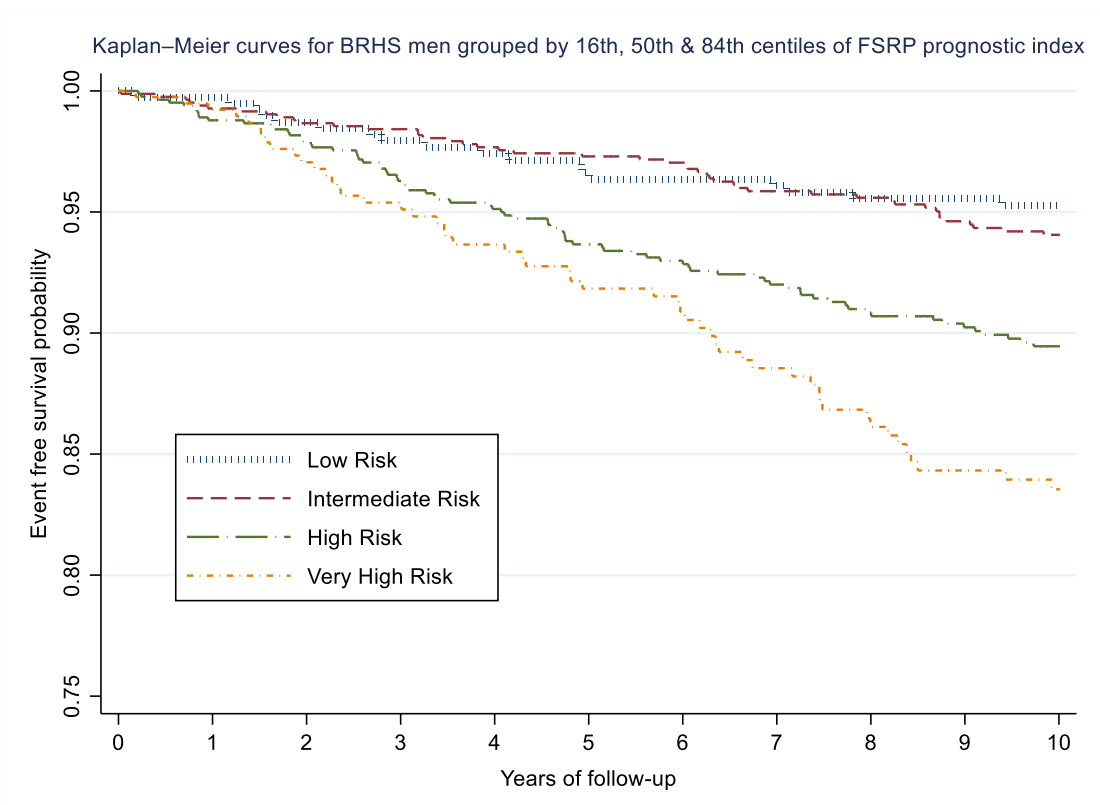
PPV: positive predictive value. NPV: negative predictive value

Appendix 5.9: Characteristics of BRHS men free of CVD in the common sub-sample used for validating FSRP, QStroke and QRISK3 for the outcome of stroke or TIA

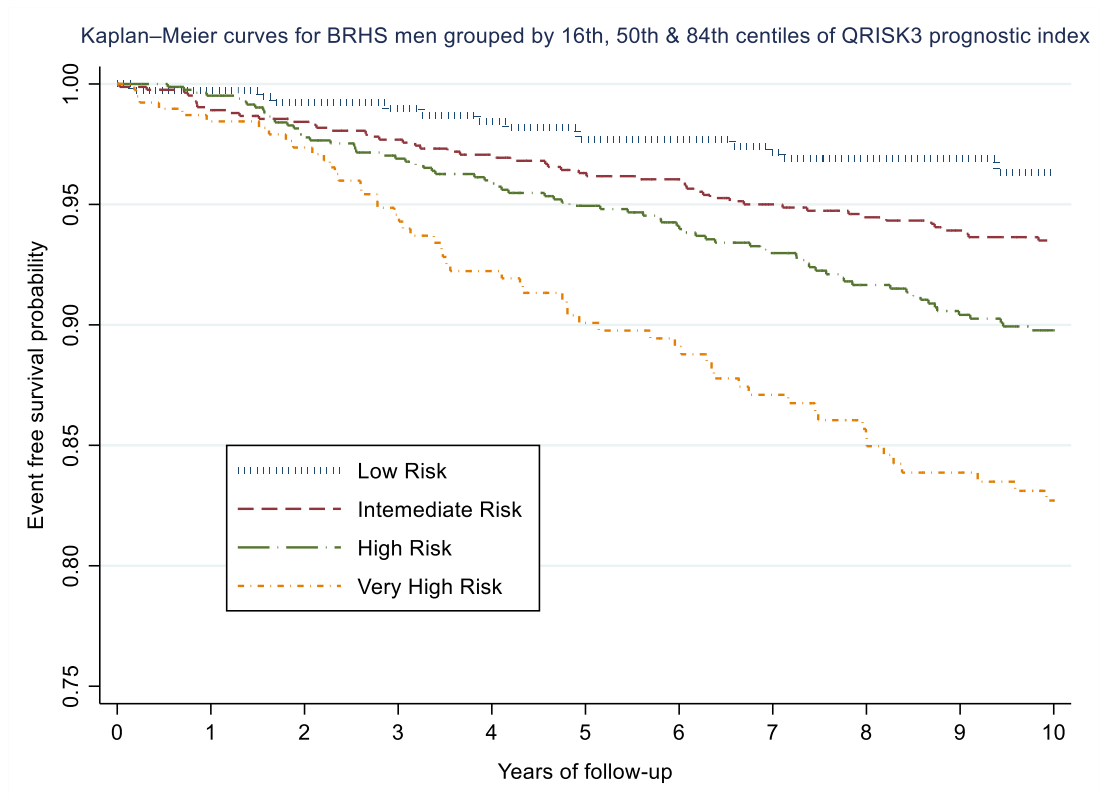
	BRHS (1998-2000) Men free of Stroke, TIA, CHD, HF, IC, AF, Anticoagulant & Statin use
Sample Size	2441
Composite of <i>Ischaemic</i> Stroke or TIA	196
Ischemic Strokes	116
Age (y)	68 (5.3), 58-81
Townsend Score	Excluded
BMI (kg/m²)	26.7 (3.5), 14-48,
SBP (mmHg)	142 (24), 81-233
Total Cholesterol: HDL Cholesterol	4.8 (1.4), 2-12
Cholesterol (mmol/l)	6.09 (1), 3-12
HDL (mmol/l)	1.34 (0.3), 0.5-3.3
Premature Coronary Heart Disease in family	5
Type 1 Diabetes	Excluded
Type 2 Diabetes	9.6
Rheumatoid Arthritis	<0.5
Chronic Kidney Disease	8.6
Hypertension Treatment	20
Left Ventricular Hypertrophy	1.2
Migraine	<0.5
Corticosteroid use	<0.5
Atypical antipsychotic use	<0.5
SLE	0
Severe Mental Illness	0
Erectile dysfunction or treatment	<0.5
Non-smoker	33
Ex-smoker	55
Light smoker	3
Moderate smoker	5
Heavy smoker	4
Current smoker	12.9
Ethnicity	99 White/not recorded Excluded
Valvular Heart Disease	Excluded

Continuous variables show mean (sd), range. Categorical variables show %.

Appendix 5.10: Kaplan-Meier curves for risk groups in a common BRHS sample of 2441 men without CVD, experiencing 196 incident stroke and TIA events over 10y



Appendices



Appendix 6

Appendix 6.1: HR [95% CI] of stroke events across NT-proBNP categories in BRHS men free of CVD followed for a median of 16y, excluding men with NT-proBNP ≥ 400 pg/ml

	Age adjusted	Age adjusted excluding elevated NT- proBNP	Model 3	Model 3 excluding elevated NT- proBNP
(a) All strokes				
Events/N	367/3241	332/3002	309/2755	280/2574
T1	1	1	1	1
T2	1.66 [1.25-2.20]	1.55 [1.16-2.08]	1.68 [1.23-2.29]	1.60 [1.16-2.21]
T3	2.24 [1.69-2.98]	1.90 [1.42-2.56]	2.22 [1.60-3.08]	1.87 [1.33-2.62]
P for trend	<0.0001	<0.001	<0.0001	<0.001
HR per sd-log	1.37 [1.22-1.53]	1.30 [1.15-1.48]	1.36 [1.19-1.56]	1.29 [1.12-1.49]
(b) Non-Fatal Strokes				
Events/N	275/3241	255/3002	230/2755	213/2574
T1	1	1	1	1
T2	1.50 [1.09-2.06]	1.37 [0.98-1.90]	1.60 [1.12-2.28]	1.47 [1.02-2.13]
T3	2.14 [1.55-2.95]	1.91 [1.38-2.66]	2.12 [1.46-3.08]	1.81 [1.23-2.66]
P for trend	<0.001	<0.001	<0.001	<0.01
HR per sd-log	1.30 [1.14-1.48]	1.27 [1.10-1.46]	1.29 [1.11-1.51]	1.24 [1.06-1.45]
(c) Fatal Strokes				
Events/N	92/3241	77/3002	79/2755	67/2574
T1	1	1	1	1
T2	2.38 [1.27-4.43]	2.38 [1.25-4.53]	1.96 [1.00-3.82]	2.04 [1.02-4.08]
T3	2.78 [1.47-5.24]	1.96 [0.99-3.89]	2.60 [1.30-5.19]	2.11 [1.01-4.40]
P for trend	<0.01	0.054	<0.01	0.046
HR per sd-log	1.60 [1.28-2.00]	1.45 [1.11-1.89]	1.59 [1.22-2.06]	1.51 [1.12-2.04]
(d) TIAs				
Events/N	206/3157	194/2933	180/2685	171/2515
T1	1	1	1	1
T2	1.14 [0.80-1.62]	1.08 [0.74-1.56]	1.17 [0.80-1.71]	1.09 [0.74-1.62]
T3	1.71 [1.20-2.44]	1.73 [1.20-2.48]	1.72 [1.15-2.56]	1.76 [1.18-2.63]
P for trend	<0.01	<0.01	<0.01	<0.01
HR per sd-log	1.22 [1.05-1.42]	1.24 [1.06-1.45]	1.26 [1.05-1.50]	1.27 [1.06-1.51]
(e) CVAs				
Events/N	528/3157	485/2933	450/2685	415/2515
T1	1	1	1	1
T2	1.42 [1.13-1.78]	1.34 [1.06-1.70]	1.43 [1.12-1.84]	1.37 [1.06-1.77]
T3	1.96 [1.56-2.46]	1.81 [1.42-2.29]	1.94 [1.49-2.52]	1.78 [1.36-2.33]
P for trend	<0.001	<0.001	<0.001	<0.001
HR per sd-log	1.31 [1.19-1.44]	1.27 [1.15-1.41]	1.33 [1.19-1.49]	1.28 [1.14-1.43]

Original tertile thresholds (pg/ml): T1 <55, T2 55-122, T3 ≥ 123 . Tertile thresholds after excluding men with elevated NT-proBNP: T1 <51, T2 51-108, T3 ≥ 109 -399. Model 3: Age plus SBP, BMI, cholesterol, glucose, physical activity, current smoking, diet; medications for BP, diabetes and statins; IL-6, eGFR and FEV1; social class and alcohol intake.

Appendices

Appendix 6.2: HR [95% CI] of stroke events across NT-proBNP categories in SABRE participants free of CVD followed for a median of 20y, excluding NT-proBNP ≥ 400 pg/ml

NT-proBNP	Age and sex adjusted	Age and sex adjusted excluding elevated NT-proBNP	Model 3	Model 3 excluding elevated NT-proBNP
Europeans				
Events/N	107/1219	99/1192	102/1150	94/1123
<34 pg/ml	1	1	1	1
34 - <100 pg/ml	1.69 [1.08-2.65]	1.66 [1.06-2.61]	1.45 [0.91-2.30]	1.49 [0.93-2.37]
≥ 100 pg/ml	2.60 [1.48-4.57]	2.01 [1.06-3.83]	1.99 [1.09-3.62]	1.52 [0.76-3.04]
P for trend	0.0009	0.03	0.0253	0.23
HR per sd-log	1.49 [1.26-1.75]	1.40 [1.14-1.73]	1.38 [1.15-1.66]	1.28 [1.02-1.59]
South Asians				
Events/N	118/1225	112/1207	101/1109	95/1093
<34 pg/ml	1	1	1	1
34 - <100 pg/ml	1.03 [0.67-1.59]	1.02 [0.67-1.58]	0.88 [0.55-1.42]	0.88 [0.55-1.42]
≥ 100 pg/ml	2.76 [1.64-4.54]	2.43 [1.40-4.21]	2.67 [1.49-4.79]	2.38 [1.27-4.44]
P for trend	<0.001	<0.01	0.0009	<0.01
HR per sd-log	1.45 [1.22-1.72]	1.35 [1.10-1.64]	1.49 [1.21-1.83]	1.35 [1.07-1.70]

Model 3: Age and sex plus SBP, BMI, cholesterol, glucose, physical activity, current smoking, diet; medications for BP, diabetes and statins; CRP, eGFR and FEV1; social class and alcohol intake.

Appendices

Appendix 6.3: Characteristics of BRHS men free of MI, stroke, HF and AF (n=3614), with (n=3241) and without (n=373) a measure of NT-proBNP

Missingness is 10% overall.

	Men with NT-proBNP		Men with NT-proBNP missing		P value
Stats	N	Mean (SD) or %	N	Mean (SD) or %	
Age (y)	3241	68.4 (5)	373	68.8 (5)	0.13
BMI (kg/m ²)	3227	26.8 (3.6)	372	27.5 (4.2)	<0.001
SBP (mmHg)	3231	142 (24)	368	145 (25)	0.03
DBP (mmHg)	3231	85 (11)	368	86 (11)	0.07
Cholesterol (mmol/l)	3233	6.05 (1)	210	5.98 (1)	0.36
Glucose (mmol/l)	3226	5.62 (5.24, 6.09)	216	5.65 (5.32, 6.10)	0.32
IL-6 (pg/ml)	3211	0.77 (0.43, 1.21)	242	0.86 (0.37, 1.35)	0.34
eGFR (ml/min/1.73m ²)	3235	75.7 (13)	210	76.7 (12)	0.32
FEV1 (L)	3210	2.63 (0.7)	368	2.59 (0.6)	0.27
Troponin T (pg/ml)	3221	13.4 (24)	230	12.9 (8)	0.41
Median (IQR)		11.4 (8.6, 15.5)		11.1 (8.6, 15.2)	
Physical Activity	3128		360		0.53
Inactive		10		12	
Occasional-Light		42		42	
Moderate-Vigorous		48		47	
Poor Diet	3002	39	345	41	0.59
Current Smokers	3236	13	373	17	0.02
Alcohol Intake	3191		366		0.10
None		10		13	
Occasional-Light		71		69	
Moderate-Heavy		20		18	
IMD	3237		373		0.81
Most deprived		16		17	
2		17		19	
3		20		20	
4		23		23	
Least deprived		23		21	
BP meds	3196	27	369	33	0.03
Statin use	3241	4	373	4	0.89
Diabetes treatment	3196	4	369	3	0.14
Prevalent Diabetes	3126	11	363	9	0.25
Prevalent Hypertension	3225	73	371	76	0.21
Prevalent TIA	3241	3	373	4	0.11
Incident Stroke	3241	11	373	14	0.07
Incident TIA	3241	6	373	7	0.65
Incident CVA	3241	16	373	20	0.11
Death from any cause	3241	63	373	65	0.61

Appendices

Appendix 6.4: Characteristics of BRHS men free of MI, stroke, HF and AF with (n=2736/3614) and without (n=878/3614) complete data on NT-proBNP and all covariates.

Missingness 24% overall

	Complete cases		Cases with data missing		P value
Stats	N	Mean (SD) or Median (Q1, Q3) or %	N	Mean (SD) or Median (Q1, Q3) or %	
Age (y)	2736	68.2 (5)	878	69.2 (6)	<0.001
BMI (kg/m ²)	2736	26.7 (3.5)	863	27.2 (4.0)	<0.01
SBP (mmHg)	2736	142 (24)	863	144 (25)	0.05
DBP (mmHg)	2736	85 (11)	863	86 (11)	0.48
Cholesterol (mmol/l)	2736	6.07 (1)	707	5.94 (1)	<0.01
Glucose (mmol/l)	2736	5.62 (5.25, 6.08)	706	5.64 (5.24, 6.11)	0.78
IL-6 (pg/ml)	2736	0.77 (0.42, 1.19)	717	0.88 (0.48, 1.31)	<0.001
eGFR (ml/min/1.73m ²)	2736	75.7 (13)	709	76.1 (15)	0.45
FEV1 (L)	2736	2.65 (0.7)	842	2.55 (0.7)	<0.001
Troponin T (pg/ml)	2736	13.3 (26)	715	13.9 (10)	0.02
Median (Q1, Q3)		11.3 (8.6, 15.4)		11.7 (9.0, 16.1)	
NT-proBNP (pg/ml)	2736	159 (353)	505	203 (330)	<0.001
Median (Q1, Q3)		80 (42, 153)		95 (46, 189)	
Physical Activity	2736		752		0.05
Inactive		9		12	
Occasional-Light		42		43	
Moderate-Vigorous		49		45	
Poor Diet	2736	38	611	43	0.07
Current Smokers	2736	13	873	15	0.05
Alcohol Intake	2736		821		<0.01
None		9		13	
Occasional-Light		71		67	
Moderate-Heavy		20		20	
IMD	2736		874		<0.001
Most deprived		15		21	
2		17		18	
3		20		20	
4		24		22	
Least deprived		24		19	
BP meds	2736	26	829	32	<0.01
Statin use	2736	4	878	5	0.44
Diabetes treatment	2736	4	829	4	0.78
Prevalent Diabetes	2641	11	848	10	0.50
Prevalent Hypertension	2736	72	860	77	<0.01
Prevalent TIA	2736	3	878	3	0.24
Incident Stroke	2736	11	878	13	0.20
Incident TIA	2736	7	878	6	0.71
Incident CVA	2736	16	878	18	0.41
Death from any cause	2736	60	878	66	<0.01

Appendices

Appendix 6.5: HR [95% CI] of stroke events across NT-proBNP categories in BRHS men free of CVD followed for a median of 16y, excluding diet.

		Crude	Crude + age	Model 1	Model 1 excluding diet	Model 3	Model 3 excluding diet
	(a) All strokes						
	Events/N	367/3241	367/3241	319/2867	345/3086	309/2755	335/2957
<55 pg/ml	80/1094	1	1	1	1	1	1
55 - 122 pg/ml	131/1067	1.89 [1.43-2.50]	1.66 [1.25-2.20]	1.64 [1.21-2.22]	1.62 [1.21-2.17]	1.68 [1.23-2.29]	1.65 [1.23-2.23]
≥123 pg/ml	156/1080	2.92 [2.23-3.83]	2.24 [1.69-2.98]	2.19 [1.60-3.01]	2.10 [1.55-2.84]	2.22 [1.60-3.08]	2.10 [1.53-2.87]
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HR per sd-log		1.54 [1.38-1.70]	1.37 [1.22-1.53]	1.35 [1.19-1.53]	1.32 [1.17-1.49]	1.36 [1.19-1.56]	1.33 [1.17-1.51]
	(b) Non-Fatal Strokes						
	Events/N	275/3241	275/3241	237/2867	258/3086	230/2755	251/2957
<55 pg/ml	66/1094	1	1	1	1	1	1
55 - 122 pg/ml	94/1067	1.64 [1.19-2.24]	1.50 [1.09-2.06]	1.59 [1.12-2.25]	1.50 [1.07-2.09]	1.60 [1.12-2.28]	1.51 [1.07-2.11]
≥123 pg/ml	115/1080	2.56 [1.89-3.48]	2.14 [1.55-2.95]	2.11 [1.47-3.03]	2.01 [1.43-2.83]	2.12 [1.46-3.08]	2.01 [1.41-2.87]
P for trend		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HR per sd-log		1.42 [1.25-1.60]	1.30 [1.14-1.48]	1.28 [1.10-1.48]	1.25 [1.08-1.43]	1.29 [1.11-1.51]	1.26 [1.09-1.46]
	(c) Fatal Strokes						
	Events/N	92/3241	92/3241	82/2867	87/3086	79/2755	84/2957
<55 pg/ml	14/1094	1	1	1	1	1	1
55 - 122 pg/ml	37/1067	3.10 [1.67-5.73]	2.38 [1.27-4.43]	1.82 [0.95-3.47]	2.11 [1.12-3.97]	1.96 [1.00-3.82]	2.29 [1.19-4.40]
≥123 pg/ml	41/1080	4.63 [2.52-8.51]	2.78 [1.47-5.24]	2.50 [1.30-4.84]	2.51 [1.30-4.82]	2.60 [1.30-5.19]	2.54 [1.28-5.04]
P for trend		<0.001	<0.01	<0.01	<0.01	<0.01	<0.01
HR per sd-log		1.94 [1.59-2.38]	1.60 [1.28-2.00]	1.58 [1.24-2.02]	1.56 [1.23-1.97]	1.59 [1.22-2.06]	1.56 [1.21-2.01]
	(d) TIAs						
	Events/N	206/3157	206/3157	186/2795	199/3006	180/2685	192/2879
<55 pg/ml	61/1078	1	1	1	1	1	1
55 - 122 pg/ml	65/1046	1.24 [0.88-1.76]	1.14 [0.80-1.62]	1.17 [0.80-1.70]	1.20 [0.84-1.73]	1.17 [0.80-1.71]	1.21 [0.84-1.74]
≥123 pg/ml	80/1033	2.04 [1.46-2.86]	1.71 [1.20-2.44]	1.83 [1.25-2.69]	1.85 [1.27-2.68]	1.72 [1.15-2.56]	1.72 [1.17-2.53]
P for trend		<0.001	<0.01	<0.01	<0.01	<0.01	<0.01
HR per sd-log		1.32 [1.15-1.52]	1.22 [1.05-1.42]	1.25 [1.06-1.48]	1.26 [1.07-1.48]	1.26 [1.05-1.50]	1.26 [1.07-1.50]
	(e) CVAs						
	Events/N	528/3157	528/3157	465/2795	499/3006	450/2685	483/2879
<55 pg/ml	133/1078	1	1	1	1	1	1
55 - 122 pg/ml	183/1046	1.61 [1.28-2.01]	1.42 [1.13-1.78]	1.42 [1.11-1.81]	1.42 [1.12-1.80]	1.43 [1.12-1.84]	1.44 [1.14-1.83]
≥123 pg/ml	212/1033	2.49 [2.00-3.10]	1.96 [1.56-2.46]	1.96 [1.53-2.53]	1.92 [1.51-2.45]	1.94 [1.49-2.52]	1.88 [1.46-2.42]
P for trend		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HR per sd-log		1.45 [1.33-1.59]	1.31 [1.19-1.44]	1.31 [1.18-1.46]	1.29 [1.17-1.43]	1.33 [1.19-1.49]	1.31 [1.17-1.45]

Model 1: Age plus SBP, BMI, cholesterol, glucose, physical activity, current smoking, diet. Model 3: Model 1 plus medications for BP, diabetes and statins; IL-6, eGFR and FEV1; social class and alcohol intake.

Appendices

Appendix 6.6: Baseline characteristics of SABRE Europeans n=1404 & South Asians n=1376 free of CHD and stroke with complete/missing data.

	Europeans				South Asians			
	Complete cases	Cases with data missing		P value	Complete cases	Cases with data missing		P value
	N=1150	N			N=1109	N		
Age (y)	53 (7)	254	52 (7)	0.05	51 (7)	267	51 (7)	0.84
BMI (kg/m ²)	26.1 (4)	253	25.8 (4)	0.33	26.1 (4)	266	26.5 (4)	0.08
SBP (mmHg)	123 (17)	253	122 (18)	0.17	125 (17)	267	126 (17)	0.43
DBP (mmHg)	77 (11)	253	77(11)	0.92	80 (11)	267	81 (10)	0.42
Cholesterol (mmol/l)	6.1 (1.1)	249	6.2 (1.2)	0.35	5.9 (1.0)	262	6.0 (1.2)	0.24
Glucose (mmol/l)	5.34 (5, 5.8)	247	5.27 (4.9, 5.7)	0.19	5.51 (5.1, 6.1)	257	5.53 (5.0, 6.3)	0.96
PA (MJ/week)	10.5 (6.8, 15.8)	254	9.9 (6, 14)	0.04	9 (4, 12.5)	267	9.5 (4, 13.3)	0.94
CRP (mg/L)	1.2 (0.5, 2.8)	51	1.3 (0.4, 2.1)	0.81	1.44 (0.7, 3.2)	96	1.68 (0.8, 3.5)	0.43
eGFR (ml/min/1.73m ²)	93 (35)	57	105 (91)	0.02	97 (35)	106	98 (32)	0.81
Alcohol (units/week)	9.1 (1.8, 20.2)	208	7.0 (1.6, 20.4)	0.77	0.98 (0, 12)	215	0 (0, 8.3)	<0.01
NT-proBNP (pg/ml)	69.9 (151) 37.3 (23, 64)	69	53.2 (51) 35.6 (22, 64)	0.50	54.7 (109) 31.0 (19, 55)	116	63.5 (158) 32.1 (19, 57)	0.67
Troponin T (pg/ml)	10.0 (4.5) 9.5 (7.9, 11.1)	78	9.0 (2.5) 8.7 (7.1, 10.0)	0.01	10.0 (3.3) 9.5 (8.0, 11.2)	121	9.9 (4.5) 8.9 (7.9, 10.6)	0.07
Male	87	254	81	0.02	85	267	72	<0.01
Poor Diet	7	254	9	0.27	5	254	4	0.81
Current Smokers	30	253	35	0.14	14	263	12	0.45
Manual Social Class	61	247	62	0.85	75	226	75	0.96
BP meds	9	253	*	0.003	13	267	10	0.14
Diabetes meds	2	254	*	0.85	9	266	8	0.57
Prevalent Diabetes	5	254	6	0.93	20	267	21	0.61
Prevalent Hypertension	23	253	19	0.18	30	267	34	0.29
Incident Stroke	9	254	6	0.08	9	267	13	0.05
Death from any cause	28	254	27	0.78	20	267	25	0.05

Data are Mean (SD) or Median (Q1, Q3) or %. * implies small numbers not disclosed.

Appendices

Appendix 6.7: HR [95% CI] of stroke events across NT-proBNP categories in BRHS men free of CVD followed for a median of 16y, adjusted for the competing risk of non-stroke deaths.

NT-proBNP	Model 3	Model 3 + Troponin T
BRHS		
All strokes /N/Competing Deaths	309/2755/1354	308/2736/1347
Low	1	1
Intermediate	1.72 [1.26-2.34]	1.71 [1.25-2.33]
High	1.96 [1.41-2.73]	1.91 [1.37-2.66]
P for trend	<0.001	<0.001
HR per sd-log	1.21 [1.07-1.37]	1.18 [1.04-1.35]
Non-fatal strokes /N/Competing Deaths	230/2755/1354	229/2736/1347
Low	1	1
Intermediate	1.64 [1.15-2.32]	1.62 [1.14-2.31]
High	1.91 [1.31-2.79]	1.89 [1.29-2.78]
P for trend	<0.001	0.001
HR per sd-log	1.17 [1.01-1.36]	1.16 [0.99-1.35]
Fatal strokes/N/Competing Deaths	79/2755/1354	79/2736/1347
Low	1	1
Intermediate	2.03 [1.05-3.95]	2.01 [1.03-3.92]
High	2.19 [1.11-4.31]	2.04 [1.03-4.04]
P for trend	0.02	0.04
HR per sd-log	1.33 [1.07-1.66]	1.26 [1.01-1.57]
TIA's/N/Competing Deaths	180/2685/1430	178/2666/1424
Low	1	1
Intermediate	1.17 [0.80-1.70]	1.19 [0.82-1.74]
High	1.52 [1.03-2.24]	1.54 [1.04-2.29]
P for trend	0.04	0.03
HR per sd-log	1.15 [0.97-1.36]	1.17 [0.98-1.39]
CVAs/N/Competing Deaths	450/2685/1240	447/2666/1234
Low	1	1
Intermediate	1.46 [1.15-1.86]	1.46 [1.15-1.87]
High	1.72 [1.32-2.23]	1.69 [1.30-2.21]
P for trend	<0.001	<0.001
HR per sd-log	1.20 [1.08-1.34]	1.20 [1.07-1.34]
SABRE Europeans All strokes /N/Competing Deaths 102/1150/500		
Low	1	1
Intermediate	1.40 [0.87-2.25]	1.39 [0.86-2.23]
High	1.71 [0.94-3.09]	1.65 [0.88-3.07]
P for trend	0.08	0.12
HR per sd-log	1.32 [1.10-1.59]	1.34 [1.08-1.65]
SABRE SAs All strokes /N/Competing Deaths 101/1109/342		
Low	1	1
Intermediate	0.86 [0.54-1.37]	0.83 [0.51-1.35]
High	2.43 [1.37-4.32]	2.28 [1.25-4.15]
P for trend	0.003	0.007
HR per sd-log	1.41 [1.13-1.77]	1.40 [1.10-1.78]

Model 3: Ag, SBP, BMI, cholesterol, glucose, physical activity, current smoking, diet, medications for BP, diabetes (and lipids in BRHS), CRP (IL-6 in BRHS), eGFR (and FEV1 in BRHS), social class and alcohol intake.

Appendices

Appendix 6.8: Risk associations between high sensitivity Troponin-T and stroke events in BRHS and SABRE participants free of CVD.

Troponin T	Model 3 + NT-proBNP	Model 3 + NT-proBNP adjusted for competing risks of non-stroke death
BRHS	Event no/N	Event no/N/Competing deaths
All strokes	308/2736	308/2736/1347
Low	1	1
Intermediate	1.18 [0.88-1.59]	1.17 [0.87-1.58]
High	1.32 [0.97-1.79]	1.23 [0.89-1.69]
P for trend	0.07	0.20
HR per sd-log	1.15 [1.01-1.31]	1.08 [0.96-1.22]
Non-Fatal Strokes	229/2736	229/2736/1347
Low	1	1
Intermediate	1.12 [0.80-1.56]	1.11 [0.79-1.55]
High	1.18 [0.84-1.68]	1.11 [0.77-1.60]
P for trend	0.34	0.57
HR per sd-log	1.10 [0.95-1.28]	1.04 [0.91-1.19]
Fatal Strokes	79/2736	79/2736/1347
Low	1	1
Intermediate	1.50 [0.80-2.85]	1.46 [0.75-2.85]
High	1.95 [1.04-3.68]	1.73 [0.89-3.34]
P for trend	0.04	0.10
HR per sd-log	1.35 [1.05-1.73]	1.20 [0.98-1.47]
TIA's	178/2666	178/2666/1424
Low	1	1
Intermediate	0.92 [0.63-1.32]	0.89 [0.61-1.30]
High	0.87 [0.59-1.28]	0.81 [0.54-1.20]
P for trend	0.48	0.29
HR per sd-log	0.94 [0.79-1.12]	0.91 [0.77-1.06]
CVAs	447/2666	447/2666/1234
Low	1	1
Intermediate	1.06 [0.84-1.35]	1.04 [0.82-1.32]
High	1.08 [0.84-1.39]	1.01 [0.78-1.31]
P for trend	0.54	0.93
HR per sd-log	1.06 [0.95-1.18]	1.01 [0.91-1.11]
SABRE EU	All Strokes/N 102/1150	102/1150/500
Low	1	1
Intermediate	0.83 [0.53-1.30]	0.83 [0.52-1.33]
High	1.22 [0.61-2.44]	1.02 [0.47-2.21]
P for trend	0.58	0.96
HR per sd-log	1.05 [0.84-1.30]	0.97 [0.78-1.21]
SABRE SAs	All Strokes/N 101/1109	101/1109/342
Low	1	1
Intermediate	1.17 [0.70-1.96]	1.17 [0.70-1.96]
High	1.54 [0.76-3.13]	1.31 [0.64-2.67]
P for trend	0.24	0.46
HR per sd-log	1.14 [0.90-1.44]	1.03 [0.81-1.31]

Model 3: Age, SBP, BMI, cholesterol, glucose, physical activity, current smoking, diet, medications for BP, diabetes (and lipids in BRHS), CRP (IL-6 in BRHS), eGFR (and FEV1 in BRHS), social class and alcohol intake. Values of hs-cTnT BRHS (tertiles): low <9.7pg/ml and high ≥13.9pg/ml; SABRE (predefined): low <9pg/ml and high ≥14pg/ml.

Appendix 7

Appendix 7.1: Incremental performance measures of NT-proBNP for stroke risk prediction in CVD free BRHS men adjusting for competing risks of death.

	BRHS-FSRP		BRHS-QStroke	
Predictors	Age, SBP, BP Treatment, Smoking, Diabetes & LVH		Age, BMI, Cholesterol:HDL ratio, SBP, BP treatment, Smoking, Diabetes, RA, CKD, Family history of Coronary Death	
Events/N/Competing deaths	208 Strokes & TIAs/2429/476		199 Ischemic Strokes & TIAs/2442/507	
Cumulative incidence function at 10y [95% CI]	8.56 [7.49-9.72]		8.15 [7.11-9.28]	
Model	Base	Plus NTproBNP	Base	Plus NTproBNP
HR [95%CI]^	-	1.25 [1.08-1.45]	-	1.28 [1.10-1.50]
Harrell's C [95% CI]	0.6299 [0.5922-0.6676]	0.6426 [0.6059-0.6794]	0.6235 [0.5865-0.6606]	0.6393 [0.6029-0.6757]
Baseline cumulative subhazard	0.0814814	0.0802806	0.0647009	0.0666979
Probability Event, Mean (range)	8.55 (2.68-42.22)	8.55 (2.47-49.51)	8.14 (2.61-23.27)	8.14 [2.23-32.46]
Adequacy Index	-	0.832	-	0.787
Fraction of new information from NTproBNP		0.168		0.213
NRI Events		0.067 [0.016-0.119]		0.040 [-0.024-0.104]
NRI Non-events		0.023 [0.005-0.041]		0.022 [0.003-0.042]
IDI		0.004 [0.001-0.007]		0.005 [0.001-0.008]
Relative IDI		0.177 [0.012-0.341]		0.332 [0.058-0.606]

^per SD-log NT-proBNP adjusted for centred prognostic index. CI: confidence intervals obtained using 1000 bootstrap samples.

BMI: body mass index, BP: blood pressure, CKD: chronic kidney disease, IDI: integrated discrimination improvement, LVH: left ventricular hypertrophy, NRI: net reclassification improvement, RA: rheumatoid arthritis, SBP: systolic blood pressure

Appendix 7.2: Incremental performance measures of NT-proBNP for stroke risk prediction in CVD free SABRE participants adjusting for competing risks of death.

	SABRE Europeans		SABRE South Asians	
Predictors	Age, Sex, BMI, SBP, BP Treatment, Smoking, Diabetes, Cholesterol:HDL ratio, CKD and Social Class			
Events/N/Competing deaths	104 Strokes/1181/515		106 Strokes/1149/351	
Cumulative incidence function at 22y [95%CI]	9.39 [7.68-11.29]		9.90 [8.08-11.93]	
Model	Base	Plus NTproBNP	Base	Plus NTproBNP
HR [95%CI]^	-	1.35 [1.11-1.63]	-	1.33 [1.10-1.62]
Harrell's C [95% C]	0.6916 [0.6446-0.7385]	0.7035 [0.6568-0.7503]	0.7356 [0.6920-0.7792]	0.7450 [0.7027-0.873]
Baseline cumulative subhazard	0.078031	0.0759291	0.0782996	0.0763397
Probability Event, Mean (range)	9.24 (1.51-54.95)	9.31 (1.39-76.61)	9.77 (1.68-60.46}	9.55 [1.64-59.53]
Adequacy Index	-	0.835	-	0.952
Fraction of new information from NTproBNP		0.165		0.048
NRI Events		0.010 [-0.063-0.082]		-0.009 [-0.029-0.010]
NRI Non-events		0.060 [0.034-0.086]		0.021 [0.013-0.030]
IDI		0.017 [0.003-0.031]		-0.0015 [-0.0019 - -0.0010]
Relative IDI		0.341 [0.071-0.612]		-0.0197 [-0.0210 - -0.0184]

^per SD-log NT-proBNP adjusted for centred prognostic index. CI: confidence intervals obtained using 1000 bootstrap samples.

BMI: body mass index, BP: blood pressure, CKD: chronic kidney disease, IDI: integrated discrimination improvement, NRI: net reclassification improvement, SBP: systolic blood pressure