

# Renal dysfunction and diastolic impairment amongst British ethnic minorities with hypertension: The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES)

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1                   **Renal dysfunction and diastolic impairment amongst British ethnic**  
2   **minorities with hypertension:**

3           **The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES)**

4                                   *Running title:* Diastolic dysfunction in ethnic groups

5  
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24   **Conflict of Interest:** none declared

1 **Abstract**

2 Renal dysfunction is frequently associated with LV hypertrophy and diastolic dysfunction in  
3 hypertensive patients. Limited data exist on renal dysfunction and diastolic impairment  
4 amongst British ethnic minorities with hypertension. We studied associations between renal  
5 impairment and diastolic dysfunction in hypertensive subjects of African-Caribbean and  
6 South Asian origin. 510 hypertensive subjects with ejection fraction  $\geq 55\%$ , no history of  
7 ischemic heart disease/valve pathology were included from the original population of the  
8 Ethnic - Echocardiographic Heart of England Screening Study (E-ECHOES). Diastolic  
9 function and cardiac remodeling were measured by echocardiography.

10 Left ventricular (LV) hypertrophy was common and present in 62% of patients with normal  
11 estimated glomerular filtration rate (eGFR,  $>90$  ml/min/1.73m<sup>2</sup>), 73% in those with eGFR  
12 60-89 and 87% with eGFR  $<60$ . On both univariate and multivariable linear regression,  
13 reduced eGFR was associated with higher LV mass index (LVMI,  $p=0.01$  and  $p=0.039$ ,  
14 respectively). On multivariable analyses, increased LVMI (but not eGFR) was an  
15 independent predictor of echocardiographic parameters of diastolic dysfunction. Higher  
16 LVMI was an independent predictor of all cause or cardiovascular death on multivariable  
17 analyses (both  $p=0.002$ ), but not eGFR.

18 LV hypertrophy is common in minority ethnic groups with hypertension, especially in  
19 presence of renal dysfunction. Increased LVMI rather than renal impairment per se is a major  
20 determinant of diastolic dysfunction and increased risk of cardiovascular or all cause death  
21 amongst hypertensive patients without end-stage renal failure.

22

1 **Introduction**

2

3 Hypertension is a major cause of diastolic dysfunction and heart failure with preserved  
4 ejection fraction, with a significant contribution to cardiovascular and overall mortality.(1)

5 Hypertension also frequently leads to renal dysfunction, which increases the risk of  
6 cardiovascular complications and death.(2, 3) However, renal dysfunction is frequently

7 associated with LV hypertrophy and diastolic impairment.(4, 5), although studies assessing  
8 role of renal failure in diastolic dysfunction in hypertension have been mostly conducted on

9 subjects of White origin with advanced or end-stage renal failure. Limited data exist on renal  
10 dysfunction and diastolic impairment amongst minority ethnic groups with hypertension.

11

12 The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES) study was a  
13 cross-sectional population survey of subjects of South Asian and African-Caribbean origin

14 aged  $\geq 45$  years. The study participants were recruited from 20 primary care centres in  
15 Birmingham, United Kingdom between September 2006 to August 2009 and had

16 comprehensive clinical assessment and echocardiography performed.(6) In this analysis, we  
17 aimed to study the associations between renal impairment and diastolic dysfunction in

18 hypertensive subjects of African-Caribbean and South Asian origin.

19

## 1 **Methods**

2

3 We included participants of the E-ECHOES study who had history of hypertension with  
4 normal left ventricular (LV) systolic function (i.e., LV ejection fraction  $\geq 55\%$  by  
5 echocardiography), no history of ischemic heart disease (i.e., no angina, previous coronary  
6 revascularization or myocardial infarction or use of nitrates) and measured plasma creatinine.  
7 Other exclusion criteria were abnormalities of cardiac valves (i.e., stenosis or more than mild  
8 regurgitation of any valve or previous valve surgery), history of peripheral artery disease,  
9 cancer, chronic obstructive pulmonary disease, atrial fibrillation, current treatment with  
10 digoxin, warfarin, ADP (adenosine diphosphate receptor) antagonists or antiarrhythmic  
11 agents (except beta-blockers or calcium antagonists). The E-ECHOES database had 5353  
12 entries including 2675 patients with hypertension. From this population, 510 patients  
13 consented to have serum creatinine measured at the time of the recruitment.

14

15 The E-ECHOES study was approved by Walsall Local Research Ethics Committee  
16 (05/Q2708/45) with all participants provided written informed consent for data collection and  
17 analysis. Cases of deaths and their causes were provided by the Office of National Statistics.

18

### 19 *Echocardiography*

20 All study participants underwent detailed echocardiographic analysis with images reviewed  
21 by a consultant cardiologist with expertise in echocardiography. Echocardiography was done  
22 in primary care settings using a portable VIVID i machine (GE Healthcare, Chalfont St Giles,  
23 UK). LV ejection fraction, dimensions of cardiac chambers, LV mass index and parameters  
24 of diastolic function (mitral valve E/A ratio; E wave deceleration time; and isovolumic  
25 relaxation time (IVRT), tissue Doppler imaging of lateral and septal mitral valve annulus to

1 quantify E/e' ratio) were also measured in accordance with current recommendations.(7)  
2 Diastolic dysfunction was determined based on E/A ratio and average septal-lateral E/e' as  
3 main criteria and additional criteria of abnormal deceleration time (<130 msec or >230  
4 msec), reduced e' velocity (e' septal <8 cm/sec or e' lateral <10 cm/sec) and increased LA  
5 diameter (>4.0 cm in men and >3.8 cm in women). Diastolic dysfunction was defined as (i)  
6 E/A <1 (in patients older 60 years only in presence of  $\geq 1$  additional factor); (ii) E/A  $\geq 1$ , E/e'  
7 8-13 and  $\geq 1$  additional factor, or (iii) E/A  $\geq 1$  and E/e'  $\geq 13$ . Coding was done by an  
8 independent physician who was not involved in any analyses or writing of the manuscript  
9 (MD, see acknowledgments).

10

11 Increased LV filling pressure was defined based on average septal/lateral E/e'  
12  $\geq 13$ ).(8) In order to assess the separate components of diastolic function, average  
13 septal/lateral e' velocity (as a measure of active relaxation) and the ratio of E/e' ratio: LV  
14 diastolic volume index (as an index of passive diastolic stiffness). LV hypertrophy was  
15 defined as LV mass index >95 g/m<sup>2</sup> in women and 115 g/m<sup>2</sup> in men.(7) Concentric  
16 hypertrophy was defined as the relative wall thickness was  $\leq 0.42$ ; eccentric hypertrophy as  
17 the relative wall thickness >0.42 (both in presence of increased LV mass index). Concentric  
18 remodelling was defined as a normal LV mass index with relative wall thickness >0.42.(7)  
19 Intra- and interobserver variability of measurements of standard parameters of diastolic  
20 function in the department was <10%.(9)

21

## 22 *Statistical analysis*

23 Normal data are presented as mean  $\pm$  standard deviation and compared using independent  
24 sample T-test. Forward stepwise regression was used to establish predictors of parameters of  
25 diastolic dysfunction with the following predictor variables tested: age, gender, history of

1 diabetes and smoking, systolic and diastolic blood pressure, heart rate, body mass index,  
2 waist circumference, use of angiotensin enzyme inhibitors or angiotensin receptor  
3 antagonists, aldosterone antagonist, alpha-blocker, calcium channel blocker, diuretic, aspirin,  
4 statin, LV mass index (the last parameter was not used in analyses of predictors of LV mass  
5 index itself). The variables for the regression analysis have been chosen based on previous  
6 literature on diastolic dysfunction and its predictors. Linear regression was used to establish  
7 predictors of continuous variable and logistic regression was used to find predictors of  
8 diastolic dysfunction and increased LV filling pressure). Cox regression analysis was used to  
9 establish predictors of all-cause mortality in the study population. For logistic regression and  
10 Cox regression analyses, patients were categorised based on eGFR level ( $\geq 90$  ml/min/1.73m<sup>2</sup>,  
11 60-89 ml/min/1.73m<sup>2</sup>, and  $< 60$  ml/min/1.73m<sup>2</sup>). IBM SPSS Statistics 21 (IBM Inc, USA)  
12 was used for statistical analyses. P-values of  $< 0.05$  were considered as statistically  
13 significant.

14

## 1 **Results**

2

3 A total of 510 patients (239 of South Asian origin and 271 of African Caribbean origin) met  
4 the analysis criteria and had information on eGFR. eGFR was normal ( $\geq 90$  ml/min/1.73m<sup>2</sup>) in  
5 352 (69%) subjects (*Group 1*), 128 (25%) had eGFR 60-89 ml/min/1.73m<sup>2</sup> (*Group 2*), 30  
6 (6%) had eGFR  $< 60$  ml/min/1.73m<sup>2</sup> (*Group 3*, included 25 patients with eGFR 30-59  
7 ml/min/1.73m<sup>2</sup>, 2 with eGFR 15-29 ml/min/1.73m<sup>2</sup> and 3 with eGFR  $< 15$  ml/min/1.73m<sup>2</sup>).

8

9 Patients with reduced eGFR were older than those with normal eGFR ( $p < 0.001$ ), had lower  
10 diastolic blood pressure ( $p < 0.001$ ), were more often prescribed aspirin ( $p = 0.007$ ) and statins  
11 ( $p = 0.001$ ) (Table 1). Calcium channel blockers were more often used in the Group 2 than in  
12 Group 1 ( $p = 0.039$ ) and Group 3 ( $p = 0.016$ ). Diuretics were more often used in Group 3 than in  
13 Group 1 ( $p = 0.024$ ). Otherwise demographic and clinical parameters were similar in the study  
14 groups.

15

### 16 *Cardiac remodelling and diastolic dysfunction*

17 LV hypertrophy was common and present in 62% of patients in Group 1, 73% in Group 2  
18 and 87% in Group 3 (Figure 1). Patients with reduced eGFR were more likely to have  
19 abnormal LV geometry (i.e., LV hypertrophy or concentric LV remodelling) compared to  
20 those with normal eGFR ( $p = 0.0498$  for the Group 2 and  $p = 0.046$  for the Group 3). None of  
21 the Group 3 patients had normal LV geometry. Concentric LV hypertrophy was the  
22 predominant type of LV geometry in patients with reduced eGFR (50% of Group 2 and 59%  
23 of Group 3) (Table 1). Diastolic dysfunction was present in 67% of Group 1 and it was more  
24 common in Group 3 (87%,  $p = 0.023$ ) with similar trend for Group 2 (75%,  $p = 0.075$ ) (Table



1 1). Increased LV filing pressure was seen in 6% of Group 1 compared to 20% of Group 3  
2 (p=0.003) with similar trend Group 2 (10%, p=0.075) (Table 1).

3

4 Both on univariate and multivariable linear regression, reduced eGFR was associated with  
5 higher LV mass index (p=0.01 and p=0.039, respectively). On univariate regression analysis  
6 reduced eGFR was associated with presence diastolic dysfunction (p=0.029), increased LV  
7 filling pressure (p=0.011), increased LA diameter index (p=0.002) and e' velocity (p=0.001)  
8 (Tables 2 and 3). On multivariable analyses including adjustment for LV mass index, eGFR  
9 was not independently predictive of these parameters, nor E/e' ratio : LV diastolic volume  
10 index (p>0.05 for all) (Tables 2 and 3). In contrast, increased LV mass index was  
11 independently associated with all echocardiographic parameters of diastolic dysfunction  
12 above.

13

#### 14 *Mortality*

15 Twenty nine deaths (6%) including 12 cardiovascular deaths occurred during follow up of  
16 71±10 months. On univariate Cox regression eGFR <60 ml/min/1.73m<sup>2</sup> was associated with  
17 increased risk of all cause death (hazard ratio (HR) 3.24, 95% confidence interval 1.08-9.78,  
18 p=0.037) (Table 4). A nonsignificant trend was seen for the risk of cardiovascular death (HR  
19 4.09, 95%CI 0.83-20.3, p=0.085). On multivariable Cox analyses, higher LV mass index was  
20 independently associated with increased risk of both all cause (HR 1.09, 95%CI 1.03-1.14,  
21 p=0.002) and cardiovascular death (HR 1.11, 95%CI 1.04-1.19, p=0.002) (Table 4), but  
22 eGFR was non-predictive.

23

## 1 **Discussion**

2

3 The study shows for the first time a significant independent association between relatively  
4 mild renal impairment and unfavorable LV remodeling in minority ethnic groups with  
5 hypertension without end-stage renal failure. In this population, reduced eGFR had an  
6 independent linear relationship with increased LV mass index after accounting for known  
7 contributors to development of LV hypertrophy.

8

9 Association of renal dysfunction with LV hypertrophy is well established in predominantly  
10 White populations.(10) Reported frequency of LV hypertrophy varies depending on severity  
11 of renal dysfunction, being in the range of 16-31% in patients with chronic kidney disease  
12 stage 3 or better, 60–75% of predialysis subjects and over 90% in dialysis patients.(4)  
13 However, the present study shows a higher than expected occurrence of LV hypertrophy  
14 amongst ethnic minority groups in the UK. Indeed, LV hypertrophy was evident in 62% of  
15 patients with normal eGFR and reached 87% in those with eGFR <60 ml/min/1.73m<sup>2</sup>.  
16 Establishment of the precise causes for the frequent occurrence of LV hypertrophy in this  
17 population would require further research but may be due to suboptimal compliance with  
18 treatments, ethnicity related factors or relatively elderly study population.

19

20 We show that LV hypertrophy is the pivotal factor of developing of diastolic dysfunction and  
21 increased LV filling pressure. Indeed, non-end-stage renal dysfunction lost its predictive  
22 value for these parameters after adjustment for LV mass index. In contrast, elevated LV mass  
23 index was independently associated with presence of both diastolic dysfunction and increased  
24 LV filling pressure. Indeed, left atrial diameter index (a marker of chronic diastolic  
25 dysfunction), isovolumic relaxation time (a measure of overall relaxation), e' velocity (a

1 measure of active relaxation) and E/e' ratio : LV diastolic volume index (an index of passive  
2 diastolic stiffness) showed no independent association with eGFR in an analysis adjusted for  
3 LV mass index. Again, high LV mass index was an independent predictor of all these  
4 characteristics of diastolic dysfunction, thus confirming the key role of LV hypertrophy in  
5 diastolic dysfunction in hypertension.

6

7 Previous studies indicate that several types of myocardial changes contribute to diastolic  
8 dysfunction in hypertension including LV hypertrophy, delayed relaxation and increased  
9 stiffness of cardiomyocytes and LV fibrosis.(11-13) In the Framingham study in the  
10 population free from any cardiovascular disease and aged 40 years or older, the LV  
11 hypertrophy was present in 16% of man and 21% of women. (14) This study of the ethnic  
12 groups in the UK shows considerably higher prevalence of LV hypertrophy, which could be  
13 due to age effect. To account the analyses for the age effect we included age in all  
14 multivariate models in this study. LV hypertrophy is primarily driven by cardiac remodeling  
15 in response to high blood pressure, but the magnitude of LV hypertrophy is also affected by  
16 extracardiac target organ damage, such as abnormal arterial stiffness, impaired cardiac-  
17 vascular coupling and renal dysfunction.(15) Chronic kidney disease is a frequent  
18 complication of hypertension and it does contribute to poor outcome in such patients.

19

20 Myocardial hypertrophy and associated cardiac remodeling parallel increase in extracellular  
21 matrix production leading to fibrosis.(16) Cardiac fibrosis is also promoted by activation of  
22 renin-angiotensin-aldosterone system, typical of hypertension and renal dysfunction.(17)  
23 Pathological cardiac fibrosis increases cardiac stiffness and impairs LV contractility, leading  
24 to both systolic and diastolic dysfunction and congestive heart failure.(18) However  
25 increased LV hypertrophy rather than cardiac fibrosis appear to be the principal factor

1 leading to diastolic dysfunction in patients with preserved LV contractility and without end-  
2 stage renal failure, as seen in our analysis.

3

4 The clinical significance of LV hypertrophy rather than eGFR reduction per se in  
5 hypertensive patients without end-stage failure is further supported by increased LV mass  
6 index (but not eGFR) being independently predictive of mortality in this study. This  
7 observation accords well with previous data from White populations, including those with  
8 end-stage renal disease.(19) In advanced renal failure, almost half of deaths have been related  
9 to cardiovascular events but risk of such events was much lower in predialysis cohorts.(2, 3,  
10 20) These data have clinical implication as 10% decrease in LV mass has been translated into  
11 a 28% reduction in cardiovascular mortality in patients receiving hemodialysis, highlighting  
12 the role of LV mass index as a useful marker of effectiveness of blood pressure control.(21)

13

#### 14 *Limitations*

15 The study population mostly included patients with normal or mildly-to-moderately impaired  
16 renal function and the results may not be applicable to patients with end-stage renal failure.  
17 **Kidney function assessment was based only on eGFR estimation.** Lack of **comparison group**  
18 of White origin prevents generalization of the findings to all ethnic groups. Associations  
19 between renal function and systolic dysfunction should ideally be analyzed in prospective  
20 cohort studies but this was beyond the scope of the current analysis.

21

#### 22 *Conclusions*

23 LV hypertrophy is common in ethnic minority groups with hypertension, especially so in  
24 presence of renal dysfunction. Increased LVMI rather than renal impairment per se is a major

1 determinant of diastolic dysfunction and increased risk of cardiovascular or all cause death  
2 amongst hypertensive patients without end-stage renal failure.

3

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20

21 **Conflict of Interest:** none declared

22

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- 16



1 Summary Table.

2 What is known about topic

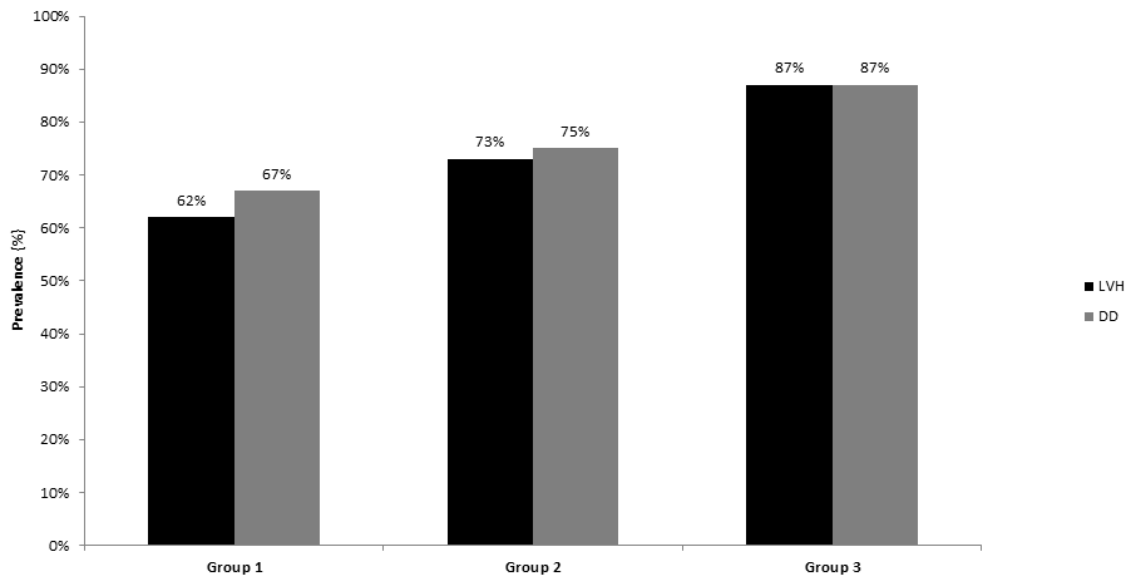
- 3 • Hypertension is a major cause of diastolic dysfunction and heart failure with  
4 preserved ejection fraction, with a significant contribution to cardiovascular and  
5 overall mortality
- 6 • Hypertension also frequently leads to renal dysfunction, which increases the risk of  
7 cardiovascular complications and death
- 8 • Renal dysfunction is frequently associated with left ventricular hypertrophy and  
9 diastolic dysfunction in hypertensive patients

10

11 What this study adds

- 12 • Increased left ventricular mass index rather than non-end stage renal impairment per  
13 se is a major determinant of diastolic dysfunction in ethnic minority groups with  
14 hypertension.
- 15 • Increased left ventricular mass index is associated with high risk of cardiovascular  
16 and all cause death amongst hypertensive patients without end-stage renal failure.

1 Figure 1. The prevalence of left ventricular hypertrophy and diastolic dysfunction  
2 across the categories of renal function.



3 DD, diastolic dysfunction; LVH, left ventricle hypertrophy; Group 1, eGFR  $\geq 90$   
4 ml/min/1.73m<sup>2</sup>; Group 2 eGFR 60-89 ml/min/1.73m<sup>2</sup> ; Group 3 eGFR <60  
5 ml/min/1.73m<sup>2</sup>.  
6