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ARTICLE

Indian Asians have poorer cardiovascular autonomic function than Europeans: this is due to greater hyperglycaemia and may contribute to their greater risk of heart disease

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Abstract
Aims/hypothesis A high prevalence of diabetes contributes to excess CHD in Indian Asians, but the underlying mechanisms are unclear. Heart rate, heart rate variability (HRV) and baroreflex sensitivity (BRS) are measures of cardiac autonomic function that are disturbed by hyperglycaemia and predict CHD. We compared these measures in Indian Asians and Europeans, and sought explanations for the observed differences.
Methods A representative sample of 149 Europeans and 151 Indian Asians was recruited from primary care, 66% of them men (aged 35–75 years), 34% women (aged 55–75 years). Heart rate, HRV, BRS and cardio-metabolic profiles were measured over four successive 5 min periods with continuous ECG and blood pressure monitoring.
Results Indian Asians were hyperglycaemic compared with Europeans (HbA_{1c} (mean ± SD) 6.5±1.2% vs 5.9±1.0%, p=0.001). They had shorter mean RR intervals ((mean ± SE) 969±13 vs 1,022±12 ms, p=0.002), lower total RR interval power ((geometric mean, 95% CI) 925 [796–1075] vs 1,224 [1,064–1,422] ms^2, p=0.008) and lower BRS ((mean ± SE) 5.7±1.0 vs 6.6±1.0 ms/mmHg, p=0.01). All measures of cardiac autonomic dysfunction were significantly associated with hyperglycaemia (mean RR interval vs HbA_{1c} r=−0.22; p<0.001). Ethnic differences in cardiac autonomic function persisted after adjustment for age, blood pressure and medication (mean RR interval 973 vs 1,021 ms, p=0.004), but were attenuated or abolished by adjusting for HbA_{1c} (979 vs 1,014 ms, p=0.06) or other markers of hyperglycaemia.
Conclusions/interpretation Indian Asians from the general population have impaired cardiovascular autonomic function compared with Europeans. This is due to greater hyperglycaemia in Indian Asians and may determine their increased CHD risk.

Keywords Asians · Autonomic function · Ethnicity · Glycated haemoglobin

Abbreviations

BRS	Baroreflex sensitivity
HF	High frequency
HRV	Heart rate variability
LF	Low-frequency
LOLIPOP	London Life Science Prospective Population Study
PWV	Pulse wave velocity

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Introduction

Indian Asians have one of the highest risks of CHD in the world [1, 2]. The increased prevalence of diabetes in Indian Asians compared with Europeans contributes to this excess risk [3], but does not fully account for it [2]. But while most risk factors, such as smoking, blood pressure and dyslipidaemia appear to have an equivalent impact on CHD in both ethnic groups, diabetes and, indeed, fasting glucose across the normoglycaemic range are stronger predictors of increased CHD mortality rates in Indian Asians [2]. In European men, for example, diabetes increased CHD mortality rates 1.5-fold, whereas the excess risk in Indian Asians was 2.8-fold. This suggests that as yet unmeasured risk factors associated with diabetes and/or hyperglycaemia may account for their greater impact on mortality rates in the Indian Asian population.

A likely candidate is cardiac autonomic function. Impaired cardiac autonomic function increases the risk of CHD and CHD death, an increase that is greater in the diabetic than in the non-diabetic population. Cardiac autonomic dysfunction is frequently observed in diabetes [4, 5]; moreover, dysfunction increases with hyperglycaemia in the non-diabetic population [6]. Impaired cardiac autonomic function has also been associated with measures of insulin resistance and central obesity, both key features of the metabolic syndrome [6–8].

Early attenuation of cardiac autonomic function can be assessed sensitively and non-invasively by heart rate variability (HRV) and baroreflex sensitivity (BRS) [9]. We therefore hypothesised that Indian Asians would have impaired cardiac autonomic function compared with Europeans and that this would be attributable to a greater degree of hyperglycaemia.

Methods

Study design The greater CHD risk in Indian Asians is observed at the general population level; explanations should also be sought at that level. Study of clinic populations, or studies excluding individuals on the basis of treatments or disease may result in a sample that is biased by ethnicity (as clinic attendance, disease and treatment vary markedly by ethnicity), making the findings uninterpretable. We therefore recruited from the London Life Science Prospective Population Study (LOLIPOP), a West London multi-ethnic, population-based study of more than 25,000 individuals investigating chronic disease and its determinants [10]. Men (aged 35–75 years) and women (aged 55–75 years) were recruited to LOLIPOP from 58 primary care lists. Primary care registration in the UK is free and the gateway to comprehensive healthcare, thus providing a highly accurate sampling frame. We recruited our study population of 300 people, aiming for equal numbers of Indian Asians (all Punjabi Sikh) and Europeans, and for the same distribution of men and women between the two ethnic groups, stratified by 5-year age bands. Participants were excluded if they had conditions that interfere with HRV assessment (e.g. atrial fibrillation), hormone replacement therapy or carotid artery stenosis, or were unable to provide informed consent. The study was approved by the local Ethics Committee and all participants gave written informed consent.

Study investigations All participants attended Imperial College NHS Healthcare Trust after an overnight fast having completed a questionnaire detailing demographic data, health behaviours and medical history. The presence of CHD, heart attack or angina, diabetes and hypertension were established on the basis of questionnaire self-report of a doctor's diagnosis. As these conditions had been tested for in LOLIPOP [10], including ECG, blood pressure and fasting blood glucose measurements, it is likely that much previously undiagnosed disease had already been detected, reducing the chance of inter-ethnic biases in detection rates. Ethnicity was confirmed with the participant, based on self-assessment and place of birth of all four grandparents. Height, weight, and waist and hip circumference were measured according to a standard protocol [11]. Sitting blood pressure was measured three times according to British Hypertension Society guidelines using a validated automated device (Omron 705CP, Henfield, UK) after 5 min rest [12]. The average of the final two readings was used in the analysis. Fasting blood tests were performed for serum glucose (hexokinase method; Roche, Basel, Switzerland), HbA_{1c} (non-enzymatic method; Toshoh, Tokyo, Japan), lipids (enzymatic colorimetric method; Roche) and insulin (by ultra-sensitive specific simultaneous ELISA assay using two high-affinity monoclonal antibodies; Roche, Indianapolis, IN, USA). Insulin assay cross-reactivity with proinsulin is <0.05%, with no detectable cross-reactivity with C-peptide. Fasting serum glucose and insulin were used to generate HOMA index values as a measure of insulin resistance [13]. Prevalence of the metabolic syndrome was estimated using the National Cholesterol Education Program criteria [14].

All investigations were carried out in the morning in a temperature-controlled room after a 30 min rest period. Autonomic function tests were performed according to a modified protocol used by us previously [15]. HRV and BRS were measured in the recumbent position for four successive 5 min periods with spontaneous breathing. Beat to beat arterial BP was recorded non-invasively using a Finometer (FMS, Amsterdam, the Netherlands) placed on the middle finger of the left hand, with the calibration

adjust mechanism switched off before recording. The ECG was monitored using an electrocardiograph (Hewlett Packard,Palo Alto, CA, USA) from lead II. These real-time signals were acquired from the analogue outputs of the respective devices and were A/D-converted at a sampling rate of 200 Hz using a custom-built data acquisition module and saved on a PC. Analysis was performed offline using software developed at the University of Leicester [16, 17]. The RR intervals were computed on a beat-by-beat basis, and interpolated with a third-order polynomial and re-sampled at intervals of 0.2 s to produce signals uniform in time. The systolic and diastolic blood pressures were defined as the greatest and lowest pressure occurring within the corresponding RR intervals. Each trace was inspected for abnormal heart rhythms that would preclude analysis. Recordings were undertaken in all participants, 19 of whom (eight European, 11 Indian Asian) were excluded from further analysis due to multiple ectopic beats preventing acquisition of an adequate ectopic-free record length ≥60 s.

Baroreflex sensitivity was calculated by beat-to-beat sequence analysis [18] in the time domain as well as using power spectral analysis [15].The time series of RR interval and systolic BP were scanned automatically to identify the sequences in which RR interval and systolic BP increased or decreased concurrently over three beats [18]. The minimum rate of change required was 0.5 mmHg/s. The linear correlation between RR interval and systolic BP was computed for each sequence. The regression slope was calculated in sequences with correlation coefficients of >0.8. The average value of the individual slopes occurring within the 5 min episode was taken as the BRS (sequence analysis). The results obtained from rises in systolic BP were combined with those from falls in systolic BP. Power spectral analysis of the RR interval and systolic BP was performed with the Welch method (via fast Fourier transform), using 40% superposition of at least four data segments with 512 samples each (102.4 s). The following indices were calculated for HRV: (1) mean RR interval; (2) mean spectral powers in the low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF) (0.15–0.4 Hz) bands for the RR intervals. The LF and HF RR powers were also expressed in normalised units (nu) calculated by dividing the corresponding LF or HF RR power by the total power above 0.03 Hz [19]. Frequency domain BRS was calculated as the alpha index (LF only) given by the square root of the ratio between averaged LF powers of RR and systolic BP [15, 20].

Central blood pressure was calculated from applanation tonometry at the radial artery [21]. Pulse transit time was measured between the carotid and femoral sites using an ECG-gated ultrasound 'foot-to-foot' method (Pulse Trace PT 2000; Micromedical, Basingstoke, UK), and transit distance was defined as the distance travelled by the pulse wave between the sites of recording [22]. Pulse wave velocity (PWV) was calculated as the distance travelled by the pulse wave divided by the transit time.

The mean RR interval was taken as the key outcome variable and reproducibility studies were performed over two sessions 48 h apart. Four recordings were taken at each session and the average of the four was taken as the session mean. The mean difference was 125.4 ms (limits of reproducibility were 0.49 and 876.5 ms) between visits. The coefficient of variation was 11%, within the limits reported in a recent review [23]; the Bland–Altman reproducibility coefficient was 27.8 [24].

Statistical analysis and sample size We have previously detected a standardised difference of 0.49 in some of the above measures [25]. Thus we calculated that with 150 individuals in each ethnic group, at 5% significance, a standardised difference of at least 0.35 in any given HRV or BRS variable between ethnic groups could be detected with 80% power and a difference of 0.40 with 90% power, allowing for a degree of data incompleteness. Statistical analysis was done using Stata (StataCorp LP, College Station, TX, USA) version 9.1. Baseline data are presented as means ± SD or medians (interquartile range) for skewed data. Skewed data were log-transformed prior to analysis. Adjusted means are presented as means ± SE or geometric means for skewed data and 95% CI. Continuous variables were compared by the Student's *t* test and adjusted analysis for key confounders performed using multivariate regression analysis. Multivariate modelling was performed in those who had complete data on confounders. Categorical variables were compared using the χ^2 test. A p value of $p<0.05$ was taken as statistically significant.

Results

We recruited 149 Europeans and 151 Indian Asians, with a response rate of 48%, which did not differ by ethnicity. Comparison of key characteristics between our sample and no or non-responders revealed no significant differences between the two. Participants in our study were on average 0.8 years older ($p=0.1$) and had a systolic pressure that was 2 mmHg lower ($p=0.2$) than that of no or non-responders. Mean fasting glucose and HbA_{1c} were identical and trends by ethnicity were similar in responders and non-responders. The only difference noted was that non-responding Indian Asians were on average 1.5 years older than responders, while European non-responders were 3 years younger.

In our sample, mean age did not differ between the two ethnic groups and around two-thirds of the sample were men (Table 1). As expected, diabetes was more common in

Table 1 Cardiovascular risk factors by ethnic group

Variable	Europeans	Indian Asians	*p* value
n	149	151	
Male, % (*n*)	66 (98)	68 (102)	0.7
Age (years)	62.6±6.6	62.1±6.4	0.5
Systolic BP (mmHg)	140±18	144±17	0.2
Diastolic BP (mmHg)	82±10	82±8	0.4
MAP (mmHg)	102±12	102±10	0.8
Pulse pressure (mmHg)	60±12	63±14	0.03
Central systolic BP (mmHg)	134±18	135±16	0.6
Heart rate (beats per min)	60±9	63±10	0.005
Weight (kg)	80.6±17.4	74.1±13	<0.001
Height (cm)	170.0±9.5	165.7±9.4	<0.001
BMI (kg/m^2)	27.8±5.3	27.0±4.4	0.1
WHR	0.93±0.10	0.97±0.10	0.001
Cholesterol (mmol/l)	5.52 (4.75, 6.16)	5.21 (4.44, 5.86)	0.005
Triacylglycerol (mmol/l)	1.32 (0.98, 1.87)	1.48 (1.04, 2.04)	0.1
Total chol/HDL ratio	4.15±1.09	4.05±0.90	0.4
Fasting glucose (mmol/l)	5.0 (4.6, 5.4)	5.1 (4.6, 5.9)	0.02
HbA_{1c} (%)	5.9±1.0	6.5±1.2	0.001
Fasting insulin (pmol/l)	37.5 (25.7, 62.5)	52.8 (34.0, 83.3)	0.004
HOMA-IR	1.19 (0.8, 2.2)	1.85 (1.0, 3.0)	0.003
Diabetes, % (*n*)	7.4 (11)	27.2 (41)	<0.001
Hypertension, % (*n*)	34.9 (52)	57.0 (86)	<0.001
Coronary heart disease, % (*n*)	10.7 (16)	9.3 (14)	0.7
PWV (m/s)	9.05	9.38	0.09
Metabolic syndrome, % (*n*)	37.6 (56)	43.7 (66)	0.3
Anti hypertensive medication, % (*n*)	24.8 (37)	39.0 (59)	0.008
Beta blockers, % (*n*)	3.4 (5)	8.0 (12)	0.09
Calcium channel blockers, % (*n*)	9.4 (14)	14.6 (22)	0.2
Diuretics, % (*n*)	8.1 (12)	8.6 (13)	0.9
ACE inhibitors, % (*n*)	10.7 (16)	13.9 (21)	0.4
ARB, % (*n*)	4.7 (7)	14.6 (22)	0.004
Ever smoked, % (*n*)	62 (90)	5 (7)	<0.001

Unless otherwise indicated, data are means ± SD or, if not normally distributed, median (25th centile, 75th centile)

ARB, angiotensin receptor blockers; Chol, cholesterol; HOMA-IR, HOMA of insulin resistance; MAP, mean arterial pressure

Indian Asians, and other indicators of hyperglycaemia and insulin resistance were more adverse. Although mean blood pressure was equivalent in the two ethnic groups, the proportion of participants on anti-hypertensive medication was greater in Indian Asians, possibly due to their higher prevalence of diabetes, where anti-hypertensive medication is prescribed at lower levels of blood pressure than in the general population.

Mean RR interval was significantly lower in Indian Asians than in Europeans (969.1±12.3 vs 1,022.3±12.2 ms [mean ± SE], p=0.002; Table 2). Absolute measures of HRV, i.e. total LF and HF power, were also significantly reduced in Indian Asians; however, the LF/HF ratio did not differ by ethnicity. When HRV was expressed in normalised units (i.e. essentially taking account of ethnic differences in total power), ethnic differences were no longer statistically significant. BRS, whether measured by power spectral or sequence analysis, was also significantly lower in Indian Asians.

Participants with diabetes had: (1) lower mean RR interval than those without (938 [95% CI 897–979] ms versus 1,009 [989–1,027], respectively, p=0.003); (2) lower LF RR interval power (215 [161–284] ms^2 versus 311 [273–354], respectively, p=0.02); and (3) lower BRS on sequence analysis (4.76 [4.14–5.47] ms/mmHg versus 6.49 [6.05–6.96], respectively, p<0.0001). Markers of hyperglycaemia, such as fasting glucose, HbA_{1c}, insulin and HOMA of insulin resistance showed a consistent negative correlation with measures of HRV and BRS (Table 3). This relationship persisted after excluding participants with diabetes (HbA_{1c} correlation coefficient −0.20, p=0.002 for mean RR interval, −0.115, p=0.056 for LF RR interval power and −0.150, p=0.02 for BRS on sequence analysis). Mean RR interval, LF RR interval

Table 2 RR interval, HRV and BRS by ethnic group

Key variable	Europeans	Indian Asians	*p* value
Participants (*n*)	141	140	
Mean RR interval (ms)	1,022±12.2	969±12.3	0.002
Total RR interval power (ms^2)	1,224 (1,064–1,422)	925 (796–1,075)	0.008
LF RR interval power (ms^2)	354 (299–416)	240 (202–281)	0.001
HF RR interval power (ms^2)	213 (176–255)	156 (129–189)	0.02
LF/HF power ratio	1.66 (1.47–1.88)	1.53 (1.36–1.73)	0.4
LF RR interval power (nu)	43 (41–47)	41 (39–44)	0.1
HF RR interval power (nu)	26 (24–29)	27 (25–29)	0.7
LF alpha index (ms/mmHg)	7.12 (6.69–7.77)	6.11 (5.64–6.62)	0.004
BRS on sequence analysis (ms/mmHg)	6.62 (6.11–7.24)	5.70 (5.21–6.17)	0.01

Unless otherwise indicated, data are age-and sex-adjusted means ± SE or, if variable log-transformed, geometric mean (95% CI)

HF, HF powers of RR interval; LF, LF powers of RR interval; LF/HF, ratio of LF/HF powers of RR interval; nu, normalised units

power and BRS on sequence analysis fell by increasing category of HbA_{1c} in both ethnic groups (Fig. 1). Although autonomic function remained poorer in Indian Asians than in Europeans in each category of HbA_{1c}, the ethnic difference, and thus statistical significance, was attenuated; i.e. for mean RR interval, the *p* value changed from $p=0.002$ in the unstratified analysis (Table 2) to $p=0.06$ (Fig. 1a); for LF RR interval power the *p* value changed from 0.001 to 0.02 (Fig. 1b), and for BRS it changed from 0.01 to 0.1 (Fig. 1c).

Blood pressure was also negatively associated with HRV and BRS, while lipids and obesity as measured by BMI were negatively associated with mean RR interval and BRS.

Beta blocker use was associated with a higher mean RR interval ((mean ± SE) 1,094±149.3 vs 990±126.3 ms, $p=0.009$). Exclusion of all participants on vasoactive medications did not alter the direction or significance of the ethnic difference in mean RR interval (Europeans 1,032±12.7 vs Indian Asians 990±13.9 ms, $p=0.02$) or LF RR interval powers (Europeans 380 [321–450] ms^2 vs Indian Asians 281 [230–340], $p=0.02$), and attenuated, but did not abolish the ethnic difference in BRS (Europeans 6.82 [6.23–7.46] ms/mmHg vs Indian Asians 6.23 [5.64–6.89] $p=0.2$).

Never-smokers had lower mean RR interval (970±145.2 ms) than ever-smokers (1,044±147.9 ms, $p<0.001$). In an analysis adjusting for smoking habit, Europeans still had higher mean RR intervals than Indian Asians (Europeans 1019±12.5 vs Indian Asians 970±12.7 ms; $p=0.007$).

Indian Asians had higher PWV, although this was of borderline statistical significance. Mean RR interval and BRS were significantly inversely correlated with PWV (correlation coefficient for mean RR interval −0.322, $p<0.001$ and for BRS −0.231, $p<0.001$) and central systolic blood pressure (correlation coefficient for mean RR interval −0.187, $p<0.002$ and for BRS −0.229, $p<0.001$).

Multivariate regression modelling was used to explore explanations for the significantly adverse cardiac autonomic function in Indian Asians (Table 4). Models incorporating

Table 3 Pearson's correlation coefficients (*r*) relating CVD risk factors to mean RR interval, HRV and BRS

Risk factor	Mean RR interval		LF RR interval powers		BRS sequence	
	r	*p* value	*r*	*p* value	*r*	*p* value
Age	−0.043	0.5	−0.227	<0.001	−0.226	<0.001
Systolic BP	−0.314	<0.001	−0.144	0.02	−0.305	<0.001
Central systolic BP	−0.187	0.002	−0.117	0.05	−0.229	<0.001
Weight	−0.025	0.7	0.180	0.002	−0.049	0.413
Height	0.195	0.001	0.168	0.005	0.106	0.08
BMI	−0.149	0.01	0.10	0.102	−0.118	0.05
WHR	−0.052	0.4	0.022	0.7	−0.095	0.1
Glucose	−0.227	<0.001	−0.021	0.7	−0.194	0.001
HbA_{1c}	−0.220	<0.001	−0.115	0.05	−0.206	<0.001
Insulin	−0.253	<0.001	0.054	0.4	−0.181	0.003
HOMA-IR	−0.043	0.5	0.056	0.4	−0.226	<0.001
Cholesterol	−0.314	<0.001	0.090	0.13	−0.305	<0.001
HDL	−0.187	0.002	−0.069	0.2	−0.229	<0.001
Triacylglycerol	−0.025	0.7	0.093	0.1	−0.049	0.413

HOMA-IR, HOMA of insulin resistance

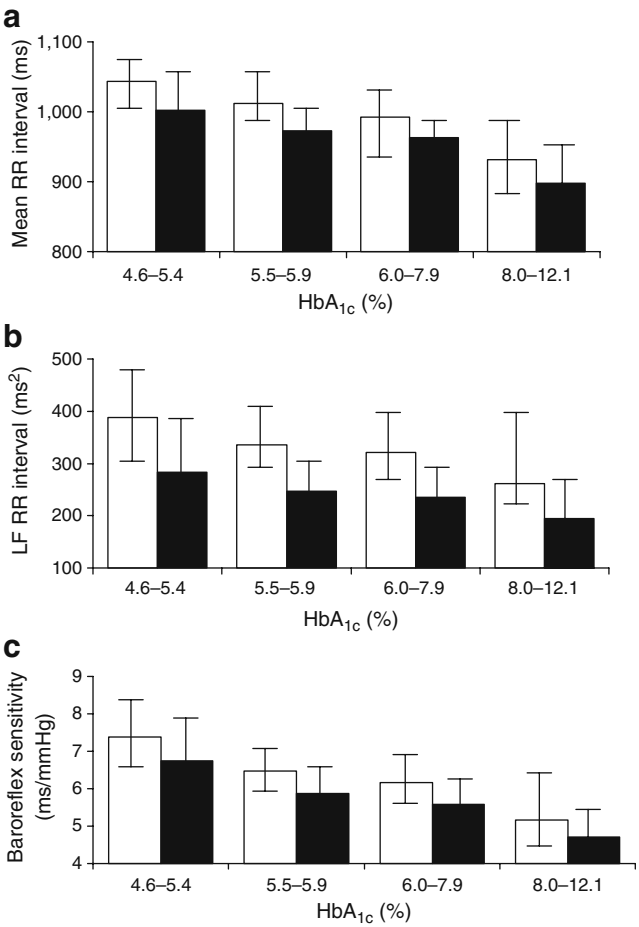

Fig. 1 RR interval (**a**), HRV (**b**) and BRS (**c**) by category of HbA_{1c} stratified by ethnicity. Values are mean and 95% CI, adjusted for age and sex. *p* values for ethnicity: (**a**) $p=0.06$; (**b**) $p=0.02$; (**c**) $p=0.1$. White bars, European; black bars, Indian Asian

age, sex and other explanatory variables were built to see which additional explanatory variable(s) best attenuated the ethnic difference in autonomic function. Measures of hyperglycaemia had the greatest ability to attenuate ethnic differences in cardiac autonomic function. After inclusion of HbA_{1c} in the multivariate model, the ethnic difference in mean RR interval and BRS, although still lower in Indian Asians, was no longer statistically significant. This adjusted analysis confirms the stratified analysis in Fig. 1, i.e. that it is hyperglycaemia that accounts for the adverse cardiac autonomic function in Indian Asians. Further addition of insulin to this tri-variate model had no additional impact on accounting for the ethnic difference in autonomic function. Measures of hyperglycaemia explained more of the difference between the two ethnic groups than adjustment for diabetes, metabolic syndrome or PWV (used as a surrogate marker of cardiovascular disease). Other variables, including blood pressure, lipids and body size measures, had little impact on accounting for the ethnic difference.

Discussion

Adult Indian Asians have poorer cardiac autonomic function, as assessed by heart rate, HRV and BRS, than Europeans. The ethnic difference in cardiac autonomic function was largely accounted for by the greater chronic hyperglycaemia in Indian Asians and was not explained to any great extent by other conventional risk factors. Attenuated cardiac autonomic function, as measured even crudely by resting heart rate, predicts future CHD events and may therefore contribute to the greater CHD risk in Indian Asians [26].

Previous studies of largely European-origin populations have shown that people with diabetes, impaired fasting glucose or elevated HbA_{1c} have reduced HRV [8, 27] and that hyperglycaemia is also associated with reduced BRS [28]. Further, we confirm here that ethnic differences in HRV, explainable by hyperglycaemia, were confined to absolute measures and that once differences in total power were taken into account, when quoting normalised units, no ethnic differences were observed, suggesting a differential effect of hyperglycaemia on absolute versus oscillatory effects [20]. Whether the association between hyperglycaemia and autonomic function is direct or due to other features of insulin resistance is unclear, as previous reports of independent associations with measures of insulin resistance, fat distribution and lipids are inconsistent, perhaps reflecting differences in study populations and differences in methods used both to measure autonomic function and insulin resistance, the latter being hard to measure with accuracy when compared with hyperglycaemia [6–8, 29]. We examined whether inclusion of fasting insulin in addition to HbA_{1c} in multivariate models further attenuated ethnic differences, but found no additional effect. This analysis would suggest that it is chronic hyperglycaemia, rather than the insulin-resistant or hyperlipidaemic aspects of the metabolic syndrome that attenuates autonomic function in Indian Asians. Acute glucose infusion rapidly alters cardiac autonomic function (measured by the QTc on ECG) [30]; in the chronic situation, accumulation of advanced glycation end-products is associated with poorer HRV [31]. In addition, chronic intensive glycaemic control improves cardiac autonomic function [32].

The mechanism by which elevated glucose across the glycaemic spectrum may cause autonomic dysfunction is unclear. Increased generation of reactive oxygen species may underpin the toxic effects of hyperglycaemia [33], given that the former alter cellular signalling and reduce bioavailability of nitric oxide [30, 34, 35]. Indeed, hyperglycaemia and autonomic dysfunction may both share a common antecedent, such as chronic inflammation [36], rather than being directly causally related.

Table 4 Multivariate models accounting for ethnic differences in RR interval, HRV and BRS

Models[d]	Mean RR interval (ms)[a]			Low frequency RR interval powers (ms^2)[b]			BRS (ms/mmHg)[c]		
	Europeans	Indian Asians	*p* value	Europeans	Indian Asians	*p* value	Europeans	Indian Asians	*p* value
No others	1,025 (1,000–1,049)	969 (944–993)	0.002	287 (255–324)	290 (257–327)	0.002	6.70 (6.14–7.30)	5.73 (5.25–6.25)	0.01
Systolic BP [e]	1,021 (998–1,044)	973 (949–996)	0.004	287 (255–324)	290 (257–327)	0.003	6.63 (6.10–7.21)	5.79 (5.32–6.30)	0.03
Glucose	1,021 (997–1,044)	973 (949–997)	0.006	287 (255–324)	290 (257–327)	0.004	6.60 (6.06–7.18)	5.82 (5.35–6.34)	0.04
HbA_{1c}	1,014 (989–1,038)	979 (954–1,004)	0.06	287 (255–321)	290 (257–327)	0.03	6.44 (5.89–7.04)	5.93 (5.42–6.48)	0.2
HOMA	1,016 (993–1,039)	978 (954–1,001)	0.03	287 (255–324)	290 (257–327)	0.003	6.53 (6.00–7.10)	5.88 (5.40–6.40)	0.09
Insulin	1,017 (994–1,041)	976 (953–1,000)	0.02	287 (255–324)	290 (257–327)	0.002	6.56 (6.02–7.14)	5.86 (5.38–7.14)	0.07
Diabetes	1,019 (995–1,044)	974 (950–999)	0.01	287 (255–324)	290 (257–327)	0.01	6.53 (5.99–7.12)	5.88 (5.39–6.42)	0.1
Cholesterol	1,023 (999–1,047)	968 (944–993)	0.002	287 (255–324)	290 (257–327)	0.02	6.62 (6.11–7.24)	5.70 (5.21–6.23)	0.02
Triacylglycerol	1,022 (999–1,046)	971 (947–995)	0.003	287 (255–324)	290 (257–327)	0.002	6.67 (6.12–7.27)	5.76 (5.28–6.28)	0.02
BMI	1,027 (1,002–1,051)	967 (943–991)	0.001	287 (255–324)	290 (257–327)	0.002	6.74 (6.18–7.34)	5.70 (5.22–6.21)	0.007
Metabolic syndrome	1,022 (999–1,046)	971 (948–995)	0.003	287 (255–324)	290 (257–327)	0.003	6.66 (6.12–7.25)	5.76 (5.29–6.27)	0.02
PWV	1,014 (991–1,037)	975 (952–997)	0.02	344 (290–403)	290 (257–327)	0.004	6.53 (6.00–7.12)	5.76 (5.29–6.27)	0.04

Values are mean (95% CI)

[a] n=275; [b] n=275; [c] n=270

[d] All adjusted for age and sex, plus other factors as stated

[e] Also adjusted for antihypertensive medication

While RR interval and HRV correlated inversely with PWV, an indicator of coronary atherosclerosis that predicts future CVD [37], inclusion of PWV in a multivariate model did not significantly attenuate ethnic differences in RR interval, HRV or BRS, suggesting that differences in levels of atherosclerosis probably do not account for ethnic differences in cardiac autonomic function.

Our finding of a reduction in BRS, as well as the reduction seen in the HF powers of mean RR interval and baroreflex powers, probably indicates a reduction in the vagal contribution to the autonomic nervous system in Indian Asians [38]. This is supported by the observation that the vagal limb is the first to be affected by diabetes [39], although increases in sympathetic activity also contribute[19].

Sympathetic overactivity and insulin resistance, and therefore the consequences of insulin resistance including hyperglycaemia, are clearly linked, but the causal direction of that association is uncertain, since insulin may act on the central nervous system to increase sympathetic outflow; alternatively, an increase in sympathetic activity could itself result in insulin resistance [40]. Our cross-sectional study cannot determine the direction of causality, as abnormalities in cardiovascular risk factors and autonomic function will, of necessity, be established in this older age group. However, it is interesting to note that hyperglycaemia and elevated heart rate are already present in children of Indian Asian origin in the UK [41].

This study has other limitations. Clearly, as a cross-sectional study, we cannot prove causality, only indicate that a causal relationship may exist, to be tested in longitudinal studies. As a population-based study, our findings are likely to be generalisable, but their interpretation is complicated by medication use and the existence of subclinical disease. However, exclusion of individuals on the basis of medication and subclinical disease would have resulted in a large number of losses in this age group and would have led to bias by ethnicity, making the study sample into a super-healthy, un-representative sample of the general population, in whom disease risks and risk factor associations would be difficult to detect. However, it is important to note that our findings were independent of medication use and smoking status, and were observable even when participants with diabetes were excluded. Subclinical or silent CHD is associated with abnormal autonomic function, although this may be confined to people with established diabetes [42]. We could only account for doctor-diagnosed CHD; however, all participants had already undergone identical tests in LOLIPOP, including ECG, thus any biases by ethnicity are diminished. Our results also show that PWV, a marker of subclinical atherosclerosis, did not impact on the ethnic difference in cardiac autonomic function. The use of 5 min as opposed to 24 h recordings may also be a limitation, although short- and long-term measures of HRV have been reported to show reasonable agreement [43] and both are predictive of mortality following myocardial infarction [44].

We have shown that, compared with Europeans, Indian Asians have adverse cardiac autonomic function, as demonstrated by lower mean RR intervals, and attenuated HRV and BRS. These differences are largely accounted for by the greater hyperglycaemia in Indian Asians. Impaired cardiac autonomic function may be a strong candidate to explain the greater risk of CHD and also the greater impact of hyperglycaemia on CHD in Indian Asians compared with Europeans. As autonomic function improves on correction of hyperglycaemia, even in the non-diabetic state [45], this represents an important interventional target when attempting to reduce the burden of cardiometabolic disease in Indian Asians.

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