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Predictors of diastolic dysfunction in ethnic groups: Observations from the Hypertensive Cohort of The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES)

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Abstract

The study aimed to establish a relationship of ethnicity to diastolic dysfunction in subjects of African-Caribbean and South Asian origins and the impact of diastolic dysfunction and ethnicity on all-cause and cardiovascular mortality.

Hypertensive subjects with ejection fraction ≥55% and no history of ischemic heart disease/valve pathology (n=1546, 830 South Asians and 716 African-Caribbeans) were identified from the Ethnic - Echocardiographic Heart of England Screening Study (E-ECHOES). Diastolic function and cardiac remodelling were measured by echocardiography.

African-Caribbean ethnicity was associated with lower prevalence of having diastolic dysfunction (odds ratio 0.67, 95% confidence interval 0.51-0.87, p=0.003) and increased left ventricular filling pressure (odds ratio 0.48, 95% confidence interval 0.34-0.69, p<0.001) as well as lower left atrial index (p<0.001). This was the case despite the fact that African-Caribbean ethnicity was independently associated with higher left ventricular mass index (p<0.001). Ninety-two deaths (6%) occurred during 68±21 months follow up. On Cox regression analysis, South Asian ethnicity (p=0.024) was predictive of all-cause death before adjustment for parameters of diastolic dysfunction, but it was no longer predictive of death after accounting for these variables.

South Asian ethnicity is independently associated with worse parameters of diastolic function in hypertension, despite African-Caribbeans having more prominent hypertrophy.

Keywords

hypertension; diastolic dysfunction; ethnicity; South Asian; African-Caribbean

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Introduction

Hypertension is a major cause of heart failure with preserved ejection fraction (HFpEF), which is commonly associated with poor quality of life and poor outcomes.(1, 2) Diastolic dysfunction and increased myocardial stiffness are recognised pathogenic factors contributing to the development of HFpEF in hypertension.(3, 4)

There are significant ethnic differences in prevalence and outcome of hypertension, with overall cardiovascular morbidity and mortality being substantially higher in South Asian and African-Caribbean ethnic groups than in the white population. Adults of African-Caribbean origin have higher blood pressure and are more prone to develop hypertension than white subjects, with more controversial data regarding people of South Asian origin.(5–7) Whilst the impact of different factors on the development of diastolic dysfunction has been extensively studied in white subjects, limited information is available on the occurrence of diastolic dysfunction in hypertensive patients of African-Caribbean and South Asian origin, and the factors associated with progression to diastolic dysfunction in these ethnic groups.

The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES) was a cross-sectional community-based survey of subjects of South Asian origin (i.e. from India, Pakistan or Bangladesh) and African-Caribbean origin aged ≥45 years. The two ethnic groups were recruited in parallel. All individuals living in the recruitment area and belonging to these ethnic groups were included if they were agreeable to participate in the study. The study individuals were recruited from September 2006 to August 2009 from 20 primary care centres in Birmingham, United Kingdom and the collected data included comprehensive clinical assessment and echocardiography.(8) The present ancillary E-ECHOES analysis assesses the prevalence of diastolic dysfunction and factors predicting its occurrence in a well-characterized population of adult African-Caribbean and South Asian hypertensive subjects. The study also evaluates the impact of diastolic dysfunction and ethnicity on all-cause and cardiovascular mortality.

Methods

We included participants of the E-ECHOES study who had a history of hypertension with normal left ventricular (LV) systolic function (i.e., LV ejection fraction ≥55% by echocardiography) and no history of ischemic heart disease (i.e., no angina, previous coronary revascularization or myocardial infarction or use of nitrates) (Figure 1). Other exclusion criteria were abnormalities of cardiac valves (i.e., stenosis or more than mild regurgitation of any valve or previous valve surgery), history of peripheral artery disease, cancer, chronic obstructive pulmonary disease, atrial fibrillation, current treatment with digoxin, warfarin, ADP (adenosine diphosphate receptor) antagonists or antiarrhythmic agents (except beta-blockers or calcium antagonists). The E-ECHOES database has 5353 entries including 2675 patients with hypertension. A total of 1546 subjects were analysed, after all exclusion criteria were applied.

The E-ECHOES study was approved by Walsall Local Research Ethics Committee (05/Q2708/45) with all participants provided written informed consent for data collection and

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analysis. Following patient recruitment data on outcomes (i.e. mortality) have been collected prospectively. This is provided by the Health and Social Care Information Centre (www.hscic.gov.uk).

Echocardiography

All study participants underwent detailed echocardiographic analysis with images reviewed by a consultant cardiologist with expertise in echocardiography. Echocardiography was done in primary care settings using a portable VIVID i machine (GE Healthcare, Chalfont St Giles, UK). LV ejection fraction, dimensions of the cardiac chambers, LV mass index and parameters of the diastolic function (mitral valve E/A ratio; E wave deceleration time; tissue Doppler imaging of lateral and septal mitral valve annulus to quantify average septal-lateral E/e' ratio) were also measured following current recommendations.(9)

Presence of diastolic dysfunction was determined based on E/A ratio and average septal-lateral E/e' as main criteria and additional criteria of abnormal deceleration time (<130 msec or >230 msec), reduced e' velocity (e' septal <8 cm/sec or e' lateral <10 cm/sec) and increased LA diameter (>4.0 cm in men and >3.8 cm in women). Diastolic dysfunction was defined as (i) E/A <1 (in patients older 60 years only in presence of ≥1 additional factor); (ii) E/A ≥1, E/e' 8-13 and ≥1 additional factor, or (iii) E/A ≥1 and E/e' ≥13. The coding was done by an independent colleague who was not involved in any analyses or writing of the manuscript (MD, please see acknowledgement). Increased LV filling pressure was defined based on average septal-lateral E/e' ≥13).(10) To assess the separate components of diastolic function, average septal-lateral e' velocity (as a measure of active relaxation) and the ratio of E/e' ratio : LV diastolic volume index (as an index of passive diastolic stiffness) were calculated. LV hypertrophy was defined as LV mass index >95 g/m2 in women and 115 g/m2 in men (concentric hypertrophy if relative wall thickness was ≤0.42 and eccentric hypertrophy if relative wall thickness >0.42). Concentric remodelling was defined as a normal LV mass index with relative wall thickness >0.42.(9) Echocardiographic measurements and measurements of blood pressure and heart rate were performed in triplicates and their averages were used for the analysis.

Statistical analysis

Data were tested for normality graphically by histogram plotting and using Kolmogorov-Smirnov test. Normal data are presented as mean ± standard deviation and compared using independent sample T-test. Regression analysis was used to establish predictors of parameters of diastolic dysfunction with the following predictor variables tested: age, gender, ethnicity, history of diabetes and smoking, systolic and diastolic blood pressure, heart rate, body mass index, waist circumference, use of angiotensin enzyme inhibitors or angiotensin receptor antagonists, aldosterone antagonists, beta-blockers, calcium channel blockers, diuretics, aspirin, statins, LV mass index (NB. the last parameter was not used in analyses of predictors of the LV mass index itself). Linear regression was used to establish predictors of continues variables and logistic regression was used to identify predictors of diastolic dysfunction and increased LV filling pressure). To further assess a possibility that observed higher LV stiffness in South Asian individuals may be related to higher prevalence of diabetes a sensitivity analysis was performed excluding people with a history of diabetes.

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Stepwise Cox regression analysis was used to establish predictors of all-cause and cardiovascular mortality in the study population. LA diameter index quartiles were coded as quartile 1 (i.e., less 1.51 cm/m^2), quartile 2 (i.e., from 1.51 to less 1.69 cm/m^2), quartile 3 (i.e., from 1.69 to less 1.88 cm/m^2), and quartile 4 (i.e., 1.88 cm/m^2 or more) with dummy variables used to assess contrasts. Proportional hazards assumption for Cox models was graphically checked by plotting partial residuals against time for continues variables and using log minus log plots for categorical variables. P-values of <0.05 were considered as statistically significant. IBM SPSS Statistics 21 (IBM Inc, USA) software was used for statistical analyses. Figure 2 was prepared using STATA 13, marginsplot command package (StataCorp, USA). The figure presents adjusted linear regression lines with standard errors for individual age categories. The adjustment was made for the same parameters as described for the multivariable linear regression analysis above.

Results

A total of 1546 subjects were included (830 of South Asian origin and 716 of African-Caribbean origin). Among the 830 South Asian patients 772 (93%) were born in India, Pakistan or Bangladesh, only 6 (0.7%) patients were born in the UK and 3 in other parts of Europe, with the rest 49 (6%) patients born in other parts of the world (mostly from countries of East Africa). The mean age of coming to the UK was 26±13 years and the mean duration since coming to the UK was 36±12 years. Among the 716 participants of African-Caribbean origin 621 (87%) were born on the Caribbean islands (majority – 547 (76%) in Jamaica), 70 (9.8%) in the UK and 25 (3.5%) in other countries. The mean age of coming to the UK was 24±11 years and the mean duration since coming to the UK was 43±13 years.

Compared to participants of South Asian origin, African-Caribbeans were older (p<0.001), had a higher body mass index (p<0.001), and higher systolic blood pressure (p=0.002), but smaller waist circumference (p<0.001), lower heart rate (p<0.001) (Table 1). There were no statistical differences in gender, LV ejection fraction, diastolic blood pressure and history of smoking.

South Asian patients had higher rates of diabetes (47% vs. 35%, p<0.001) and more frequently received angiotensin converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonists and statins, but less often amlodipine, diuretics and alpha-blockers. There was no significant difference in utilisation of aspirin or beta-blockers between the two ethnic groups.

Diastolic dysfunction

Overall 73% of South Asian subjects and 72% of African-Caribbean participants had diastolic dysfunction (p=0.74). On logistic regression analysis, independent predictors of diastolic dysfunction were more advanced age, female gender, South Asian ethnicity, higher LV mass index, diastolic blood pressure, heart rate, waist circumference and use aldosterone antagonists (Table 2).

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Increased left ventricular filing pressure

Increased LV filling pressure was found in 14% of South Asian patients and 11% of African-Caribbean patients (p=0.09). On logistic regression analysis, independent predictors of increased LV filling pressure were advanced age, female gender, South Asian ethnicity, higher LV mass index and systolic blood pressure (p<0.001 for all).

e' velocity

On linear regression analysis, independent predictors of lower e' velocity were advanced age, female gender, history of diabetes, higher LV mass index and lower waist circumference and diastolic blood pressure (p<0.001), but not the ethnicity (Table 3, Figure 2).

Ratio of E/e' ratio: LV diastolic volume index

On linear regression analysis, independent predictors of higher ratio of E/e' ratio: LV diastolic volume index were advanced age, female gender, higher LV mass index, systolic blood pressure, South Asian ethnicity (p<0.001 for all), history of diabetes (p=0.01) and smoking (p=0.027), higher body mass index (p=0.004) and heart rate (p=0.024). South Asian ethnicity remained independently associated with higher LV stiffness in a sensitivity analysis excluding individuals with history of diabetes (Table 3).

LV mass index

On linear regression analysis, predictors of LV mass index were advanced age, male gender, African-Caribbean ethnicity, higher waist circumference and systolic blood pressure (p<0.001), history of diabetes (p=0.02), use of beta-blockers (p=0.01) or calcium channel blockers (p=0.04).

LA diameter index

On linear regression, independent predictors of higher LA diameter index were advanced age, female gender, South Asian origin, higher values of body mass index, LV mass index, heart rate (p<0.001 for all), diastolic blood pressure (p=0.002) and history of smoking (p=0.003).

All-cause and cardiovascular death

Ninety-two deaths (6%) including 26 cardiovascular deaths occurred during a follow up of 68±21 months. On Cox regression analysis without adjustment for parameters of diastolic dysfunction, independent predictors of all-cause death were advanced age (p<0.001), history of smoking (p<0.001), South Asian ethnicity (p=0.024) and higher heart rate (p=0.009) (Table 4). After additional adjustment for parameters of diastolic dysfunction (i.e., LV mass index, e' velocity, E/e' ratio : LV diastolic volume index, quartiles of LA diameter index, presence of diastolic dysfunction and increased LV filling pressure [E/e' ≥13]) independent predictors of all-cause death were advanced age (p<0.001), male gender (p=0.049), history of smoking (p=0.012), higher heart rate (p=0.003) as well as presence of diastolic dysfunction (p=0.035) and the top quartile of LA index (p=0.002, vs. 1st quartile). After adjustment for parameters of diastolic dysfunction, ethnicity was no longer an independent predictor of all-cause death.

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Only advanced age (p<0.004) was the independent predictor of cardiovascular death. After additional adjustment for parameters of diastolic dysfunction above, independent predictors of cardiovascular death were increased LV filling pressure (p<0.001), history of smoking (p=0.008) and the top quartile of the LA diameter index (p=0.045, vs. 1st quartile).

Discussion

In this study we showed, for the first time, significant differences in characteristics of diastolic dysfunction in ethnic minority groups in the United Kingdom. South Asian ethnicity was independently associated with the presence of diastolic dysfunction and increased LV filling pressure, which paralleled a higher overall mortality associated with this ethnic group. Of interest, this was despite African-Caribbeans having more prominent LV hypertrophy. In contrast, South Asian ethnicity was associated with higher LA diameter index, a recognised marker of chronic diastolic dysfunction and higher E/e' ratio : LV diastolic volume index as an index of passive diastolic stiffness.

The pathophysiology of diastolic dysfunction is complex and still poorly understood. Under physiological conditions, LV pressure rapidly decays after systole, allowing low filling pressures and adequate diastolic filling. In diastolic dysfunction LV filling is compromised as a result of impairment in active (i.e., myocardial relaxation) and/or passive stiffness (increased cardiac stiffness).(11, 12) This ventricular filling defect, in turn, might reduce cardiac output contributing to heart failure symptoms in HFpEF patients. This is supported by both interventional experiments and by large population-based studies carried out using a non-invasive approach to measure diastolic stiffness.(13–15)

The present study suggests that African-Caribbeans are less likely to have diastolic dysfunction despite higher myocardial mass and thickness and more extensive concentric myocardial remodelling. The fact that African-Caribbean vs. South Asian ethnicity was not associated with higher e' velocity may suggest that the intrinsic velocity of myocardial relaxation might be preserved in these patients despite myocardial thickening. This indicates relatively benign nature of LV hypertrophy in African-Caribbean, which poses a relatively low risk of diastolic dysfunction. This observation also calls for the presence of increased passive diastolic stiffness in South Asian people that lead to diastolic dysfunction despite lower myocardial mass and thickness. This possibility is supported by higher E/e' ratio: LV diastolic volume index (an index of passive diastolic stiffness) associated with South Asian ethnicity. Excessive myocardial fibrosis is a plausible explanation, although its assessment was beyond the scope of this population-based study.

The present study does not give a direct answer on how the ethnicity-related differences in diastolic dysfunction are translated into clinical outcomes. However, it provides evidence that the ethnic differences extend beyond mild changes in diastolic dysfunction and are associated to progression towards increased LV filling pressure. Published evidence, although mostly derived from white population shows that such changes are not benign and are strongly related to increased risk of cardiovascular events.(16, 17) Indeed, ethnic minorities may represent an independent predictor of increased mortality in HFpEF.(18, 19)

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The factors causing increased LV mass in African-Caribbean subjects are not clear but they may have a genetic predisposition. Although children of African-Caribbean origin might even have lower blood pressure compared to white children, African-Caribbeans have higher blood pressure and more often develop hypertension later in their adult life.(20, 21) Ethnic differences in blood pressure begin to emerge in adolescence and early adulthood.(22–24) The Health Surveys for England showed a crossover in blood pressure (i.e., African-Caribbeans higher than whites) somewhat later, at 30-40 years of age.(25) Even after adjustment for age, body mass index, smoking, and alcohol intake African-Caribbeans still have higher odds of having hypertension.(26) Smaller nocturnal blood pressure falls and a higher prevalence of non-dipping seen in African-Caribbeans may contribute to the higher levels of hypertension-related complications seen in African-Caribbeans.(27) No such phenomenon was seen in South Asians.

In a UK-based study of highly trained nationally ranked athletes black sportsmen had greater LV wall thickness and LV mass compared to white athletes thus indicating a possibility of genetic predisposition to LV hypertrophy.(28) Large meta-analyses of genome-wide studies have found many loci significantly associated with higher blood pressure.(29) Of the 34 loci identified in the meta-analyses, 26 loci showed ethnic variations and they could be implicated in ethnic differences in hypertension.

Which factors could predispose to diastolic dysfunction in South Asian individuals despite lower LV mass? Genetic or acquired predisposition to LV fibrosis may play a role. For example, diabetes is more common in South Asians and it has a negative impact on LV diastolic function in this ethnic group.(30) Microalbuminuria is more frequent in the UK South Asians compared with white people, being associated with South Asian origin even after adjustment for hypertension, diabetes and age.(31) This may indicate higher susceptibility of South Asians to target organ damage (e.g., endothelial dysfunction). The enlarged LA could predispose to increased risk of developing atrial fibrillation that would further negatively impact diastolic function, but such analysis was beyond the scope of this study.

Hypertension was shown to be one of the leading attributable risk factors for mortality in South Asians but some controversy exists in this regard.(5) For example, South Asians were less likely to be adherent to antihypertensive medications, which contributed to excess in mortality.(32) In a large registry of patients with newly diagnosed hypertension, South Asians were reported to have lower mortality and risk of cardiovascular disease outcomes compared to whites.(6) The clinical implication of ethnic differences in diastolic dysfunction in South Asians thus merits further investigation.

The study shows that South Asian ethnicity is independently associated with higher all-cause death in patients with hypertension, before the adjustment for parameters of diastolic function. This parallels to the independent association of South Asian ethnicity with diastolic dysfunction in this population of hypertensive subjects (dilated left atrial can be considered a marker of longer-term abnormalities of diastolic dysfunction in patients without valvular pathology and atrial fibrillation).(10) Ethnicity was no longer

independently predictive of mortality after adjustment for parameters of diastolic dysfunction.

Limitations

The analysis does not cover white population, but our group previously showed in a subset of the participants of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) trial that African-Caribbean origin was linked to higher E/e' ratio vs. white subjects.(33) This much bigger study with more detailed assessment of diastolic dysfunction and cardiac geometry expands those observations in relation to South Asian cohort and it sheds some light on cardiac changes contributing to diastolic dysfunction in ethnic groups. LA size was assessed based on its diameter rather than volume. The ethnic differences observed in the analysis could be, at least partly, related to body composition, which was not assessed in the E-ECHOES study.(34, 35) The generalizability of the findings to ethnic groups in other regions (e.g., Asia or Africa) may be limited since both studied ethnic groups were recruited in the UK. Finally, the study does not provide mechanistic insight into pathways linking the observed differences and these need to be addressed by separate studies.

Conclusions

In ethnic groups recruited in the UK, South Asian ethnicity is associated with worse characteristics of diastolic function in hypertension, which parallels a higher mortality associated with this ethnic group. This occurs despite the fact that African-Caribbeans have more prominent LV hypertrophy. The findings likely reflect higher myocardial stiffness in South Asians possibly due to excessive fibrosis.

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Summary Table

What is known about topic

- Hypertension is a major cause of heart failure with preserved ejection fraction, which is commonly associated with poor quality of life and poor outcomes.
- Diastolic dysfunction and increased myocardial stiffness are recognised pathogenic factors contributing to the development of heart failure.
- Ethnic differences play a major role in coronary artery disease and hypertension.

What this study adds

- The present study shows for the first time that South Asian ethnicity is independently associated with worse parameters of diastolic function in hypertension, which parallels a higher mortality associated with this ethnic group.
- This occurs despite the fact that African-Caribbeans have more prominent hypertrophy and more distinct concentric remodelling.
- The findings are likely reflecting higher myocardial stiffness in South Asians possibly due to excessive fibrosis.

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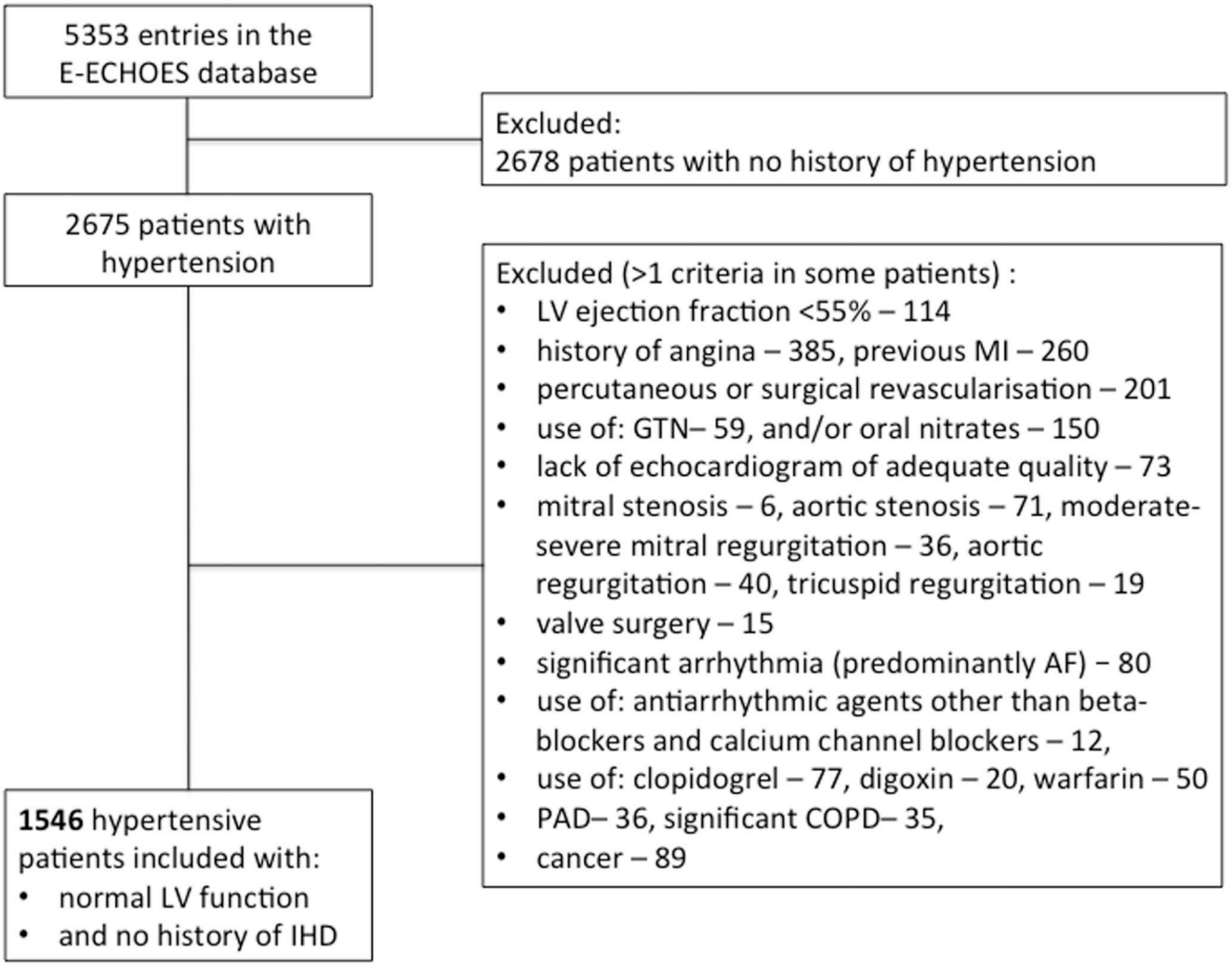

Figure 1. Study analysis flow chart.

E-ECHOES, The Ethnic-Echocardiographic Heart of England Screening Study; COPD, chronic obstructive pulmonary disease; GTN, glycerol trinitrate; IHD, ischemic heart disease; LV, left ventricular; PAD, peripheral artery disease.

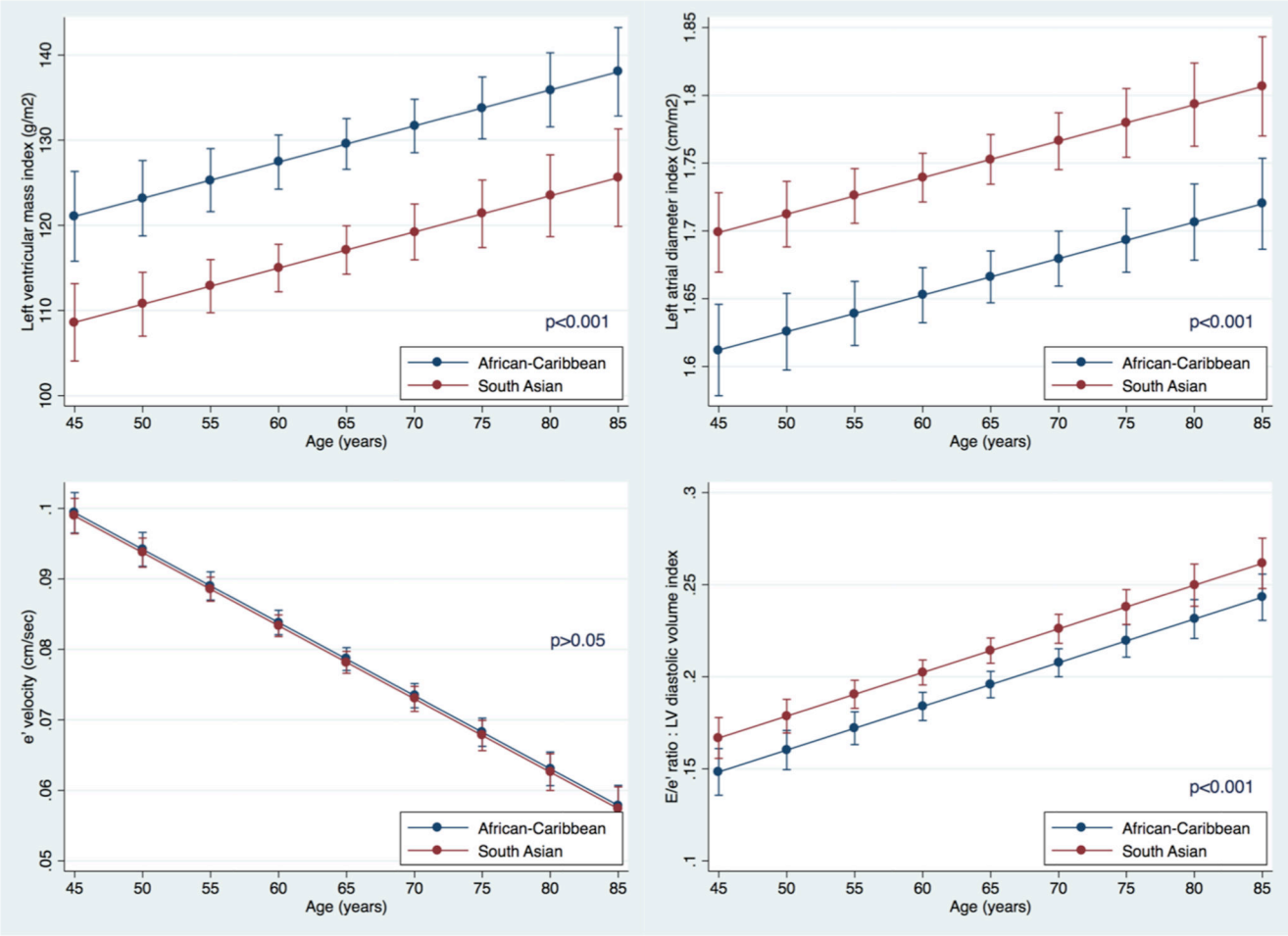

Figure 2. Relationship between ethnicity and echocardiographic measured of diastolic dysfunction on multivariable linear regression models.

The plots present adjusted regression lines with standard errors for specific age categories.

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Table 1

Patient characteristics

Parameter	South Asian		African-Caribbean		p value
	n	value	n	value	
Demographic and clinical characteristics					
Age, years	830	62±10	716	65±11	<0.001
Male gender	830	357 [43%]	716	302 [42%]	0.74
Diabetes	830	392 [47%]	716	250 [35%]	<0.001
Smoking	830	71 [9%]	716	110 [15%]	0.26
Body mass index, kg/m^2	825	29±5	715	30±6	<0.001
Waist circumference, cm	830	100.2±13	716	99.8±13	<0.001
Systolic blood pressure, mmHg	830	147±20	716	150±19	0.002
Diastolic blood pressure, mmHg	830	84±11	716	84±10	0.86
Heart rate, bpm	830	81±14	716	78±13	<0.001
Echocardiography					
Left ventricular ejection fraction, %	830	66±6	716	66±6	0.22
End-diastolic diameter index, cm/m^2	830	2.46±0.3	716	2.38±0.30	<0.001
Left ventricular mass index, g/m^2	815	115±38	713	131±43	<0.001
Left atrial diameter index, cm/m^2	820	1.74±0.3	715	1.67±0.27	<0.001
E/e' (medial-lateral)	809	8.19±2.41	701	7.77±2.31	0.001
E/e' ratio : LV diastolic volume index	794	0.21±0.10	694	0.20±0.09	0.064
Isovolumic relaxation time, msec	825	94±16	705	98±15	<0.001
Diastolic dysfunction	830	583 [73%]	716	501 [72%]	0.74
Increased left ventricular filling pressure	799	109 [14%]	695	75 [11%]	0.09
Left ventricular geometry: *Normal*		127 [16%]		67 [9%]	<0.001
Concentric remodelling		211 [26%]		126 [18%]	
Eccentric hypertrophy		122 [15%]		110 [15%]	
Concentric hypertrophy		347 [43%]		409 [57%]	
Medications					
ACEIs or ARAs	830	363 [44%]	716	243 [34%]	<0.001
Aldosterone antagonists	830	182 [22%]	716	127 [18%]	0.040
Alpha-blockers	830	37 [4%]	716	74 [10%]	<0.001
Aspirin	830	334 [40%]	716	274 [38%]	0.43
Beta-blockers	830	131 [16%]	716	108 [15%]	0.70
Calcium channel blockers	830	295 [36%]	716	424 [59%]	<0.001
Diuretics	830	299 [36%]	716	350 [49%]	<0.001
Statins	830	488 [59%]	716	360 [50%]	0.001

ACEI, angiotensin converting enzyme inhibitors; ARA, angiotensin receptor antagonists.

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Table 2

Logistic regression analysis of factors associated with diastolic dysfunction and increased left ventricular filling pressure

	Odds ratio [95% confidence interval]	p value
Diastolic dysfunction (n=1473), Chi-Square statistic 302, p<0.001		
Age, per 1 year	1.10 [1.08-1.12]	<0.001
Female gender	1.72 [1.32-2.24]	<0.001
African-Caribbean origin	0.67 [0.51-0.87]	0.003
Diastolic blood pressure, per 1 mmHg	1.03 [1.02-1.04]	<0.001
Heart rate, per 1 bpm	1.03 [1.02-1.04]	<0.001
Waist circumference, per 1 cm	1.03 [1.02-1.04]	<0.001
Aldosterone antagonist use	1.41 [1.01-1.97]	0.04
Left ventricular mass index, per 1 g/m^2	1.01 [1.00-1.01]	<0.001
Increased left ventricular filling pressure (n=1476), Chi-Square 128, p<0.001		
Age, per 1 year	1.06 [1.04-1.07]	<0.001
Female gender	2.48 [1.73-3.56]	<0.001
African-Caribbean origin	0.48 [0.34-0.69]	<0.001
Systolic blood pressure, per 1 mmHg	1.02 [1.01-1.03]	<0.001
Left ventricular mass index, per 1 g/m^2	1.01 [1.00-1.01]	<0.001

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Table 3

Linear regression analysis of factors associated with parameters of diastolic dysfunction, cardiac remodelling

	B ± standard error	Beta	P value
Left ventricular mass index (n=1528, overall r^2=0.15)			
Age, per 1 year	0.49±0.09	0.13	<0.001
Female gender	-14.2±1.97	-0.17	<0.001
African-Caribbean origin	12.9±2.05	0.16	<0.001
Waist, per 1 cm	0.45±0.08	0.14	<0.001
Systolic blood pressure, per mmHg	0.31±0.05	0.15	<0.001
Beta-blocker	6.90±2.69	0.06	0.01
History of diabetes	4.62±2.04	0.06	0.02
Calcium channel blocker	4.23±2.01	0.05	0.04
Left atrial diameter index (n=1523, overall r^2=0.21)			
Body mass index, per kg/m^2	-0.014±<0.01	-0.29	<0.001
Left ventricular mass index, per g/m^2	0.002±<0.01	0.23	<0.001
Female gender	0.088±0.02	0.16	<0.001
African-Caribbean origin	-0.082±0.01	-0.15	<0.001
Age, per 1 year	0.003±<0.01	0.11	<0.001
Heart rate, per 1 bpm	-0.002±<0.01	-0.10	<0.001
Diastolic blood pressure, per mmHg	-0.002±<0.01	-0.08	0.002
History of smoking	-0.046±0.02	-0.077	0.003
e' velocity (n=1492, overall r^2=0.27)			
Age, per 1 year	-0.10±<0.01	-0.46	<0.001
Waist, per 1 cm	<0.01±<0.01	-0.13	<0.001
Diastolic blood pressure, per mmHg	<0.01±<0.01	-0.16	<0.001
Left ventricular mass index, per g/m^2	-0.01±<0.01	-0.14	<0.001
Female gender	-0.50±0.10	-0.11	<0.001
History of diabetes	-0.40±0.10	-0.08	0.001
E/e' ratio : LV diastolic volume index (n=1476, overall r^2=0.15)			
Age, per year	<0.01±<0.01	0.265	<0.001
Female gender	0.04±0.01	0.203	<0.001
Systolic blood pressure, per mmHg	<0.01±<0.01	0.131	<0.001
Left ventricular mass index, per g/m^2	<0.01±<0.01	-0.107	<0.001
History of diabetes	0.01±0.01	0.065	0.010
African-Caribbean origin	-0.02±0.01	-0.097	<0.001
Body mass index, kg/m^2	0.00±<0.01	0.075	0.004
Heart rate, per 1 bpm	<0.01±<0.01	0.056	0.024
History of smoking	0.01±0.01	0.061	0.027
E/e' ratio : LV diastolic volume index (only patients without diabetes included) (n=870, overall r^2=0.15)			
Age, per year	0.002±<0.001	0.244	<0.001
Female gender	0.047±0.006	0.256	<0.001
Systolic blood pressure, per mmHg	0.01±<0.001	0.106	0.001

	B ± standard error	Beta	P value
Heart rate	0.001±<0.001	0.085	0.007
African-Caribbean origin	-0.018±0.006	-0.100	0.002

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Table 4

Stepwise forward Cox regression analysis of factors associated with any death and cardiovascular death (n=1546)

	Hazard ratio [95% confidence interval]	p value
Any death (without adjustment for parameters of diastolic function*), Chi-Square 102, p<0.001		
Age, per 1 year	1.11 [1.08-1.13]	p<0.001
History of smoking	2.33 [1.50-3.63]	p<0.001
African-Caribbean origin	0.60 [0.39-0.93]	0.024
Heart rate, per 1 bpm	1.02 [1.01-1.03]	0.009
Any death (with adjustment for parameters of diastolic function*), Chi-Square 111, p<0.001		
Age, per 1 year	1.09 [1.06-1.12]	p<0.001
Female gender	0.61 [0.38-1.00]	0.049
History of smoking	1.89 [1.15-3.10]	0.012
Heart rate, per 1 bpm	1.02 [1.01-1.04]	0.003
Presence of diastolic dysfunction	2.25 [1.06-4.78]	0.035
Increased LA diameter index vs. 1 quartile		0.003
4 quartile	2.92 [1.51-5.66]	0.002
Cardiovascular death (without adjustment for parameters of diastolic function*), Chi-Square 8.5, p=0.004		
Age, per 1 year	1.06 [1.02-1.10]	0.004
Cardiovascular death (with adjustment for parameters of diastolic function*), Chi-Square 27, p<0.001		
Increased LV filling pressure	4.99 [2.09-11.9]	p<0.001
History of smoking	3.03 [1.33-6.91]	0.008
Increased LA diameter index vs. 1 quartile		0.045
4 quartile	4.39 [1.21-15.9]	0.024

*Parameters of diastolic dysfunction included LV mass index, e' velocity, E/e' ratio : LV diastolic volume index, quartiles of LA diameter index, presence of diastolic dysfunction and increased LV filling pressure (*E/e' ≥13).* LA, left atrial; LV, left ventricular.