Full title: Consequences of ethnic differences in cardiometabolic disease in older age: the Southall And Brent REvisited (SABRE) tri-ethnic population cohort

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Sponsor

University College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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British Heart Foundation (Ref: CS/13/1/30327)

This protocol describes the SABRE V3 study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Contents

Background

By 2020, a quarter of the UK population will be aged over 60 years[1], and a fifth of the total population will be from an ethnic minority. The expression of CVD in older age differs from that observed in middle aged populations. The ratio of coronary heart disease (CHD) to stroke events is approximately 3:1 in people aged under 65, but changes to 1.5:1 in older people[2]. Important consequences of CVD in older age include heart failure, which is rare in middle age, but occurs in over 10% of people aged 75+[2;3], and is associated with significant morbidity and mortality[4;5]. CVD is also a key risk factor for cognitive decline and dementia. The already significant individual and societal burden of dementia, preceded by cognitive decline, will rise dramatically as a consequence of increasing longevity[6]. In people aged ≥75 years the population prevalence of cognitive dysfunction is between 20-25%[6;7].

These ageing demographic trends also apply to first generation migrant South Asians and African Caribbeans, who form the largest ethnic minority populations in the UK. However, very little is known about the health in older age of ethnic minority groups living in the UK. The SABRE study, supported by the UK Medical research Council, Diabetes UK, the Wellcome Trust and the British Heart Foundation , recruited 2346 Europeans, 1710 South Asians, and 801 African Caribbeans aged 40-69 years from the general population in 1988-90(Baseline: V1) [8]. All South Asians and African Caribbeans were first generation migrants.

Heart failure: Data on ethnic differences in heart failure and left ventricular (LV) function from the UK are limited and conflicting[9-12]. Limitations of previous studies include reliance on clinician diagnosis of heart failure, small case numbers, hospital rather than population based samples, and no longitudinal data. At the recent SABRE examination (2008-11), prevalence of putative heart failure, based on exertional breathlessness and ankle swelling, was 7% in Europeans, 14% in South Asians, and 12% in African Caribbeans. Both ethnic minority groups had significantly poorer diastolic and long axis systolic function than Europeans on tissue Doppler. Diabetes increases heart failure risk four fold, and may be associated with a distinct diabetic cardiomyopathy. Elevated HbA1c levels were associated with worse diastolic function to a significantly greater extent in South Asians compared with Europeans; there was a similar non-significant trend for African Caribbeans compared with Europeans.

Cognitive function: CVD is a major risk factor[13] and diabetes and the spectrum of hyperglycaemia appear to be strong determinants of cognitive decline[14-18]. It is unclear whether the effect of diabetes on cognitive function is mediated via associated CVD risk factors, and their combined impact on micro and macrovascular damage, or whether hyperglycaemia per se and associated metabolic disorders play an independent part[14]. Risk factors, including diabetes and obesity measured in middle age more strongly predict cognitive function and decline than profiles assessed in older age[19-21].

People of Black African descent appear to have poorer cognitive function and greater dementia prevalence than European origin comparators, although this may be attributable

to testing bias[22;23], with limited evidence for a greater risk of dementia in association with diabetes[24]. Data on South Asians in India are conflicting, and may not reflect risks in high income countries[25-27].

Cognitive function was measured during the 2008-11 SABRE visit. There was evidence in both South Asians and African Caribbeans of a greater impact of mid-life diabetes compared to Europeans on relative cognitive dysfunction measured within ethnic groups; age and sex adjusted odds ratios for the effect of mid-life diabetes on lowest 10% cognitive function were 1.86, 2.80 and 1.20 respectively. Likewise, baseline diabetes was associated with 0.33 SD lower hippocampal volume in South Asians, versus just 0.10 of an SD in Europeans(fully adjusted models).

Stroke and CHD: In SABRE, diabetes in middle age was more strongly predictive of stroke in South Asians (hazard ratio 2.5, 95% CI 1.8,3.4), and African Caribbeans (3.0 (1.8,4.8) than Europeans (1.3 (0.8,2.1)(p ethnicity/diabetes interaction 0.04 and 0.02 respectively)[28]. This greater adverse effect of diabetes on stroke in ethnic minorities could not be explained by conventional risk factors[28]. These novel findings require confirmation and exploration with larger event numbers. SABRE is relatively unique in its multi-ethnic composition, with risk factors measured in middle age, and event follow up into older age; it is therefore well placed to study this phenomenon further. Whether ethnic differentials in CVD risk diminish or persist in older age is unknown: they may even increase. Low current smoking rates in middle age in both ethnic minorities afforded considerable CVD protection[28]. Since then, widespread smoking cessation in Europeans has diminished the ethnic differential in prevalence of current smokers, unmasking the impact of excess diabetes and hypertension in ethnic minority groups in older age.

Toxic diabetes: Diabetes is likely to be the single most important determinant of differences in excess morbidity in older age in these ethnic minorities. By the age of 80, 20% of Europeans, 50% of South Asians and 40% of African Caribbeans have diabetes[29]. Further, we report that diabetes increases the risk of fatal and non-fatal stroke to a greater extent in both ethnic minorities, and of CHD in South Asians, compared to Europeans[28]. The metabolic phenotype of diabetes differs by ethnicity; South Asians are dyslipidaemic, and have excess visceral adiposity, while African Caribbean men have favourable lipid profiles and are less centrally obese[30;31].

The observed increased sensitivity to the cardiovascular/cognition effects of diabetes in South Asians and African Caribbeans requires confirmation and explanation. Single risk factors cannot capture the complex disturbances in metabolic profiles that may underlie development of diabetes and subsequent CVD. In addition, diabetes is also associated with adverse haemodynamic effects, including elevated central pressure, reduced arterial compliance, elevated nocturnal pressure and increased carotid intima media wall thickness[32-34]. Metabolomic and haemodynamic profiles have been measured at the 20 year SABRE investigation[8], enabling causal analysis in this follow-up.

Gender and CVD: By original study design, the majority of SABRE participants are men, (76% European, 83% South Asian and 57% African Caribbean), as men experience greater CVD risk. However women make up a greater proportion of our older population

due to selective survival. There are gender differences in the phenotypic expression of, and aetiological pathways to, CVD. While the ratio of CHD to stroke is 2:1 in men, it is 1:1 in women. Diabetes increases the risk of CVD in women to a greater extent than in men[35]. We have shown that the female protection from incident CVD is less marked in ethnic minority groups than in Europeans, so that, for example, incident CVD in South Asian women is equivalent to or greater than that for European men[28]. Even basic information, such as the burden of CVD, and its consequences in older age, in ethnic minority women, is lacking.

SABRE offers an unrivalled opportunity to understand determinants of and ethnic differences in decline in cardiometabolic health with ageing. This includes LV and cognitive function, exercise tolerance, cardiovascular events and diabetes. We will be able to identify mid-life targets and thresholds for intervention, which may differ by ethnicity and which will inform subsequent pilot studies and clinical trials.

Study objectives

Hypotheses

1. Five year decline in systolic and diastolic cardiac function, and global cognitive function and hippocampal volumes, will be greater in ethnic minority groups than in Europeans. The ethnic differential will be explained by the excess burden of diabetes, and associated adverse metabolomic and haemodynamic effects.

2. The impact of mid-life risk factors (1988-91) will be stronger than, and independent of, those measured in older age (2008-11) on current levels of, and 5 year change in cardiac and cognitive function (2014-17).

3. Women will have worse cardiac and cognitive function than men in all ethnic groups with a stronger association with diabetes.

4. Ethnic minorities will continue to experience a significantly higher stroke rate than Europeans. This will be explained by their excess of diabetes, and increased susceptibility to its adverse effects.

Questions to be addressed

1. How large are ethnic /sex differences in cardiac function, cognitive function and hippocampal volumes in older age?

2. To what extent do cardiac function, cognitive function and hippocampal volumes change over a 5 year period in each ethnic group?

3. Which risk factors measured in mid-life and in early old age are most strongly associated with current cardiac and cognitive function and hippocampal volumes and with 5 year changes in these parameters? Can these risk factors explain ethnic differences in cardiac and cognitive function?

4. How large are gender differences in current disorders of cardiac and cognitive function and in their associations with current risk factors?

5. Do ethnic differences in incident cardiometabolic disorders persist into older age?

6. Which risk factors or risk factor profiles measured in mid-life and early old age are most strongly associated with incident cardiometabolic disorders and which best explain ethnic differences in incidence?

Participants

Original cohort participants

SABRE survivors, now aged around 75 years (IQR 69-80), will be invited for clinic investigation (V3, 2014-17) and/or to complete a health and lifestyle questionnaire and/or to allow access to their health-related records

Additional recruitment of partners

To boost numbers of women, partners of index SABRE participants will be recruited. Partner recruitment has scientific and practical advantages. Many risk factors, measured and unmeasured, operate at a familial level. Including family members enables both adjustment for and exploration of the role of shared familial environments.

Additional recruitment of African Caribbean participants

As our baseline studies included only a small number of African Caribbean participants, we propose to boost the sample by recruiting de novo 100 African Caribbean first generation migrants between the ages of 60 and 80 with or without spouses or partners. These additional new participants will increase power for cross-section al analyses to address hypotheses 1 and 3 and for future prospective analyses of incident cardiometabolic disorders. Exclusion criteria will be as noted below for existing SABRE study participants.

Inclusion criteria

All surviving SABRE study participants who took part in the baseline studies together with their partners will be invited to take part in the V3 follow-up.

Newly identified first generation African Caribbean migrants within the same age range of the original SABRE cohort and their partners.

Exclusion criteria

Inability to give informed consent

Those who have informed the study team that they do not wish to participate in future SABRE related research.

Those who live overseas (and for whom we have contact details) will not be invited to attend clinic, although they will be invited to complete the study questionnaire.

Clinic exclusion criteria:

Terminal illness or severe comorbidities affecting attendance or study investigations.

Design

Observational cohort and cross-sectional study. The original study participants provided their NHS numbers at the time of the baseline studies (1988-91). Participants are flagged with the Office for National Statistics who provide details of deaths and cancer registrations (we have Section 251 support for this ongoing follow-up).

Contact and recruitment

For the previous (V2) 20 year follow-up (2008-2011)we traced surviving participants using their NHS numbers by means of the NHS Strategic Tracing Service. Of the 3,440 survivors traced at that time, 2128(62%) agreed to participate in some way. 559 (16%) said that they did not wish to be contacted again, 6 were unable to give consent, 70(2%) were away or unwell and the remainder either did not respond or declined to participate at that time.

For this third stage of SABRE we propose to request updated addresses and GP details for surviving members of the cohort, again using NHS numbers, for all those who participated at V2 and consented to future contact or follow-up.

Once traced, we will write to each person inviting them, together with their partners, to take part in V3. Two copies of the information leaflet, consent form and questionnaire will be enclosed, together with two reply paid envelopes. We will make telephone contact with, or send one reminder, to non-respondents. At V2, 80 participants requested study information and questionnaires to be provided in Punjabi. As at V2 we will send translate all study documentation into Punjabi for these participants.

New African Caribbean participants will be recruited via visits to local churches and community centres in Brent by our research study team or via visits to local GP practices. We will also place advertisements about the study in local and national newspapers. In addition, participants will be recruited from those approached to participate in DELPHIC at UCLH, Royal Free and St Pancras CNWL Hospitals. DELPHIC(Delirium and Population Health Informatics Cohort, REC 16/LO/1217, http://www.hra.nhs.uk/news/research-summaries/delirium-and-population-health-informatics-cohort-delphic-study/#sthash.wsYwEiVt.dpuf). The DELPHIC team will be trained to identify suitable participants and will ask them to complete the initial consent form which is used for all new participants (SABRE V3_Consent form_post_v1_3_110516), giving consent for a member of the SABRE research team to contact the person regarding the study.

A further source of new participants is the UCL BioResource (http://www.uclhospitals.brc.nihr.ac.uk/research/programmes/ucl-bioresource). The UCL BioResource is a research register, establishing a pool of volunteers with and without health problems who are willing to be approached to participate in research studies investigating the links between genes, the environment, health and disease. We have

established that UCL BioResource has volunteers of African and African Caribbean descent and aged 60+, who can be recalled for contact by the SABRE study team. We have applied for SABRE to be adopted as a stage 2 BioResource study.

Clinical follow-up

All UK based participants will be invited for clinical follow-up. Those who consent will be asked to attend our clinic at University College London in the morning after a light breakfast. Participants will be offered transport or reimbursement of travel costs. Participants will be offered a £30 gift voucher at the end of their clinic visit.

Morbidity follow-up and health and lifestyle questionnaire

Participants will be asked to complete a health and lifestyle questionnaire and they will receive a £5 gift voucher after they have done this.

Participants will be asked to give permission for the SABRE research team to have access to data extracted from linked health –related records, both now and in the future. These records may include general practice databases, Hospital Episode Statistics(HES), Myocardial Ischaemia National Audit Project(MINAP), cancer registration data and may include other databases as yet undefined.

Participants have the option of consenting to any or all of the above three parts of the study (or not at all).

If the response rate falls below 80% for surviving west and north-west London based participants who attended clinic at V2, then we will ask the National Centre for Social Research (NatCen) to supply trained interviewers to visit people at home as at V2. NatCen has bilingual interviewers who speak Punjabi, Urdu and Hindi and assisted the previous V2 SABRE study recruitment by conducting home visits to non-responders.

Deceased participants

Over 1250 participants have died since the baseline study; of these 200 have died since the V2 follow-up. All accessible primary care records of deceased participants were reviewed at V2 (with Section 251 support). We propose to continue this process at V3 for recently deceased participants.

Measurements to be made at V3 clinic

Pilot study- healthy volunteers

Prior to the start of the main V3 follow-up we propose to invite 12 healthy volunteers of similar ages to our cohort, in order to assess feasibility of the planned procedures listed below. We will ask our participating GP surgeries to contact willing participants on our behalf. A separate information leaflet and consent forms are provided and these volunteers will also receive reimbursement of travel costs plus a £30 gift voucher.

Metabolic markers

a) Blood, urine and saliva samples will be collected. Bloods will be analysed for metabolic, haematological and inflammatory markers, aliquots of whole blood, serum and plasma will be stored for future analysis including DNA extraction for epigenetic analyses. Urine will be analysed for the albumin/creatinine ratio. Saliva will be analysed for amylase content.

b) metabolic disturbance (including advanced glycation end products (AGES)) which may be found in the skin, using the non-invasive Miraculins SCOUT AGE reader (http://www.veralight.com/media/docs/2012/DR-200353_Rev%20A.pdf)[36] . Participants place their arm on the AGE reader for approximately one minute.

Body composition and anthropometry

a) Bioimpedance will be used to assess body water content, using a Tanaka 410 device. This information will complement body composition measures (lean and fat mass) obtained by DEXA scanning.

b) DEXA scanning (Hologic horizon)will be used to assess bone density, body composition (lean and fat mass) and aortic calcification[37-40].

c) Ultrasound will be used to measure liver fat content and fibrosis(according the National Health and Nutrition Survey protocol)[41]and to measure thickness of muscle in the thigh (vastus lateralis) and lower leg (gastrocnemius) muscles [42;43]

d) Height, leg length, weight and waist , hip and thigh circumferences according to the SABRE baseline and V2 protocol.

Blood pressure

Resting blood pressure (brachial (in both arms) and ankle) (average of second and third of three measurements in the sitting, lying and standing positions using OMRON 705CP-II) according to the v2 protocol. Central BP and pulse wave velocity will be measured using a PulseCor device.

Electrocardiogram (ECG)

12 lead ECG according to the baseline and V2 protocols [30;44].

Echocardiography and carotid ultrasound imaging

a) Echocardiography will be used to measure left ventricular structure and function. Echocardiography will be performed using a Philips IE33 ultrasound system and DICOM cineloops recorded for offline using commercial software (QLab, Philips) and additional custom written MATLAB programs based on previous studies [45;46]

b) Carotid intima –media thickness will be measured using B mode ultrasound in a 10 mm segment of the far wall of the left common carotid artery (CCA) proximal to the carotid bulb[47].

Cerebral imaging

Cerebral magnetic resonance imaging will be performed according to the Cardiovascular Health Study protocol and including volumetric analyses, as at V2 [48] to determine

presences of subclinical cerebrovascular disease such as infarcts and white matter hyperintensities. Hippocampal and total brain volumes will also be measured as these are associated with cognitive function.

Respiratory function, exercise capacity, physical activity

a) Respiratory spirometry will be used to assess lung function (forced expiratory volume or vital capacity) [49]. This information will inform the team as to whether there is functionally limiting lung disease which may impact upon ability to exercise or which should be taken into account when assessing cardiovascular function , disability and quality of life

b) Exercise capacity will be measured using the long distance corridor walk [50]. Participants (if able) will be asked to walk 400 metres in laps along a corridor after a 2 minute warm-up walk . Heart rate, blood pressure, blood oxygen saturation (SaO2), muscle blood flow and oxygen consumption will be monitored before and (where possible) continuously during the test.

c) To assess usual physical activity, participants will be fitted with an Actigraph (GT3X plus) physical activity monitor to wear for 3 days following the clinic visit [51].

Cognitive function

A series of cognitive function tests and the geriatric Depression Scale will be administered as at V2. These include tests of global functioning, verbal fluency, assessment of reasoning and delayed recall, attention and mental flexibility and of factors observed to interfere with test performance (e.g visual or hearing impairment and reading literacy). These tests have been previously validated in a multi-ethnic setting and were used at V2 in the SABRE cohort [52-58].

Balance, vision, sensation, limb strength

a) The QuickScreen test will be used to assess balance, sensation and vision (http://www.neura.edu.au/research/facilities/falls-and-balance-research-group/quickscreen) . This has 5 components including a test of vision, lower limb position and strength, reaction time to a light stimulus and body sway when standing on a firm foam rubber surface[59].

b) The handgrip test will be used to assess grip strength.

Quality control and biological variation

a) Split blood samples will be taken from 100 willing participants (with permission and evenly mixed by gender and ethnicity) to assess laboratory QC.

b) The same willing people will be asked to return within three months for repeat of some tests (excluding DXA, anthropometrics, Quickscreen, cognitive function assessment, ECG and cerebral MRI) to assess within-individual biological variation and clinic measurement reliability. We will also repeat retinal photography as performed at V2 in this subset to assess progression of retinal pathology.

Data collection methods will be consistent with those employed at V1 and V2 wherever possible. For those who do not speak English, an interpreter will be available at the clinic as at V2.

Health and Lifestyle Questionnaire

This includes topics from the baseline(V1) and V2 questionnaires:

- history of cardiovascular disease, diabetes and other serious disorders,
- chest pain,
- breathing difficulties,
- leg pain,
- weight and size,
- smoking,
- alcohol consumption,
- physical activity,
- medication use,
- sleep
- home, work and social circumstances
- activities of daily living
- family and leisure activities
- family history of diabetes and cardiovascular disease
- overall health and quality of life

In addition questions will be asked about reproductive history and sexual function, hearing and visual problems and disability, recall of childhood wellbeing, physical activity and diet, ethnicity and religion.

Statistics and data analysis

Sample size and power

Questionnaire completers from V2 include those obtained by post, phone and home visit, as well as those who attended clinic. All V2 clinic attenders indicated that they would be happy to re-attend. Allowing for attrition due to mortality and loss to follow-up, we anticipate 80% re-attendance, and 80% attendance of 'available' partners, a total of 1765 attendees. Questionnaire completion brings the total to 2675. There are no comparable data on change in outcomes in older ethnic groups; therefore we have used comparisons between people with and without diabetes as a proxy for ethnic group comparisons. Standardised difference in change in cerebral volume, and key individual cognitive function tests either annually or over a 3 year period, comparing people with and without diabetes, varies from 0.14 to 0.2735[60].   Similarly, 5 year decline in LV function varies from 0.5 to 1 SD in people with diabetes[61]. We are well powered to detect ethnic differences in

continuous variables of much lower magnitudes than this. Detectable differences in events are similar to those observed previously[62;63].

	Europeans	South Asians	African Caribbeans
SABRE Survivors at end 2011	1729	1330	674
Detectable risks for incident new CHD	1	1.4	0.6
Detectable risks for incident new stroke	1	1.7	1.9
V2 Questionnaire completers/clinic attenders	974/684	734/522	303/232
V3 Questionnaire completers/clinic attenders (index participants)	779/550	587/420	242/186
Detectable standardised differences between ethnic groups for Clinic attenders Questionnaire completers	 Reference Reference	 0.18 0.16	 0.23 0.21
Detectable risks for heart failure	1 (8%)	1.6 (12.4%)	1.7 (13.0%)
V3 Partner clinic attendance (men/women) V3 Partner questionnaire completers (men/women)	56/238 77/430	30/216 60/380	27/42 40/80
Detectable standardised gender differences within ethnic group (index participants+partners) Clinic attenders Questionnaire completers	 0.20 0.16	 0.24 0.18	 0.35 0.29

Loss to follow up

For those unable to attend clinic, local GP clinic and home visits will be offered as at V2. Basic investigations, cognitive assessments, and echocardiography (using a portable Vivid-i) will be performed. We have experience of performing these investigations for clinical and research purposes at distant sites.

Follow up of non-responders

As at V2, we will request pseudonymised HES data together with pseudonymised data from other databases such as MINAP for those who do decline or who do not respond to

our V3 invitation, in order that we may assess the bias in our findings which may be attributable to refusal and non-response.

Statistical analyses

We will show unadjusted ethnicity and sex-specific tabulations of risk factors and risk factor profiles at V1, V2 and V3.

Change in (V2-V3) cardiac function, cognitive function and hippocampal volumes (index participants only). We will show unadjusted changes for each outcome measure (V2 minus V3) in each ethnic and sex group. Linear regression will be used to model V1(mid-life) and V2 (later-life) risk factors as predictors of changes (adjusted for V2 levels of each change variable). These analyses will compare changes and risk factor associations with changes by ethnicity and by sex. We will use multivariable modelling to identify potential explanations for any observed ethnicity- or sex-related differences in change outcomes.

Cross-sectional outcomes: Current (V3) cardiac function, cognitive function and hippocampal volumes, prevalent CHD, stroke, diabetes and metabolic disturbances (index participants + partners):

We will use linear regression to model continuous outcomes (appropriately transformed as necessary) and logistic regression to model dichotomous outcomes (both methods with robust standard errors to account for clustered (partner) data). We will describe ethnic and sex differences in cross-sectional associations between risk factors and outcomes. In the whole study group, we will identify independent associations between risk factors and outcomes in multivariable analyses including risk factors found to be associated with outcomes on univariable analyses ($p < 0.10$). Finally, we will identify potential explanations for any observed ethnicity/sex-related differences.

Analyses of incident events (CHD, stroke, diabetes: index participants only)

We will employ proportional sub-distribution hazards regression[64] to examine ethnic and sex differentials in event rates and to address competing risks of loss to follow-up and deaths from other causes. Potential explanations for ethnic differentials in event rates will be explored using measures from both V1 (midlife) and V2 (later life) as covariates in multilevel models.

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