ADVERSE EFFECT OF DIABETES AND HYPERGLYCEMIA ON ARTERIAL STIFFNESS IN EUROPEANS, SOUTH ASIANS AND AFRICAN CARIBBEANS IN THE SABRE STUDY

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Brief Title: Ethnic differences in arterial stiffness

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Abstract

Objectives: Ethnic minority groups in the UK experience marked differences in cardiovascular disease risk. We investigated differences in arterial central hemodynamics, stiffness and load in a tri-ethnic population-based cohort.

Methods: 1312 participants (70±6y) underwent echocardiography and measurement of brachial and central blood pressure to assess central arterial hemodynamics including central pulse pressure (cPP), arterial stiffness (cPP/stroke volume (SV)), systemic vascular resistance (SVR) and load (E_a).

Results: Brachial and central systolic blood pressures were similar in all ethnic groups. Compared to Europeans, cPP, cPP/SV and E_a were higher in South Asians. In contrast, cPP/SV was lower in African Caribbeans despite higher mean arterial pressure, higher SVR and higher diabetes prevalence. cPP/SV and E_a remained significantly higher in South Asians and significantly lower in African Caribbeans after multivariate adjustment. Diabetes and higher HbA_{1c} were more strongly associated with higher cPP/SV in South Asians than in Europeans (p interaction=0.045 and 0.005 respectively); higher HbA_{1c} was also more strongly associated with increased E_a in South Asians than Europeans (p interaction=0.01). There was no evidence of an interaction between glycemia and cPP/SV in African Caribbeans.

Conclusion: Compared to Europeans, South Asians have unfavourable arterial function. Diabetes and hyperglycemia have a more deleterious effect on cPP/SV and E_a in South Asians. In contrast African Caribbeans have more favourable arterial function than Europeans and South Asians. These differences may contribute to the differential ethnic rates of cardiovascular disease.

Key Words: diabetes, hyperglycaemia, ethnicity, blood pressure, hemodynamics, arterial stiffness

Introduction

People of South Asian and African Caribbean origin experience marked differences in cardiometabolic disease compared to people of European origin. Both ethnic minority groups are more insulin resistant, and have a 3-4 fold excess of diabetes.(1) Stroke mortality is almost doubled in both South Asians and African Caribbeans, but, while coronary heart disease (CHD) mortality is elevated in South Asians, African Caribbeans experience CHD mortality rates that are 50% lower than the comparator European population despite the higher rates of diabetes.(2) This marked ethnic difference is unexplained by conventional risk factors.(2)

Elevated blood pressure (BP) is a major risk factor for CHD and stroke.(3) Hypertension is more prevalent in African-Caribbean populations,(4) but observed differences in brachial BP do not appear to account for the nearly twofold excess of stroke and cannot explain lower rates of CHD. (2, 5) In contrast, differences in brachial BP between South Asians and Europeans are generally small and inconsistent(6). Recent evidence indicates that central (aortic) systolic or pulse pressure and increased arterial stiffness predict CHD and stroke independently of brachial BP. (7, 8) Central hemodynamics, aortic stiffness and arterial load may therefore better explain ethnic differences in cardiovascular risk. Previous studies of arterial stiffness in South Asian or African Caribbean people have often been restricted to clinic or hospital populations, with relatively small numbers.(9-15) Information on ethnic differences in central hemodynamics is also incomplete. A recent study which pooled central augmentation index (AI_x) values from 5 separate studies reported that African Americans and Andean Hispanics had higher, whereas American Indians had lower AI_x than British whites or Chinese people.(16) However this analysis of ethnic haemodynamic differences was limited by the differing

methodologies used to measure central pressure, and the diverse geographical settings.

We therefore investigated UK-based ethnic differences in central hemodynamics, arterial stiffness and arterial load as a potential explanation of ethnic differences in CHD risk. We also explored the potential role of diabetes/hyperglycaemia in any differences observed in ethnic minority groups.

Methods

Study Population

Participants were recruited from clinic attendees for the 20 year follow-up visit for the Southall and Brent REvisited (SABRE) study, a tri-ethnic population-based cohort consisting of white European, first generation migrant South Asian and African Caribbean men and women. Details of the cohort have been published (17) . Participants were recruited from primary care between 1988 -1991, when they were aged 40-69 years. 4857 participants took part in the original study (2346 Europeans, 1710 South Asians and 801 African Caribbeans). Surviving participants were invited to attend the 20 year follow-up investigation between 2008 and 2011 when they were aged 58 to 86y. 1438 participants attended for follow-up investigation. A detailed account of the SABRE cohort at follow-up is given in Online Figure 1 in the online-only Data Supplement. Approval was obtained from the local research ethics committee and all participants gave written informed consent, including consent to primary care record review. Follow-up clinic attendees were as a group healthier than the entire cohort at baseline; however we have shown that survival rates and

baseline heath of clinic attendees were similar by ethnicity (2) as shown in Online Table 1 in the online-only Data Supplement.

Investigations

Participants fasted and refrained from alcohol, smoking and caffeine intake for at least 12h prior to attendance and omitted any medication on the morning of investigation. A questionnaire was completed which detailed health behaviours, medical history and medication.

Clinic measurements

Height, weight, waist and hip circumference and blood pressure were measured under standardised conditions.(17) Fasting samples were analysed for blood glucose, glycosylated haemoglobin (HbA_{1c}), insulin, triglycerides, total cholesterol (TC) and high density lipoprotein (HDL-C) cholesterol. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated.(18) Diabetes was diagnosed on the basis of patient or GP report or clinic blood samples according to the 1999 World Health Organisation guidelines.(19) Diabetes duration was established by GP report or from questionnaire. CHD was defined as a coronary event or revascularisation identified by medical record review, and adjudicated by an independent committee.

Seated brachial systolic (bSBP) and diastolic (DBP) blood pressure was measured after 10 minutes rest as the mean of the final two of three readings using a validated brachial blood pressure device (Omron 705CP). Hypertension was defined as physician diagnosed hypertension or participant reported hypertension in people receiving blood pressure (BP) lowering medication. Central hemodynamics were

measured using a SphygmoCor device (AtCor, Sydney, Australia) (20). Radial artery pressure was calibrated to bSBP and DBP according to the manufacturer's instructions. Central systolic BP (cSBP), mean arterial pressure (MAP), central pulse pressure (cPP), augmentation index (AI_x), augmentation pressure (P_{aug}), end-systolic BP and central to brachial pulse pressure amplification (PP_{Amp}) were calculated. Carotid to femoral pulse wave velocity (cfPWV) was measured in accordance with a recent consensus document(21) using a continuous wave directional Doppler probe (Micro-Medical Pulse Trace 2000 system). Due to an equipment breakdown, cfPWV was only measured in 960 individuals (442 Europeans, 349 South Asians and 169 African Caribbeans).

Transthoracic echocardiography was performed as previously described. (22) In brief, data sets were acquired over 4 cardiac cycles during held respiration using a 5.0-1.0Hz phased array transducer (S5-1) on a Philips iE33 ultrasound device and analysed using Philips Qlab 7.0. End diastolic (EDV) and systolic volume (ESV) were used to calculate stroke volume (SV). Ejection fraction (EF) was calculated as EF=(SV/EDV) *100. Systemic vascular resistance (SVR) was calculated as mean arterial pressure (mmHg)/cardiac output (ml/min) × 8. While cfPWV is considered the 'gold standard' measure of arterial stiffness we additionally calculated the elasticity coefficient, (the ratio of central pulse pressure to stroke volume, cPP/SV, i.e. the inverse of total arterial compliance).(23) Total arterial elastance (E_a) a measure of overall arterial load(24) was calculated as the ratio of end systolic pressure to SV.

Statistical analysis

Data are reported as mean±SD or median (interquartile range) for skewed data and n (%) for categorical data. Skewed data were natural log (ln) transformed before analysis. Statistical analyses were performed using Stata 12.0 (StatCorp LP, Tx). Comparisons of ethnic groups were made using analysis of variance or covariance (ANOVA or ANCOVA) followed by post-hoc testing if $p< 0.05$ by ANOVA. Multivariable regression was also performed: covariates (age, sex, height, waist hip ratio (WHR), heart rate, MAP, BP treatment, TC:HDL-C ratio, diabetes, HOMA-IR CHD and smoking were chosen *a priori* based on their known influence on arterial function. Possible interactions by gender and diabetes status were sought and data from both sexes were pooled, with adjustment for sex in all multivariable models. Separate sex results can be found in Online Tables 2-4 in the online-only supplement. A p value of <0.05 was considered statistically significant.

Results

Characteristics of participants are shown in Table 1. South Asian and African Caribbean people were more likely to have hypertension and diabetes than Europeans. South Asians had higher prevalence rates of CHD and were more centrally obese; African-Caribbeans had higher BMI and a lower prevalence of CHD compared to both Europeans and South Asians. Brachial and central hemodynamics and measures of arterial elasticity/stiffness (cPP/SV, cfPWV) and load (E_a) are presented in Table 2. After adjusting for age and sex, both bSBP and cSBP were slightly higher in African Caribbeans. DBP was significantly lower in South Asians and higher in African Caribbeans compared to Europeans; consequently compared with Europeans, bPP and cPP were higher in South Asians,

and lower in African Caribbeans than Europeans. In contrast, MAP was equivalent in South Asians, but higher in African Caribbeans, than Europeans. AI_x and P_{aug} were significantly higher in South Asians but did not differ in African-Caribbeans compared to Europeans. There was no significant inter-ethnic difference in P_{amp}. SVR was higher in South Asians and African Caribbeans compared to Europeans. Compared to Europeans, cPP/SV was significantly higher in South Asians and lower in African Caribbeans (Table 2); these differences were also maintained after indexation of cPP/SV to body surface area (not shown). E_a was higher in South Asians and similar in African Caribbeans compared to Europeans. cfPWV was slightly lower in African Caribbeans but not significantly so. When cPP/SV was compared in only those participants in whom cfPWV was measured it remained significantly different by ethnicity (European = 0.83±0.01; South Asian = 0.95±0.02; African-Caribbean =0.81±0.02; $p < 0.001$ by ANCOVA and $p<0.001$ for comparison between Europeans and South Asians).

To seek explanations for these ethnic differences, further multivariate analysis was performed. After additionally adjusting for height, WHR, BP treatment, MAP, TC:HDL-C, diabetes, HOMA-IR, CHD and smoking (Table 3), differences in PP, cPP and P_{aug} between Europeans and South Asians were attenuated and became non-significant. In contrast, the greater SVR, cPP/SV and E_a in South Asians versus Europeans remained significant after multivariable adjustment. After multivariable adjustment bSBP, bPP, cSBP cPP, AI_x, P_{Aug} and cPP/SV were significantly lower and DBP remained significantly higher in African Caribbeans.

Ethnicity as a modifier of the effect of diabetes on arterial function

Given the high prevalence of diabetes and its known effect on arterial function, we explored whether ethnicity modified the associations between diabetes and measures of arterial hemodynamics, stiffness (cPP/SV) and load (E_a). Diabetes or elevated HbA_{1c} was found to exert a more detrimental effect on cPP/SV and E_a in South Asians than Europeans (Figure 1) in models adjusted for age and sex. Further adjustment for height, WHR, MAP, BP treatment, heart rate, TC:HDL-C, CHD and smoking had minimal effects on these interactions and there was no interaction between ethnicity and insulin resistance assessed as HOMA-IR on measures of arterial hemodynamics, cPP/SV and E_a (data not shown).

Association of arterial resistance, stiffness and load with CHD

Using logistic regression we investigated the association of SVR, , cPP/SV, cfPWV and E_a with CHD. Associations are presented as age, sex and ethnicity adjusted standardised odd ratios [95%] confidence intervals in Online Table 5 in the online-only Data Supplement. cPP/SV was the most strongly associated variable with CHD (0.26 [0.10,0.41], p=0.002), followed by cfPWV (0.17 [0.02,0.3], p=0.03). SVR and E_a were not significantly associated with CHD (SVR (0.008 [-0.14,0.16], p=0.9) and E_a (0.06 [-0.09,0.21], p=0.5)).

Discussion

In this tri-ethnic population-based study in the UK, we show marked inter-ethnic differences in central arterial BP, vascular resistance (SVR), stiffness (cPP/SV) and arterial load (E_a). After adjustment for known risk factors, people of South Asian origin still had unfavourable SVR, cPP/SV and E_a. In contrast, people of African Caribbean origin had more favourable cPP/SV than Europeans but had higher mean arterial pressure and elevated SVR. We also found that diabetes/hyperglycaemia was associated with worse cPP/SV and E_a in South Asians than Europeans.

Little is known regarding arterial central hemodynamics, stiffness and load in South Asian people. Two small UK-based studies(12, 15) have previously reported that PWV is higher in South Asians. In the main analysis we did not observe a significant difference in cfPWV between ethnic groups, although cPP/SV was elevated. When we stratified by sex we observed significantly higher cfPWV in South Asian women and lower cfPWV in African Caribbean women (online Tables 3 and 4) but we did not see this pattern in men. The difference between the two arterial stiffness measures in men (cfPWV and cPP/SV) may reflect the smaller numbers of participants in whom cfPWV was measured, or the inability of cfPWV to assess stiffening of the proximal aorta(25). The latter explanation is more likely in view of the preserved difference in cPP/SV in the sub-sample in whom cfPWV was measured. The results presented in online Table 4 show that cPP/SV is more strongly associated with CHD than cfPWV which suggests that cfPWV may have more limited prognostic value in elderly individuals.

A previous study(14) showed that an indirect measure of arterial stiffness was elevated in South Asian stroke survivors compared with Europeans. This difference was explained by the higher stiffness index in South Asian people with diabetes, although an interaction between ethnicity and diabetes was not looked for. This finding in a highly selected sample is consistent with our observation of greater stiffness and a more adverse effect of diabetes on aortic stiffness in a population-based sample of South Asians, despite similar hypertension treatment rates and MAP. We also show that the adverse effects of hyperglycaemia on stiffness and load are not confined to people with diabetes, but extend across the glycaemic spectrum as measured by HbA_{1c}.

In contrast, despite similarly high rates of medication for hypertension, African Caribbeans had elevated BP (DBP and MAP), and higher SVR, yet did not have unfavourable arterial central hemodynamics, stiffness (cfPWV) and load (E_a). This is consistent with some(9), but not all(11), previous UK findings. Most previous work comparing Black African-origin with White European-origin populations has been undertaken in the US. These studies, have generally found higher central BP in African Americans, although findings with regard to arterial stiffness are less consistent. Birru et al (26) reported that PWV was higher in African American women, but the Multi-Ethnic Study of Atherosclerosis also failed to find any difference in large arterial elasticity in African Americans compared to White, Hispanic or Chinese Americans, although small artery elasticity was increased(13). We observed the opposite to Birru, the favourable hemodynamic pattern observed in African Caribbean women was reflected in a lower cfPVW . It may be relevant to note that the situation is different in America. Since the 1970's African Americans

have been observed to be at higher risk of CHD than White Americans(27), unlike the UK where African Caribbeans are at lower risk of CHD than Europeans(2).

We interpret our findings in the light of known ethnic differences in risks of CHD. Our group has previously reported that rates of CHD are elevated in South Asians and are lower in African Caribbeans compared with European-origin populations and that these differences were not explained by conventional risk factors. Table 4 summarises the ethnic differences in cardiovascular/hemodynamic risk factors in South Asians and African Caribbeans compared to Europeans. We propose that differences in arterial hemodynamics/stiffness could play a role in explaining these ethnic differences. Arterial stiffness predicts CHD independently of conventional risk factors including mean BP.(28-30). Increased arterial stiffness reduces the capacitative buffering (Windkessel) effect of the aorta, increases the hemodynamic afterload imposed on the LV, effects myocardial blood flow, increases myocardial oxygen demand, and increases susceptibility to sub-endocardial ischemia.(31) This explanation is consistent mechanistically with the known ethnic differences in CHD. Increased arterial stiffness could contribute to increased rates of CHD observed in South Asians, while favourable arterial haemodynamics/stiffness would explain the lower rates of CHD observed in African Caribbeans.

Our findings therefore also provide a potential mechanism to explain why diabetes and hyperglycemia are particularly adverse for risk of CHD in South Asian people(2) since they are associated with greater arterial stiffness in South Asian people than in

Europeans or African-Caribbean people. Diabetes and hyperglycemia have been reported to be associated with increased arterial stiffness,(32) although the strength of association has previously been reported as weak,(33) and we observed no significant relationship between diabetes or glycosylated haemoglobin in Europeans or African Caribbeans in this study. It is possible that more aggressive management of BP in people with diabetes contributes to this effect. The effect of diabetes on arterial stiffness has been attributed to increased oxidative stress, impaired endothelial function, accelerated fibrosis and accumulation of advanced glycation end products (AGEs) in the vasculature. Why diabetes and hyperglycaemia should exert a more deleterious effect on arterial stiffness in South Asians is uncertain. We have shown that South Asians are diagnosed at a younger age and have greater diabetes duration; moreover we know that individuals experience years of hyperglycaemia before diabetes diagnosis.(34) Given our observation that the greater impact of hyperglycaemia on stiffness occurs across the glycaemic spectrum, it is likely that South Asians are exposed to greater levels of hyperglycaemia over much longer periods, resulting in more adverse effects on the vasculature, although it is unclear why this effect would not be apparent in African Caribbeans who also experience an increased risk and duration of diabetes.(1) It is possible that other mechanisms acting in South Asian people, such as worse endothelial function(14) and/or a higher pro-inflammatory background (35) contribute, but further studies are required to investigate this question.

SABRE is one of the largest and longest running multi-ethnic studies worldwide. Participants were recruited from primary care without exclusion, thereby minimising selection bias at the outset of the study. As mentioned in the methods section, this

follow-up study was limited to survivors who were willing and able to attend clinic. Clinic attendees were healthier at baseline than those who did not survive or failed to attend; however we have shown that survival rates and baseline heath of clinic attendees were similar by ethnicity(2), so this limitation is unlikely to have biased comparisons. A further limitation is that the majority of South Asians in this study (53%) are of Punjabi Sikh origin, and although most people of South Asian ethnicity have an increased prevalence of diabetes and CVD, our findings may not apply to all South Asians. Similarly, our findings cannot necessarily be extrapolated to people of South Asian or African Caribbean ethnicity living outside the UK, people outside the age range studied, or to second or third-generation migrants. A final limitation is the calculation of our arterial elasticity coefficient, while SV is directly calculated by echocardiography cPP is indirectly estimated.

In conclusion, compared to Europeans, South Asians have unfavourable arterial function and diabetes and hyperglycemia have a more deleterious effect on arterial stiffness and load. In contrast, African Caribbeans have more favourable arterial stiffness than Europeans and South Asians despite higher BP and higher SVR. These differences may contribute to the differential ethnic rates of cardiovascular disease.

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References

1. Tillin T, Hughes AD, Godsland IF, Whincup P, Forouhi NG, Welsh P, et al. Insulin resistance and truncal obesity as important determinants of the greater incidence of diabetes in Indian Asians and African Caribbeans compared with Europeans: the Southall And Brent REvisited (SABRE) cohort. Diabetes Care. 2013;36(2):383-93.

2. Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, Forouhi NG, et al. The Relationship Between Metabolic Risk Factors and Incident Cardiovascular Disease in Europeans, South Asians, and African Caribbeans SABRE (Southall and Brent Revisited)-A Prospective Population-Based Study. J Am Coll Cardiol. 2013;61(17):1777-86.

3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

4. Agyemang C, Bhopal R. Is the blood pressure of people from African origin adults in the UK higher or lower than that in European origin white people? A review of cross-sectional data. JHumHypertens. 2003;17:523-34.

5. Chaturvedi N, McKeigue PM, Marmot MG. Resting and ambulatory blood pressure differences in Afro-Caribbeans and Europeans. Hypertension. 1993;22:90-6.

6. Agyemang C, Bhopal RS. Is the blood pressure of South Asian adults in the UK higher or lower than that in European white adults? A review of cross-sectional data. JHumHypertens. 2002;16:739-51.

7. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J. 2010;31(15):1865-71.

8. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(13):1318-27.

9. Rajkumar C, Mensah R, Meeran K, Armstrong S, Bulpitt CJ. Peripheral arterial compliance is lower in Afro-Caribbeans compared to white Caucasians with type 2 diabetes after adjustment for blood pressure. J Hum Hypertens. 1999;13:841-3.

10. Zion AS, Bond V, Adams RG, Williams D, Fullilove RE, Sloan RP, et al. Low arterial compliance in young African-American males. American Journal of Physiology - Heart and Circulatory. 2003;285:H457-H62.

11. Strain WD, Chaturvedi N, Dockery F, Shiff R, Shore AC, Bulpitt CJ, et al. Increased arterial stiffness in Europeans and African Caribbeans with type 2 diabetes cannot be accounted for by conventional cardiovascular risk factors. Am J Hypertens. 2006;19:889-96.

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

13. Duprez DA, Jacobs DR, Jr., Lutsey PL, Herrington D, Prime D, Ouyang P, et al. Race/ethnic and sex differences in large and small artery elasticity--results of the multi-ethnic study of atherosclerosis (MESA). Ethn Dis. 2009;19(3):243-50.

14. Gunarathne A, Patel JV, Kausar S, Gammon B, Hughes EA, Lip GY. Glycemic status underlies increased arterial stiffness and impaired endothelial function in migrant South Asian stroke survivors compared to European Caucasians: pathophysiological insights from the West Birmingham Stroke Project. Stroke. 2009;40(7):2298-306.

15. Rezai M-R, Wallace AM, Sattar N, Finn JD, Wu FCW, Cruickshank JK. Ethnic Differences in Aortic Pulse Wave Velocity Occur in the Descending Aorta and May Be Related to Vitamin D. Hypertension. 2011;58:247-53.

16. Chirinos JA, Kips JG, Roman MJ, Medina-Lezama J, Li Y, Woodiwiss AJ, et al. Ethnic differences in arterial wave reflections and normative equations for augmentation index. Hypertension. 2011;57(6):1108-16.

17. Tillin T, Forouhi NG, McKeigue PM, Chaturvedi N, Group SS. Southall And Brent REvisited: Cohort profile of SABRE, a UK population-based comparison of cardiovascular disease and diabetes in people of European, Indian Asian and African Caribbean origins. Int J Epidemiol. 2012;41(1):33-42.

18. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21(12):2191-2.

19. Organization WH. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva1999 1999.

20. Chen C-H, Nevo E, Fetics B, Pak PH, Yin FCP, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radical tonometry pressure - validation of generalised transfer function. Circulation. 1997;95(7):1827-36.

21. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens. 2012;30(3):445-8.

22. Park CM, March K, Ghosh AK, Jones S, Coady E, Tuson C, et al. Left-ventricular structure in the Southall And Brent REvisited (SABRE) study: explaining ethnic differences. Hypertension. 2013;61(5):1014-20.

23. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol. 1998;274(2 Pt 2):H500-H5.

24. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation. 1992;86(2):513-21.

25. Hickson SS, Butlin M, Graves M, Taviani V, Avolio AP, McEniery CM, et al. The relationship of age with regional aortic stiffness and diameter. JACC Cardiovasc Imaging. 2010;3(12):1247-55.

26. Birru MS, Matthews KA, Thurston RC, Brooks MM, Ibrahim S, Barinas-Mitchell E, et al. African-American ethnicity and cardiovascular risk factors are related to aortic pulse-wave velocity progression. Am J Hypertens. 2011;24(7):809-15.

27. Sempos C, Cooper R, Kovar MG, McMillen M. Divergence of the recent trends in coronary mortality for the four major race-sex groups in the United States. Am J Public Health. 1988;78:1422-7.

28. Fagard RH, Pardaens K, Staessen JA, Thijs L. The pulse pressure-to-stroke index ratio predicts cardiovascular events and death in uncomplicated hypertension. J Am Coll Cardiol. 2001;38(1):227-31.

29. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014;63(7):636-46.

30. Millar JA, Lever AF, Burke V. Pulse pressure as a risk factor for cardiovascular events in the MRC Mild Hypertension Trial. Journal of hypertension. 1999;17(8):1065-72.

31. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y. Coronary circulation in dogs with an experimental decrease in aortic compliance. J Am Coll Cardiol. 1993;21:1497-506.

32. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia. 2008;51(4):527-39.

33. Cecelja M, Chowienczyk P. Arterial stiffening: cause and prevention. Hypertension. 2010;56(1):29-30.

34. Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R, Baltimore Longitudinal Study of A. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes. 2003;52(6):1475-84.

35. Forouhi NG, Sattar N, McKeigue PM. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. IntJObesRelat Metab Disord. 2001;25:1327-31.

Figure legends

Figure 1: Bar charts showing A) cPP/SV and B) E_a categorized by diabetes status and ethnicity. P values are for significant ethnicity x diabetes interactions. Linear regression between C) cPP/SV and D) E_a and HbA_{1c} in Europeans South Asians, and African Caribbeans; points and confidence intervals have been omitted for clarity. All values adjusted for age and sex. P values are for significant ethnicity x HbA_{1c} interactions.

Table 1: Participant characteristics

	European n= 589	South Asian n= 459	African Caribbean n=214	P value
Male, n (%)	457 (78)	388 (85) **	110 (51) **	<0.001
Age, y	69.7±6.2	69.0±6.1	70.1±5.9¶	0.03
Height, cm)	170±9	166±9**	165±9**	<0.001
BMI, kg/m^2	27.9±5	26.3±4**	29.2±6**¶¶	<0.001
Waist-hip ratio	0.97±0.08	1.00±0.07**	0.96±0.08¶¶	<0.001
Hypertension, n (%)	336 (57)	346 (75) **	169 (79) **	<0.001
Receiving antihypertensive medication, n (%)	321 (55)	343 (75)**	163 (76)**	<0.001
Diabetes, n, (%)	112 (19)	186 (41) **	88 (41) **	<0.001
Diabetes duration, y	5 (0,10)	9 (2, 19)*	9 (14,19)**	0.02
On diabetes medication	62 (11)	136 (30)**	68 (32)**	<0.001
On lipid lowering medication	281 (48)	308 (67)**	109 (51)	<0.001
CHD, n (%)	118 (20)	159 (35) **	27 (13)*	<0.001
Ejection fraction, %	61 (10)	62(9)	64 (9)**¶¶	<0.001
TC:HDL-C	3.50(2.9,4.2)	3.42 (2.8,4.2)	3.25(2.6,3.8)*¶¶	<0.001
Triglycerides, mmol/l	1.18 (0.9,1.6)	1.19 (0.9,1.6)	0.88 (0.7,1.1)**¶¶	<0.001

HbA_{1c}, %	5.9 (5.6,6.2)	6.2 (5.9,6.9)**	6.2 (5.9,6.9)**	<0.001
[mmol/mol]	[41(38, 44)]	[44(41, 52)]	[44(41, 52)]	
HOMA-IR	1.10 (0.7,1.7)	1.30 (0.8,2.0)	1.00 (0.7,1.5)	0.3
Smokers, n (%)	47 (8)	18 (4) **	12 (6) **¶¶	<0.001

Data are mean ± SD or median (25^{th}-75^{th} percentile for skewed data) for numerical data and n (%) for categorical data. BMI, body mass index; HbA1c, glycosylated haemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; TC:HDL-C, total cholesterol: high density lipoprotein cholesterol ratio.

*p<0.05,**p<0.01 compared to Europeans; ¶ p<0.05, ¶¶ p<0.01 African Caribbeans, compared to South Asians by post-hoc test after ANOVA.

Table 2: Ethnic differences in arterial hemodynamics, stiffness and load

Measure	European	South Asian	African Caribbean	p ANCOVA
bSBP, mmHg	141.5±0.7	142.4±0.8	143.7±1.1	0.2
DBP, mmHg	84.7±0.4	82.8±0.5**	88.0±0.7**¶¶	<0.001
bPP, mmHg	56.8±0.5	59.6±0.6**	55.7±0.9¶¶	<0.001
MAP, mmHg	104.3±0.5	103.4±0.5	106.6±0.8**¶¶	0.004
HR, bpm	65.1±0.5	63.3±0.5*	62.6±0.8**	0.005
cSBP, mmHg	132.1±0.6	133.5±0.7	134.4±1.1	0.1
cPP, mmHg	46.6±0.5	58.0±0.6**	45.6±0.9¶¶	<0.001
AI_x, %	29.8±0.4	31.8±0.5**	29.7±0.7¶	<0.001
P_{Aug}, mmHg	14.5±0.3	16.5±0.3**	14.1±0.5¶¶	<0.001
PP_{Amp}, mmHg	10.2±0.2	9.6±0.2	10.1±0.3	0.1
SVR, MPa·s/m^3	226±3	244±3**	236±5¶	<0.001
cPP/SV, mmHg/ml	0.86±0.01	0.97±0.02**	0.80±0.02*¶¶	<0.001

E_a, mmHg/ml	2.29±0.03	2.48±0.03**	2.28±0.05¶	0.004
ln cfPWV, [geometric mean] m/s	2.40±0.01 [11.5]	2.39±0.01 [11.3]	2.36±0.02 [10.9]	0.3

Data are mean ± SE adjusted for age and sex. [brachial systolic (bSBP) and diastolic (DBP) blood pressure, brachial pulse pressure (bPP), mean arterial pressure (MAP), Heart rate (HR), central systolic BP (cSBP), central pulse pressure (cPP), augmentation index (AI_x), augmentation pressure (P_{aug}), central to brachial pulse pressure amplification (PP_{Amp}) ,Systemic vascular resistance (SVR), Arterial stiffness/elasticity coefficient,(cPP/SV), total arterial elastance (E_a), carotid to femoral pulse wave velocity (cfPWV). *p<0.05,**p<0.01 compared to Europeans; ¶ p<0.05, ¶¶ p<0.01 African Caribbeans, compared to South Asians by post-hoc test after ANOVA.

Table 3: Ethnic differences in arterial hemodynamics, stiffness and load after multivariable adjustment.

Measure	European	South Asian	African Caribbean	p ANCOVA
bSBP, mmHg	142.3±0.4	142.5±0.4	140.4±0.6**¶¶	0.02
DBP, mmHg	84.3±0.2	84.1±0.2	86.3±0.3**¶¶	<0.0001
bPP, mmHg	58.1±0.5	58.4±0.6	54.1±0.8**¶¶	0.0001
cSBP, mmHg	133.1±0.3	133.7±0.3	131.0±0.5**¶¶	<0.0001
cPP, mmHg	48.1±0.4	48.8±0.5	43.8±0.7**¶¶	<0.0001
AI_x, %	30.6±0.3	31.3±0.4	29.0±0.6*¶¶	0.004
P_{Aug}, mmHg	15.4±0.2	15.9±0.3	13.1±0.4**¶¶	<0.0001
PP_{Amp}, mmHg	10.0±0.2	9.6±0.2	10.3±0.3¶	0.1
SVR¥, MPa·s/m^3	228±3	244±3**	232±5	0.004
cPP/SV, mmHg/ml	0.88±0.01	0.95±0.02**	0.79±0.02**¶¶	<0.0001
E_a, mmHg/ml	2.29±0.03	2.47±0.03**	2.27±0.05¶¶	0.0006
Log_n cfPWV, [geometric mean] m/s	2.40±0.01 [11.6]	2.38±0.02 [11.3]	2.35±0.02 [11.0]	0.2

Data are mean ± SE adjusted for age, sex, height, waist hip ratio, mean arterial pressure, antihypertensive treatment, heart rate, total:high density lipoprotein cholesterol, diabetes, HOMA-IR ,diagnosed coronary heart disease and smoking. ¥

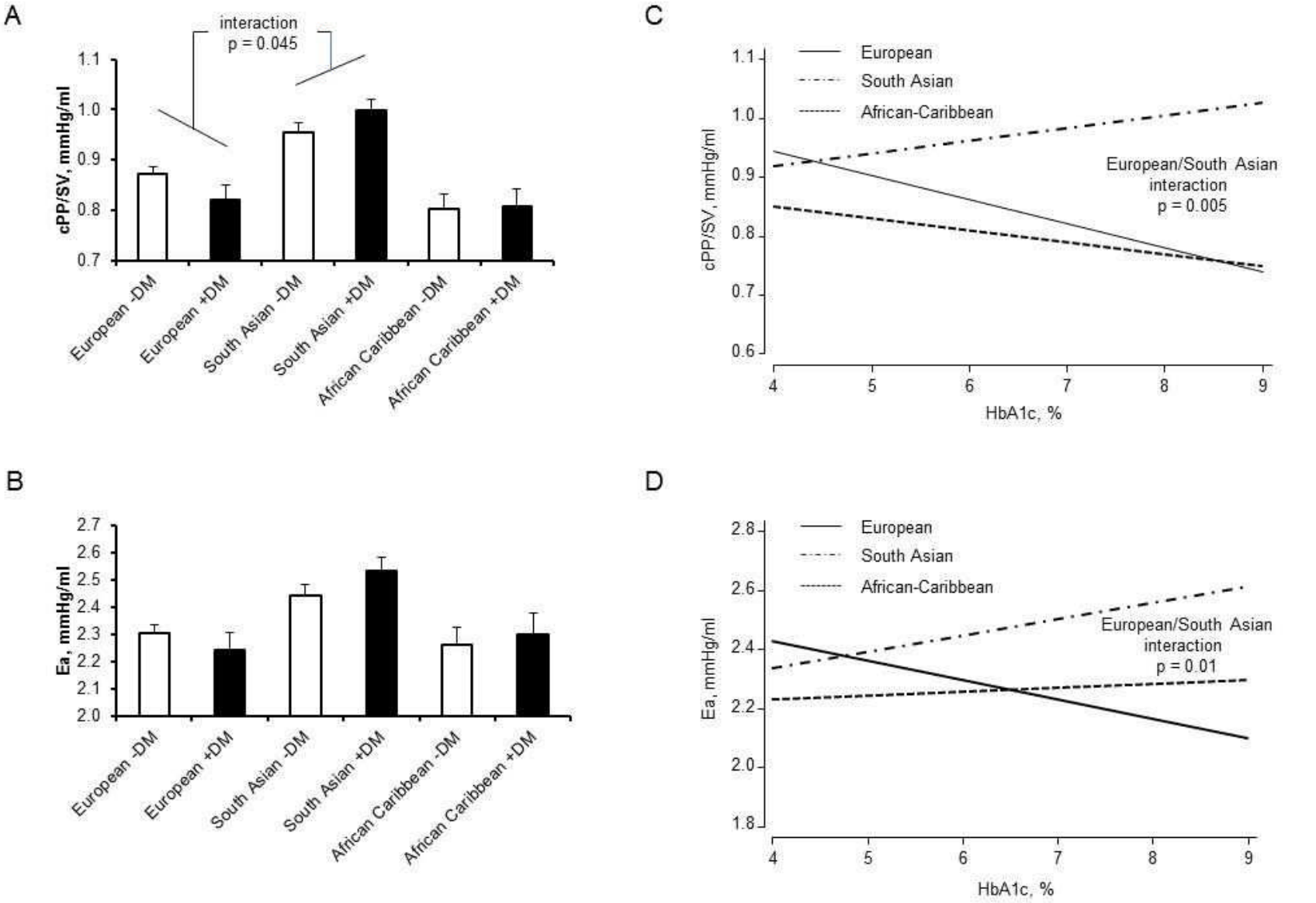
mean arterial pressure omitted from model. Abbreviations as in table 2.

*p<0.05,**p<0.01 compared to Europeans ; ¶ p<0.05, ¶¶ p<0.01 African Caribbeans, compared to South Asians by post-hoc test after multivariable regression.

Table 4: Symbolic summary table comparing cardiovascular risk parameters in South Asians and African Caribbeans to Europeans

	Age and sex adjusted		Fully adjusted	
	South Asian	African Caribbean	South Asian	African Caribbean
Diabetes	↑	↑	-	-
CHD	↑	↓	-	-
Stroke	↑	↑	-	-
Hypertension	↑	↑	-	-
bSBP/cSBP	↔	↑	↔	↓
DBP	↓	↑	↔	↑
MAP	↔	↑	-	-
bPP/cPP	↑	↓	↔	↓
AIx	↑	↔	↑	↓
P_{Aug}	↑	↔	↔	↓
PP_{Amp}	↔	↔	↔	↔
SVR	↑	↑	↑	↔
cPP/SV	↑	↓	↑	↓
E_a	↑	↔	↑	↔
cfPWV	↔	↔	↔	↔

Fully adjusted model: age, sex, height, waist hip ratio, mean arterial pressure, antihypertensive treatment, heart rate, total:high density lipoprotein cholesterol, diabetes, HOMA-IR, diagnosed coronary heart disease and smoking. Abbreviations as in table 2


A
interaction
p = 0.045
cPP/SV, mmHg/ml
1.1
1.0
0.9
0.8
0.7
European -DM
European +DM
South Asian -DM
South Asian +DM
African Caribbean -DM
African Caribbean +DM
B
Ea, mmHg/ml
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
European -DM
European +DM
South Asian -DM
South Asian +DM
African Caribbean -DM
African Caribbean +DM
C
European
South Asian
African-Caribbean
European/South Asian
interaction
p = 0.005
cPP/SV, mmHg/ml
1.1
1.0
0.9
0.8
0.7
0.6
4
5
6
7
8
9
HbA1c, %
D
European
South Asian
African-Caribbean
European/South Asian
interaction
p = 0.01
Ea, mmHg/ml
2.8
2.6
2.4
2.2
2.0
1.8
4
5
6
7
8
9
HbA1c, %