The impact of ethnicity on the progression of diabetic nephropathy: A prospective observational study.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001855
Article Type:	Research
Date Submitted by the Author:	26-Jul-2012
Complete List of Authors:	Mohiuddin, Atif; Royal London Hospital, Nephrology Ali, Omer; Royal london hospital, Nephrology Mathur, Rohini; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Dreyer, Gavin; Royal London Hospital, Nephrology Hull, Sally; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Yaqoob, Magdi; Royal London Hospital, Nephrology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Diabetes and endocrinology, Renal medicine
Keywords:	Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Chronic renal failure < NEPHROLOGY, End stage renal failure < NEPHROLOGY, Nephrology < INTERNAL MEDICINE

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

The impact of ethnicity on the progression of diabetic nephropathy: A prospective observational study.

[1] *A. Mohiuddin Senior clinical fellow

[1*]O. Ali Core medical trainee

[2]R. Mathur Research Fellow

[1]G. Dreyer Specialist registrar in nephrology

[2] S. Hull Reader in Primary Care Development

[1]M.M Yaqoob Professor of nephrology, Head of the Department of Experimental Medicine and Nephrology, William Harvey Research Institute, Queen Mary College.

[1] Department of Nephrology, Royal London Hospital, London.

2 Department of Primary Care, Barts Health, London, UK

*Dr Mohiuddin and Dr Ali contributed equally.

[*]Corresponding author

Professor M.M.Yaqoob.

Department of Nephrology

Royal London Hospital

Whitechapel road

London E1 1BB

Email: m.m.yaqoob@qmul.ac.uk

Word count: 2336 excluding references

Keywords: Diabetic nephropathy, end stage kidney disease, eGFR, blood pressure, proteinuria.

Abstract:

Objectives: To compare the rate of progression of diabetic chronic kidney disease (DCKD), development of end stage kidney disease (ESKD) and mortality in different ethnic groups.

Design: Prospective observational study.

Setting: Tertiary Renal unit.

Participants: All eligible patients with DCKD during 2000 – 2009 were included. Patients presenting with acute ESKD were excluded.

Main outcome measures: Primary end points were decline in eGFR, incidence of ESKD and mortality in different ethnic groups. Secondary end points were blood pressure and glycaemic control, proteinuria and use of angiotensin converting enzyme inhibitors (ACEi) / angiotensin receptor blockers (ARBs).

Results: 329 patients (age 60 years ± 11.9, 208 men) were studied. 149 south Asians, 105 Caucasians and 75 blacks were analysed. Mean follow up was over 6 years and similar in all 3 cohorts. Baseline eGFR was higher in south Asians (44±21 ml/min) than Caucasians (38±19 ml/min, p value 0.02) but similar to Blacks (39±21 ml/min). Baseline systolic BP was significantly higher in Black (158±26mmHg) and Caucasians (146±23 mmHg) compared with south Asians (136±24 mmHg p value<0.001). The incidence of ESKD and mortalities was similar in the 3 groups.

ACEi or ARBs use, HBA1C and proteinuria were similar. Unadjusted analysis showed higher rate of eGFR decline in Black (5.38 ± SEM 0.77 ml/min/year) and south Asians (4.42±0.43) than Caucasians (2.67±SEM 0.33, p 0.002 and 0.01 respectively). After adjustment for multiple variables difference in progression between Black and Caucasians disappeared but persisted in south Asians (p 0.04). Systolic BP (p value <0.001) and baseline proteinuria (p value 0.02) were the other predictors of DCKD progression.

Conclusion: Black and south Asians have higher rate of DCKD progression. This is explained by higher BP in blacks but south Asians progressed rapidly despite low BP. Optimal target BP in south Asians with DCKD remains unclear.

Introduction:

Diabetic nephropathy (DN) is the leading cause of end-stage kidney disease (ESKD) in United Kingdom (UK), accounting for 21% of all causes of ESKD in UK[1]. Suboptimal glycaemic and blood pressure (BP) control, development of albuminuria and family history are important risk factors for progression of DN. There is a higher prevalence of diabetes mellitus (DM), hypertension and ESKD in south Asian and Afro- Caribbean populations. Age and sex standardised prevalence ratios for hypertension are 2.6 and 1.8 in Afro-Caribbean and south Asians respectively compared to whites. Prevalence ratios for DM are 2.7 and 3.8 respectively[2, 3, 4,5,6]. Diabetic nephropathy and end stage kidney disease are significantly more common in south Asian populations compared to Caucasians with a reported relative risk of up to 14 [4] . Similarly a number of studies have shown that there is higher prevalence of diabetic nephropathy and end stage kidney disease in Afro- Caribbean populations [7,8,9] . One of these studies suggested a relative risk of 5.8 in south Asians and 6.5 in Afro-Caribbean for underlying cause of RRT to be diabetes, compared with Caucasians[7]. There is also 3.5 times higher mortality in south Asian and Afro-Caribbean population with diabetes compared to Caucasians in England and Wales[10]. The higher incidence of ESKD in south Asians and Afro-Caribbean with diabetes may be related to higher incidence of DM, hypertension and relatively poor control of DM and hypertension but it may also be the result of faster progression of DN. There are conflicting reports on progression of diabetic nephropathy in these population subgroups. Higher rates of kidney function decline have been reported in some studies while others have failed to show this trend[11-15,20].

Most of these studies comparing progression of diabetic nephropathy in ethnically diverse populations have either been small or had short duration of follow up. Our kidney centre serves an ethnically diverse population including Caucasian, south Asian and Afro-Caribbean descent population. We analysed data from a cohort of patients with DN under regular follow up in the kidney unit to address the following;

Firstly to assess the rate of kidney function decline in Caucasian, Afro-Caribbean and south Asian populations while controlling for the effects of glycaemic control, BP control, proteinuria, medications, chronic kidney disease (CKD) stage and baseline demographic characteristics. Secondly, to examine the incidence of renal replacement therapy (RRT), death and composite of death and RRT as one of the outcomes. Finally, to analyse the effect of different BP levels on rate of progression in these diverse ethnic groups.

Materials and Methods:

All adult patients above the age of 18 years with biopsy proven or clinical diagnosis of diabetic nephropathy (where all secondary causes were excluded) attending kidney outpatient clinics were included in the study. Any other diagnosis of chronic kidney disease, and those presenting acutely with ESKD were excluded from the study.

Patients started on dialysis or those who were transplanted were censored at that time point.

Patients were divided into three ethnic groups. The south Asian population included patients of Indian, Bangladeshi and Pakistani descent. The Afro-Caribbean population were of African and Caribbean descent while the Caucasians were of European decent.

A cohort of 356 patients suffering from DN followed up prospectively was analysed. The study period spanned between 2000 and 2009.

Data collection: All the data was captured electronically in an in-house renal information technology programme (File maker pro) at every kidney clinic visit. This also included office BP measured in sitting position using cuffs appropriate for individuals and all clinical events and changes in medication are updated automatically.

GFR was calculated based on 4 variable MDRD equation (eGFR) which was corrected for Afro-Caribbean populations.

Serum creatinine was measured using Roche Modular Platform automated analyser.

Proteinuria was determined using protein creatinine ratio (Roche Modular Platform automated analyser) and spot urine sample at every clinic visit.

Glycated haemoglobin (HBA1C) was used to assess glycaemic control (BioRad Turbo 2 automated analyser). BP, HBA1C, proteinuria and eGFR data was collected every 6 months.

Statistical methods: Outcome variable creation;

Six monthly eGFR values were combined to form an annual average for each patient for each year of the study. The outcome variable was annual change in eGFR. This was calculated by subtracting baseline eGFR from final eGFR and dividing the difference by total months of follow up and multiplying by 12.

Baseline variables were created for: Average eGFR, systolic BP (SBP), Diastolic BP (DBP) and HBA1C value. PCR was considered both as a linear variable and a binary variable (presence or absence of proteinuria at baseline defined as PCR>15)

Medications were coded a constant variable (present vs never present) for ACE, ARB, or dual blockade if patient had taken these medication for at least 1 year during study period.

Descriptive analysis

Bivariate statistics outlining the population breakdown by ethnicity and age group were conducted. Average length of follow up was calculated for each of the above groups. Significant differences between ethnic and age groups were examined using linear regression for the numerical baseline variables and logistic regression for the categorical variables.

Multivariate Regression

Linear regression analysis was used to determine whether the annual change in eGFR differed by ethnic group or age group. Unadjusted analyses were conducted for differences in rate of progression in ethnic group.

The first model was adjusted for baseline SBP, PCR, HbA1c, ACE use, ARB use, dual Blockade, age and sex. The second fully adjusted model added in baseline DBP and mean values for SBP, DBP, PCR and HbA1c. The final adjusted model used the same variables as model 2 but replaced baseline PCR value with baseline presence of proteinuria.

Results:

Out of a total of 356 eligible patients a total of 329 patients with more than 6 years follow up were analysed, 27 patients were excluded because 10 presented as ESKD and 17 patients has no ethnicity data. The baseline characteristics are shown in table1.

Baseline GFR was higher in south Asians but systolic BP was higher in Caucasians and Afro-Caribbean groups. Afro-Caribbeans had the highest systolic and diastolic BP. Baseline urinary PCR did not differ significantly between the three groups (p value 0.06). There was a trend towards higher baseline proteinuria in south Asians but this did not reach statistical significance. During the entire study period BP remained significantly higher in afro-Caribbean compared to south Asians and Caucasians.
However, proteinuria and glycaemic control was comparable in the three groups.

The three populations were different in that south Asians were younger and had shorter duration of diabetes and low baseline BP. Afro-Caribbean had shorter duration of diabetes but had higher baseline BP. Relatively higher percentage of south Asians were in CKD stage 2 (22% p value 0.01) but there was no difference in prevalence of other CKD stages in 3 ethnic groups. However, during the entire study only afro-Caribbean had a significantly higher systolic and diastolic BP. On the contrary PCR and HbAic were similar in the three groups (Table 2).

The annual crude rate of decline of eGFR was significantly higher in afro-Caribbean and south Asians compared with Caucasians (Table 3). However the incidence of ESKD and of all cause mortality was similar between the three groups.

On univariate analysis (table 4) several recognised parameters in addition to ethnicity were associated with progression of diabetic nephropathy. However on multivariate analysis mean systolic BP, proteinuria and south Asian ethnicity were the only independent predictors of eGFR decline. This suggests that high crude rate of decline in eGFR in afro-Caribbean was hypertension related.

Discussion:

In this single centre prospective study of patients with diabetic nephropathy, a faster rate of progression was seen in afro Caribbean and south Asian populations. Higher rate of progression in south Asians has been reported before by Shaw et al and Earle et al[11,13]. However patients in both studies had significantly smaller numbers than our study and their patient had early CKD at baseline compared with our population who had moderately severe baseline CKD (stage 3B). One small study (39 patients) by Koppiker et al had suggested no difference in rate of progression between Caucasians and south Asians[15]. However complete data was available in only 36 patients with much more advanced kidney failure (baseline creatinine 270µmol/l for Caucasians and 273 µmol/l for south Asians). BP control and glycaemic control was also much poorer compared to our study. Salifu et al[12] also suggested that there was no significant difference in progression of diabetic nephropathy between Black and Caucasian populations with equivalent diabetic control. In our study population however, significant difference in progression was noted despite no difference in baseline and mean diabetic control between 3 study populations because of sub optimal BP control in the afro-Caribbean population in our study.

Generally BP control in afro-Caribbean populations is more difficult and may contribute towards a faster rate of kidney function decline. One study showed that there was no significant difference in rate of kidney function decline after adjusting for the effects of glycaemic control in afro-Caribbean populations compared with Caucasians while others have shown significant difference despite equivalent BP and glycaemic control. A difference in the use of antihypertensive medication including renin angiotensin blocking medication (RAAS) has also been suggested[15,17,18].

In our study, high systolic BP (SBP) was associated with higher rate of progression in all regression models. South Asian had significantly lower baseline and final SBP compared with Caucasian. Afro- Caribbean had a significantly higher baseline and mean SBP compared with Caucasians. In our previous study we observed a higher prevalence of BP>150/90 in Blacks in a community based cohort with mild CKD[19] , a result which is confirmed by this study. The higher rate of DN progression could be explained by higher systolic BP in afro Caribbean but south Asian had a higher rate of progression despite relatively low baseline,

mean and final BP. General guidelines for BP control do not take ethnicity into account. Different BP targets may be indicated in different ethnic populations and a large randomised study to explore this possibility is warranted. Diastolic BP was not predictive of faster rate of DN progression in multivariate analysis. Like all other studies, proteinuria was a significant independent predictor of rapid eGFR decline but there was no difference in the degree of proteinuria between the groups and therefore this could not explain the differences in the rate of progression.

There was no difference in glycaemic control (baseline, mean and final) to explain higher rate of progression in these ethnicities. Baseline or mean HBA1C was not significantly associated with progression of DN in multivariate analysis. This was also suggested by Crook et al who had analysed data from 155 patients with DN (87.7% AC) that diabetic control predicted extra-renal micro vascular complications but not renal survival in patients with moderate to severe kidney disease[14].

There was a high mortality rate and incidence of end stage kidney disease requiring renal replacement therapy in all population groups.This may be explained by the high-risk baseline population and long duration of follow up. This did not differ significantly in sub groups because our study was not adequately powered to detect this difference. It is important to note however, that although south Asians had a higher baseline eGFR and a high rate of progression, a longer duration of follow up may have translated into a higher incidence of ESKD.

Current national chronic kidney disease (CKD) guidelines do not include ethnicity as a risk factor for CKD[16]. Therefore the management of CKD in ethnic minorities is similar to that for the Caucasian population. Studies suggest that BP and glycaemic control is worse in ethnic minorities[17,18] which may be associated with higher cardiovascular risk and predispose to faster progression of CKD to ESKD. Identification of high risk groups of progressive DN offers the potential to provide targeted health care in the areas where ethnic minority populations are prevalent.

Conclusion:

This study clearly demonstrates that rate of progression of CKD in patients with diabetes mellitus is faster in afro-Caribbean and south Asians compared to Caucasians. However, south Asians patients have a faster rate of progression independent of BP, proteinuria and glycemic control. This calls for further research into probably drawing up different set of guidelines for this patient group that will ultimately have a global health economic impact.

Table 1

Characteristic	Caucasian Mean±SD	Afro Caribbean Mean±SD	South Asian Mean±SD	Significance (p value)
No	105	75	149	
Age	61.3±12.6	62.4±11.3	57.8±11.4)	0.005
Male (%)	62	66	66	0.9
T2 DM(%)	85	100	98	<0.001
Duration of diabetes (years)	18.3±11.6	13.4±7.1	13.9±12.9	0.001
Duration of follow up (years)	6.79±2.3	6.33±2.7	6.39±2.3	
Diabetic retinopathy (%)	84	81	76	0.11
IHD(%)	28.5	21.3	38.6	0.05
PVD	15.2	10.6	12	0.69
CVD	10.4	8	10.6	0.58
Statin use	83.8	80	80.8	0.84
ACE use (%)	72.4	70.7	73.7	0.91
ARB use	34.3	40	41.2	0.44
Dual Blockade	14.3	17.3	20	0.61
Baseline eGFR	38±19	39±21	44±21	0.02
Baseline Serum Creatinine(µmol/l)	148±70	171±90	132±60	
Baseline SBP	146.6±26	158.3±23	136.6±24	<0.001
SBP>150mm HG(%)	40	56	20	<0.001
Baseline DBP	76±11	83±15	75±11	0.002
Diastolic BP>90mmHG	8	18	7.7	0.06
Baseline HBA1C	8.47±1.8	8.83±2.2	8.74±1.9	0.7
HBA1c <8(%)	44	38	44	0.7
Baseline PCR mg/mmol Mean±SD	163±206	152±184	235±335	0.1
PCR>45 mg/mmol (%)	65	64	72	0.56
Baseline CKD stage				
CKD1(%)	1.9	2.67	2	0.93
CKD2(%)	9.52	9.33	22	0.01
CKD3(%)	50.48	49.33	48	0.96
CKD4(%)	32.38	30.67	20.67	0.15
CKD5(%)	5.71	8	7.33	0.82
Current smoker(%)	18.6	13.6	13	0.6

Table 2

	White	Black	South Asian	Sig White vs Black	Sig Whit vs SA	Sig Black vs SA
PCR(med IQR)	80(29-246)	91(29-235)	125.5(45-311)	0.85	0.13	0.1
Mean systolic	137.6(15.6)	149.5(24)	134.01(20)	<0.001	0.07	<0.001
Mean diastolic	74(11)	79(29)	74(23)	<0.001	0.6	<0.001
Mean HBA1C(mean SD)	8.18(1.8)	8.6(1.9)	8.29(1.7)	0.07	0.55	0.15

Table 3

Characteristic	Caucasian Mean±SEM	Black Mean±SEM	South Asian Mean±SEM	P value Black vs Caucasians	P value South Asian vs Caucasians	P Value AC vs SA
eGFR decline/year	2.67±0.33	5.38±0.77	4.42±0.42	0.002	0.001	0.11
Renal replacement therapy(%)	32	44	39	0.11	0.29	0.46
Death (%)	16.2	20	18.8	0.5	0.6	0.82

Table 4a

Variable	Significance (p value)
Afro-Caribbean ethnicity	0.002
South Asian ethnicity	0.01
Younger age	0.03
Baseline HBA1C	0.006
Baseline PCR	<0.001
Baseline systolic BP	<0.001
Baseline diastolic BP	0.01

Table 4b

Characteristic	Significance (p value)
Mean systolic BP	<0.001
Baseline Proteinuria	0.02
South Asian Descent	0.04

Legends for tables and figures:

Table 1: The baseline characteristics of the study groups.

Table 2: Shows the mean/median readings for PCR, BP and HBA1C of the study groups.

Table 3: Shows the decline in eGFR, RRT and mortality in different ethnic groups.

Table 4a: Univariate analysis showing the parameters in addition to ethnicity that were associated with progression of diabetic nephropathy.

Table 4b. Multivariate analysis showing mean systolic BP, proteinuria and south asians were the only independent predictors of eGFR decline.

Figure 1: Shows the annual mean eGFR (± SEM) decline in different ethnic groups over the study period.
The annual crude rate of decline of eGFR was significantly higher in afro-Caribbean and south Asians compared with Caucasians.

Figure 2: Shows the annual mean (± SEM) systolic and diastolic change in BP in different ethnic groups.

During the entire study period BP remained significantly higher in afro-Caribbean compared to south Asians and Caucasians.

Figure 3: Shows the annual mean (± SEM) change in glycemic control as measured by HbA1c in different ethnic groups.

There was no statistical difference in glycemic control between the groups.

Figure 4: Shows the annual mean (± SEM) change in PCR in different ethnic groups.

There was no statistical difference in the degree of proteinuria between the groups.

References:

1- Byrne C, Ford D, Gilg J, et al. UK ESRD Incident Rates in 2008: national and centre-specific analyses. UK Renal registry report 2009.

2- Crook ED, Patel SR. Diabetic nephropathy in African-american patients. Cuur Diab Rep 2004;4(6):455-46.

3- Cappuccio FP, Cook DG, Atkinson RW, et al . Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in south London. Heart 1997 78(6):555-563.

4- Burden AC, McNally PG, Feehally J, et al. Increased incidence stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med 9:641–645, 1992.

5- Feehally J, Burden AC, Mayberry JF, et al. Disease variations in Asians in Leicester.Q J Med86:263–269, 1993.

6- Karter A, Ferrara A, Liu J, et al. Ethnic Disparities in Diabetic Complications in an Insured Population. Nephrol Dial Transplant. 2006; 21(8):2178-83.

7- Roderick PJ, Raleigh VS,Hallam L, et al. The need and demand for renal replacement therapy amongst ethnic minorities in England. J Epi-demiol Comm Health 1996;50:334-9.

8- Friedman EA. Diabetic nephropathy in blacks. Transplant Proc 1993;25:2431.

9- Cruickshank JK. Diabetes: contrasts between peoples of black (West Afri can), Indian and white European origin. In: Cruickshank JK, Beevers DG,eds. Ethnic factors in health and disease. London: Wright, 1989.

10- Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends 1997;28:122–7.

11- Shaw P, Baboe F, van Es L, et al. South-Asian type 2 diabetic patients have higher incidence and faster progression of renal disease compared with Dutch-European diabetic patients. Diabetes Care 2006; 29 (6): 1383-1385.

12- Salifu M, Shah S, Iqbal M et al. Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. Am J Nephrol 2009;30:261-267.

13- Earle KK, Porter KA, Ostberg J, et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001;16(2):286-90.

14- Crook ED, Patel S. Glycemic control predicts diabetic extrarenal microvascular complications but not renal survival in patients with moderate to severe chronic kidney disease. EthnDis. 2006;16(4):865-71.

15- Koppiker N, Feehally J, Raymond N, et al. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. Diabet Med. 1998;15(1):60-5.

16- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association and the Royal College of General Practitioners. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. London: Royal College of Physicians; 2006.

17- Duru O, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the kidney early evaluation program (KEEP). Am J Kidney Dis 2008;51:192-8.

18- Davis TM. Ethnic diversity in type 2 diabetes. Diabet Med. 2008;25 Suppl 2:52-6.

19- Dreyer G, Hull S, Aitken Z, et al. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM (2009) 102 (4): 261-269.

20- Kanaya AM, Adler N, Moffet H, et al. Heterogeneity of Diabetes Outcomes Among Asians and Pacific Islanders in the U.S.The Diabetes Study of Northern California (DISTANCE). Diabetes care 2011; 34(4): 930-937.

Figure 1

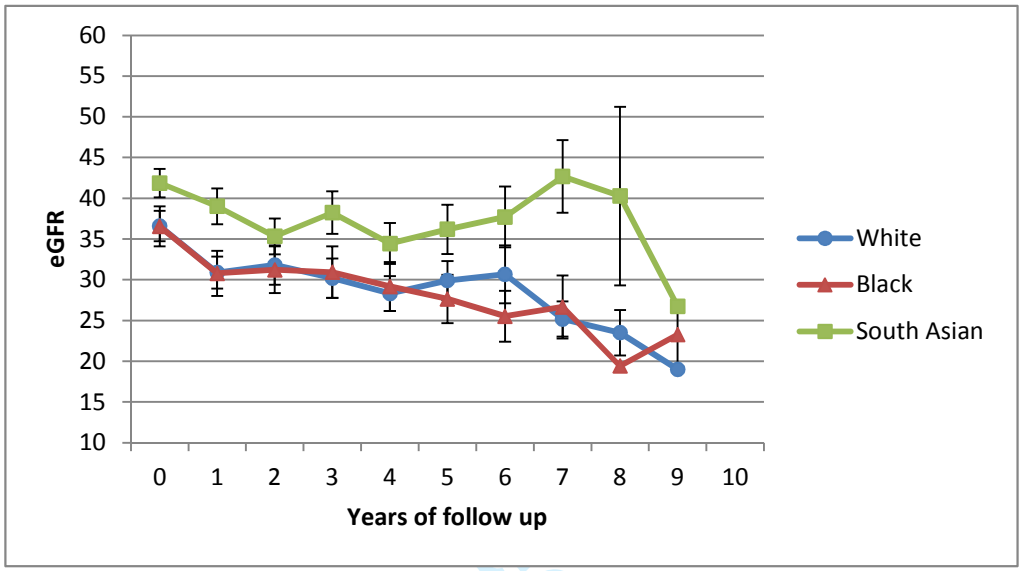


Figure 2

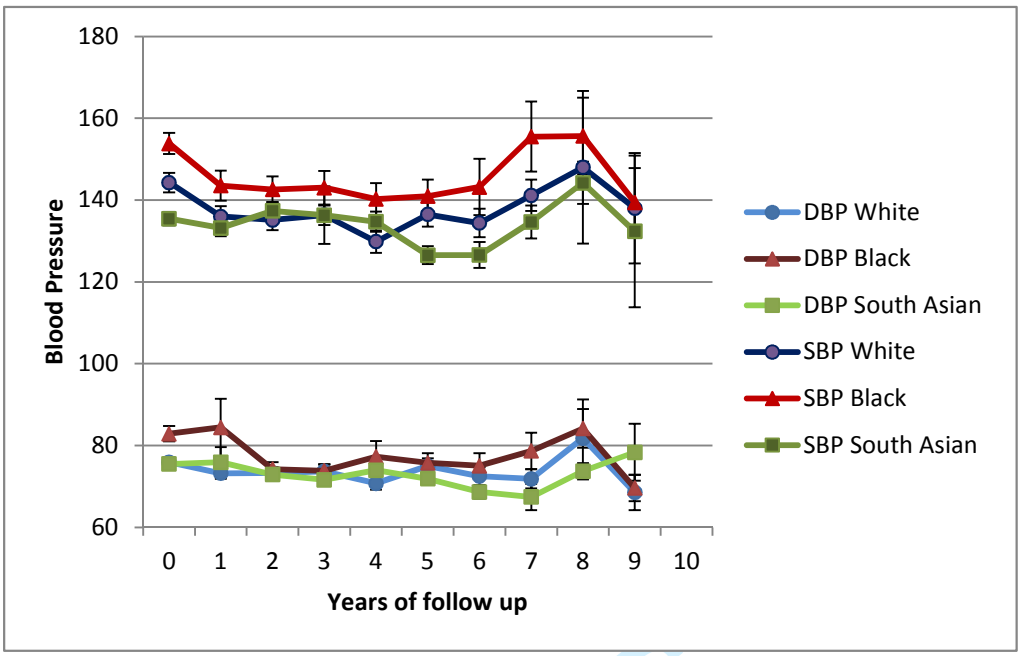


Figure 3

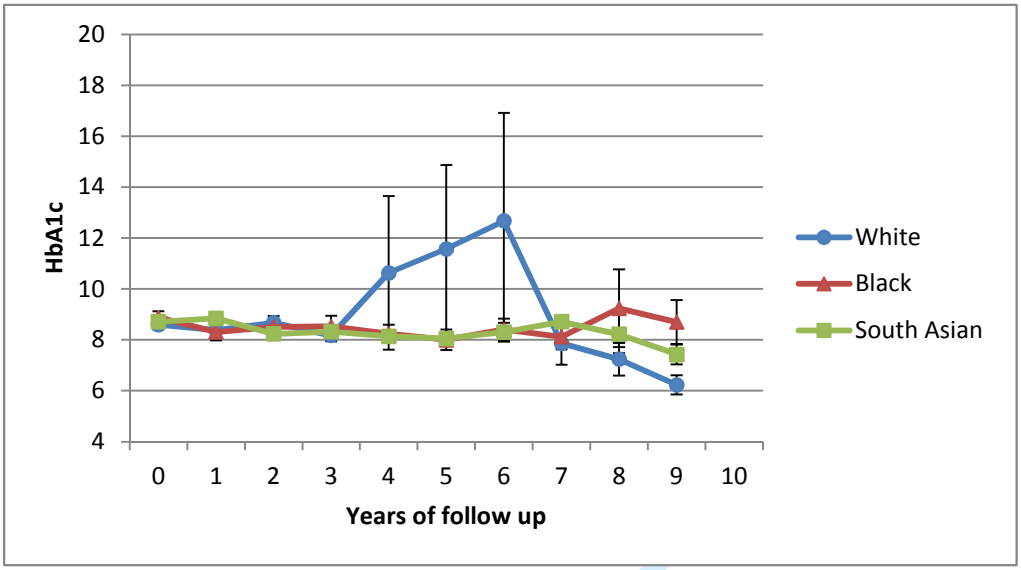
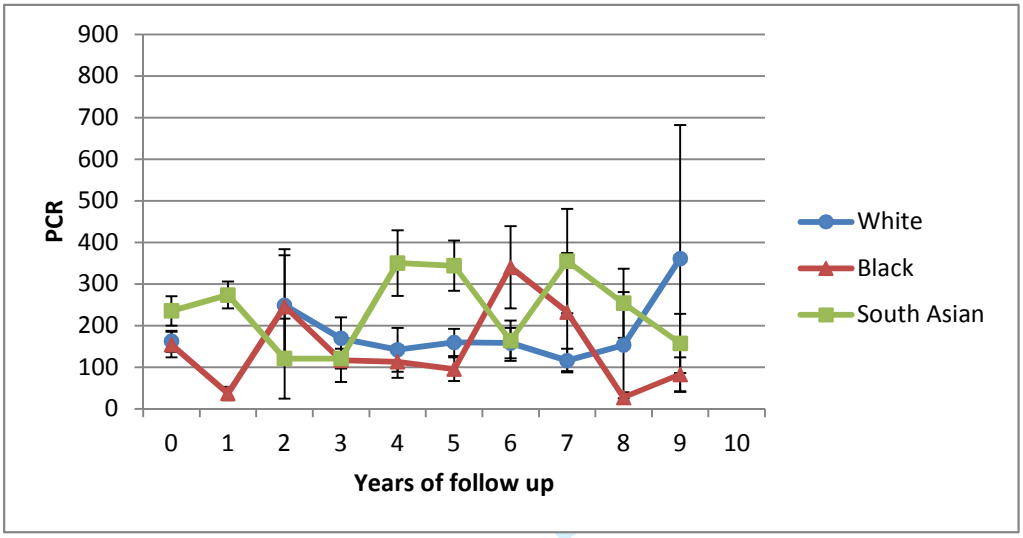


Figure 4



The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ editions and any other BMJPGL products and sublicences to exploit all subsidiary rights, as set out in our licence.

All authors listed have contributed sufficiently to the project to be included as authors. Dr Mohiuddin and Dr Ali contributed equally as first authors. To the best of our knowledge, no conflict of interest, financial or other, exists.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other peer-reviewed media.

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001855.R1
Article Type:	Research
Date Submitted by the Author:	19-Nov-2012
Complete List of Authors:	Ali, Omer; Royal london hospital, Nephrology Mohiuddin, Atif; Royal London Hospital, Nephrology Mathur, Rohini; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Dreyer, Gavin; Royal London Hospital, Nephrology Hull, Sally; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Yaqoob, Magdi; Royal London Hospital, Nephrology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Diabetes and endocrinology, Renal medicine
Keywords:	Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Chronic renal failure < NEPHROLOGY, End stage renal failure < NEPHROLOGY, Nephrology < INTERNAL MEDICINE

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

[1*]O. Ali Core medical trainee

[1*]A. Mohiuddin Senior clinical fellow

[2]R. Mathur Research Fellow

[1]G. Dreyer Specialist registrar in Nephrology

[2] S. Hull Reader in Primary Care Development

[1]M.M Yaqoob Professor of Nephrology

[1] Department of Nephrology, Royal London Hospital, London.

2 Department of Primary Care and Public Health, Queen Mary, University of London

*Dr Mohiuddin and Dr Ali contributed equally.

[*]Corresponding author

Professor M.M.Yaqoob.

Department of Nephrology

Royal London Hospital

Whitechapel road

London E1 1BB

Email: m.m.yaqoob@qmul.ac.uk

Word count: 2660 excluding tables and references

Keywords: Diabetic chronic kidney disease, end stage kidney failure, blood pressure, proteinuria.

Abstract:

Objective: To compare the rate of progression of diabetic chronic kidney disease in different ethnic groups.

Design: Prospective longitudinal observational study.

Participants: All new patients attending a tertiary renal unit in east London with diabetic chronic kidney disease between 2000 and 2007 and followed up till 2009 were included. Patients presenting with acute end stage kidney failure were excluded.

Main outcome measures: The primary outcome was annual decline in estimated glomerular filtration rate (eGFR) in different ethnic groups. Secondary end points were the number of patients developing end stage kidney failure and total mortality during the study period.

Results: 329 patients (age 60 years ± 11.9, 208 men) were studied comprising 149 south Asian, 105 White and 75 Black patients. Mean follow up was over 6 years and similar in all 3 groups. South Asians were younger and had a higher baseline eGFR, but both systolic and diastolic blood pressure was higher in blacks ($p<0.05$). Baseline proteinuria was highest for south Asian groups followed by White and Black groups. Adjusted linear regression analysis showed that an annual decline in eGFR was not significantly different between the three groups. The number of patients developing end stage kidney failure and total mortality was similar between the three groups. Angiotensin converting enzyme or angiotensin receptor blockers use, and glycated haemoglobin (HbA1C) were similar at baseline and through out the study period.

Conclusion: We conclude that ethnicity is not an independent factor in the rate of progression renal failure in patients with diabetic chronic kidney disease.

Introduction:

Diabetic chronic kidney disease (DCKD) is one of the leading cause of end-stage kidney failure (ESKF), accounting for 21% of all such cases in the UK[1]. Suboptimal glycaemic and blood pressure control, development of albuminuria and family history are important risk factors for the development of chronic kidney disease in diabetic patients. There is a higher prevalence of diabetes mellitus (DM) and ESKF in black and south Asian populations with prevalence ratios for DM of 2.7 and 3.8 respectively[2, 3, 4,5,6]. Diabetic chronic kidney disease and end stage kidney failure are significantly more common in south Asian populations with a reported relative risk of up to 14 compared to Whites[4]. Similarly, a number of studies have demonstrated a higher prevalence of diabetic chronic kidney disease and end stage kidney failure in Black populations[7,8,9]. One such study suggests a relative risk of 5.8 in south Asians and 6.5 in Blacks[7]. Mortality is also 3.5 times higher in south Asian and Black populations with diabetes compared to Whites in England and Wales[10]. The higher incidence of ESKF in south Asian and Black populations may be related to higher incidence and poorer control of diabetes and hypertension. However, it may also be related to faster progression of diabetic chronic kidney disease in ethnic minority populations. There are conflicting reports on progression of diabetic chronic kidney disease in these population subgroups. Higher rates of kidney function decline have been reported in some studies while others have failed to show this trend[11-14,19].

Most studies comparing progression of diabetic chronic kidney disease in ethnically diverse populations have either been small or had short duration of follow up. The renal clinic at the Royal London Hospital in east London serves an ethnically diverse population in a large urban centre. The aim of our study is firstly to determine whether the rate of kidney function decline differs by ethnic group after controlling for demographic characteristics and clinical parameters known to be associated with progression of chronic kidney disease, and secondly, to examine the number of patients developing ESKF and total mortality by ethnicity.

Materials and Methods:

Population

The study was conducted at the Royal London hospital, which serves as a tertiary referral centre for three primary care trusts in east London; Newham, Tower Hamlets and City & Hackney, with a combined GP registered population of 885,625 at the end of 2011. The prevalence of CKD among diabetics, based on a local study, is 18%[18].

All adult patients above the age of 18 years with biopsy proven or clinical diagnosis of diabetic chronic kidney disease (where all secondary causes were excluded) attending our kidney outpatient clinic were included in the study. Any other diagnosis of chronic kidney disease, and those presenting acutely with ESKF were excluded from the study.

Ethnicity was self-assigned by the patient. Patients were grouped according to the ethnic categories of the 2001 census. For the purpose of this study patients of Indian, Bangladeshi and Pakistani ethnicity were analysed together as the South Asian subgroup. Patients of African and Caribbean ethnicity were grouped together to form the Black subgroup, though we recognize that these groupings may conceal underlying heterogeneity. Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009.

Clinical data collection

Data was captured electronically using an in-house renal information technology programme (File maker pro) at every clinic visit. This included blood pressure measured in sitting position using cuffs appropriate for individual and all clinical events and changes in medication. Ethical approval was sought, but not required, due to the observational nature of the study utilizing routinely collected, anonymised patient data.

Baseline variables were collected at the first clinic visit and subsequently updated at every clinic visit. The study variables were defined as follows; ischaemic heart disease (IHD) included patients who were had a documented history of angina, myocardial infarction or cardiac revascularization. Diabetic retinopathy included patients who had been formally assessed by the diabetic ophthalmology clinic. Peripheral vascular disease (PVD) included patients with a history of intermittent claudication or documented vascular disease on an angiogram, and cerebrovascular disease (CVD) included patients with a past history of transient or persistent vascular neurological deficit.

Estimated glomerular filtration rate (eGFR) was calculated based on the 4 variable MDRD equation which includes a correction for black ethnicity. Serum creatinine was measured using Roche Modular Platform automated analyser. Proteinuria was determined using protein creatinine ratio (Roche Modular Platform automated analyser). Protein creatinine ratio (PCR) was only calculated for patients who had positive proteins on a urine dipstick, and thus individuals with no PCR data were considered to have a value less 15. This was based on a separate unit practice development observation on all dipstick negative urine samples in diabetic patients when analysed had PCR < 15. Glycated haemoglobin (HbA1C) was used to assess glycaemic control (BioRad Turbo 2 automated analyser). Data on systolic and diastolic blood pressure, HbA1C, proteinuria and eGFR were collected every 6 months.

Data coding

Data was cleaned, coded, and analysed using Stata 10. Baseline variables were created for: Average eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), PCR and HbA1c value. PCR was considered both as a linear variable and a binary variable (presence or absence of proteinuria at baseline defined as PCR>15). Medications were coded a constant variable (ever present vs never present) for angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or dual blockade.

Descriptive analysis

Bivariate statistics outlining the population breakdown by ethnicity were conducted. Average length of follow up was calculated for white, black, and south Asian groups. Significant differences in the mean baseline value for numerical variables were estimated using linear regression. Logistic regression was used to examine ethnic differences in the distribution of categorical variables.

Statistical Methods

Unadjusted and adjusted linear regression models were used to determine whether the annual change in eGFR differed by ethnic group. For this analysis, the eGFR values collected every 6 months were collapsed together to form annual averages. To investigate whether the annual decline in eGFR was modified by ethnicity, an interaction term between years of follow up and ethnic group was utilized. The adjusted analysis controlled for age at baseline, gender, presence or absence of vascular disease (defined as any prior diagnosis of CVD, PVD, or IHD), presence or absence of drug treatment (defined as any prior prescription of ACEi, ARBs, or dual blockade), presence or absence of proteinuria at baseline (defined as a baseline PCR value of greater than 15), and baseline eGFR. In addition, the analysis interaction terms to examine the effect of blood pressure and HbA1C being controlled to target in each year of follow-up. The BP target was set at <= 130/80 mmHg and the HbA1C target was <=7.5%.

Results

Population

Out of a total of 356 eligible patients a total of 329 patients with more than 6 years follow up were included. Twenty seven patients were excluded because 10 presented with ESKF and 17 patients had no ethnicity data. Less than 10% of the patients had missing data, which was attributed to missing clinics and less than 5% were lost to

follow up due to death or relocation. The baseline characteristics are shown in table1.

The south Asian group was the youngest, with a shorter duration of diabetes and lower baseline blood pressure in comparison to Whites. Black groups have the shortest duration of diabetes but higher baseline systolic and diastolic blood pressure. Baseline eGFR was highest for south Asian groups and lowest for White groups. Mean HbA1C did not differ between ethnic groups, while baseline proteinuria was highest for south Asian groups followed by White and Black groups. Prevalence of IHD was highest for south Asian patients. Prevalence of other co-morbidities, smoking, and drug prescription did not differ by ethnic group.

Primary end point *(Annual decline in eGFR):*

The overall annual decrease in eGFR was -1.69 in the total population. In the unadjusted linear regression analysis the annual decline in eGFR in white, black and south Asian groups was -1.78, -2.07 and – 1.45 respectively. There was no significant difference in the rate of decline in eGFR between the three groups (Table 2).

Furthermore the adjusted linear regression analysis indicated no significant differences in the annual change in eGFR between the ethnic groups over the entire study period. However the analysis showed that control of blood pressure, gender and degree of renal impairment at baseline were significant predictors of progression (Table 3).

Secondary end points:

The number of patients developing ESKF and total mortality was similar between the three groups (Table 4).

Discussion:

In this single centre longitudinal prospective observational study of patients with diabetic chronic kidney disease the overall annual decrease in eGFR was -1.69 in all three groups. No differences in the rate of progression by ethnic group were evidenced. To date, this is the largest study of its kind in the literature. Higher rates of chronic kidney disease (CKD) progression in south Asians have been reported before by Shaw et al and Earle et al[11,13]. However patients in both studies had significantly smaller numbers than our study and their patients had early CKD at baseline compared with our population who had moderately severe renal impairment at presentation which was an independent predictor of progression of renal failure. One small study (39 patients) in the United Kingdom by Koppiker et al, suggested no difference in the rate of progression between Whites and south Asians[14]. However complete data was available in only 36 patients. Another study in the United States, Salifu et al[12] also suggested that there was no significant difference in progression of diabetic kidney disease between Black and White populations with equivalent diabetic control. Our results are in agreement with these studies by demonstrating lack of interaction between ethnicity and the rate of decline in kidney function.

Blood pressure and glycaemic control are important risk factors for progression of diabetic chronic kidney disease. Generally blood pressure control is more difficult to achieve among Black populations and may contribute towards a faster rate of kidney function decline. One study showed that there was no significant difference in rate of kidney function decline after adjusting for the effects of glycaemic control in Black populations compared with Whites, while others have shown significant difference despite equivalent BP and glycaemic control. A difference in the use of antihypertensive medication including renin angiotensin blocking medication (RAAS) has also been suggested[14,16,17]. In this study there was no significant difference in glycaemic control or the use of renin angiotensin blocking medications in the three groups. However, Blacks

had a significantly higher baseline systolic, diastolic and above target blood pressure. In our previous study we observed a higher prevalence of BP>150/90 in Blacks in a community based cohort with mild CKD[18], a result which is confirmed by this study in a hospital based cohort of patients with DCKD. Although, in this study there was no significant difference in the decline of kidney function between the ethnic groups, the adjusted analysis showed that the lack of control of blood pressure below the target of 130/80 mmHg was independently associated with rapid decline of eGFR underscoring the importance of optimal blood pressure management as a key modifiable risk factor. Moreover, as expected gender and severity of renal impairment were the other significant predictors of progression of diabetic kidney disease (Table 3).

There was relatively a high mortality rate and prevalence of ESKF requiring renal replacement therapy in the entire cohort (Table 4). This may be explained by the high-risk population as shown by high prevalence of overt vascular disease and moderately severe renal impairment at presentation and long duration of follow up. However, there was no significant difference in total mortality and prevalence of end stage kidney disease between the different ethnic groups (Table 4). It is important to note however, that south Asians had a higher baseline eGFR, and this could be explained in part, by ethnic differences in referral patterns to our centre. Primary care physicians may be more likely to refer south Asians with early diabetic kidney disease compared to Whites, reflecting concern that diabetic kidney disease in south Asians is more difficult to control and is associated with a faster rate of decline.

Current national chronic kidney disease (CKD) guidelines do not include ethnicity as a risk factor for CKD[15]. Therefore the recommendation for the management of CKD in general and DCKD in particular for patients from different ethnic minority groups is similar to that for the white population. The results of this study suggest that there is no need for different set of guidelines for different ethnic groups at present and efforts should be directed at determining the reasons behind sub-optimal blood pressure

targets in certain ethnic groups.

Strengths and weaknesses of the study

Strengths of this study include the large number of cases, the completeness of ethnicity and clinical data recording and the prolonged period of follow up. The communities from which these patients are drawn include some of the most socially deprived and multi-ethnic populations in England, hence our results will be of interest to commissioning organisations throughout the UK.

Weaknesses include combining ethnic subgroups into three broad categories, which may mask differences in treatment or progression. We are also unable to identify differences in referral thresholds and patterns by the GP practices in the localities. Other perceived weakness of the study could be combining diabetic patients with type 1 and 2 for analysis. However, in real life setting only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred because of variable period of undiagnosed type 2 diabetes mellitus. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro and micro-vascular chronic complications of diabetes [20].

Conclusion

This study clearly demonstrates that there is no interaction between ethnicity and the rate of progression of chronic kidney disease in patients with diabetes mellitus. Furthermore the prevalence of renal replacement therapy indicating end stage kidney failure, and mortality was also similar between the three groups.

Tables

Legend for tables

Table 1: Baseline characteristics of study participants by ethnic group

Table 2. Unadjusted regression for annual change in eGFR

Table 3: Adjusted linear regression

Table 4: Number of patients developing end stage kidney failure and total mortality

Table 1: Baseline characteristics of study participants by ethnic group

Characteristic	White	Black	South Asian	P value
N	*105*	*75*	*149*	
Baseline Measures				
Mean age	61.3±12.6	62.4±11.3	57.8±11.4)	0.005
Male (%)	61.5	66.2	65.8	0.741
T2DM (%)	85	100	98	<0.001
Duration of diabetes (years)	18.3±11.6	13.4±7.1	14.0±12.9	0.013
Duration of follow up (years)	6.0±2.3	5.0±2.7	5.6±2.4	0.045
Diabetic retinopathy (%)	84	81	76	0.110
Mean eGFR	38.1±19	39.0±21	44.3±21	0.039
Mean Systolic BP	146.6±26	158.3±23	136.6±24	<0.001
Systolic BP >130 mmHG (%)	78.1	86.7	61.7	<0.001
Mean Diastolic BP	76±11	83±15	75±11	0.002
Diastolic BP >80 mmHG (%)	46.7	53.3	37.6	0.066
Mean HBA1c	8.5±1.8	8.8±2.2	8.7±1.9	0.445
HBA1c >7.5% (%)	67.6	69.3	71.1	0.833
PCR>15 mg/mmol (%)	58.2	47.5	64.4	<0.001
Constant Measures				
IHD (%)	28.6	21.3	38.9	0.020
PVD (%)	15.2	10.7	12.1	0.626
CVD (%)	10.5	8.0	10.7	0.799
Statin use (%)	83.8	80.0	80.4	0.742
ACE use (%)	72.4	70.7	73.7	0.894
ARB use (%)	34.3	40.0	41.2	0.519
Dual Blockade (%)	14.3	17.3	20.1	0.483
Current smoker (%)	18.6	13.6	13.1	0.609

*Mean values ± standard deviation

Table 2. Unadjusted regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change***	***95% CI***	***P value***
Overall pop	*-1.69*	*-1.87, -1.53*	*<0.001*
- Slope in White	-1.78	-2.06, -1.49	--
-Additional decline in Black population	-0.31	-0.78, 0.152	0.189
-Additional decline in south Asian population	0.32	-0.06, 0.07	0.099

The annual decline in White patients is -1.78 ml/min
The annual decline in Black patients is -2.07 ml/min
The annual decline in south Asian patients is -1.45 ml/min

Table 3: Adjusted linear regression

Predictor Variables	*Annual Change*	*95% CI*	*P value*
- Years of follow up (Slope in reference pop)	-1.93	-2.31, -1.56	<0.001
- Black * time (Black additional slope)	-0.19	-0.68, 0.30	0.438
- SA * time (South Asian additional slope)	0.08	-0.31, 0.48	0.676
Time varying variables			
BP<=130/80 * time	0.62	0.27, 0.98	**<0.001**
hbA1C <=7.5 * time	0.03	-0.33, 0.39	0.883
Constant variables			
Ethnicity (white is reference category)			
- Black ethnicity	-1.67	-4.97, 1.64	0.322
- SA ethnicity	-0.51	-3.25, 2.23	0.716
Age	0.03	-0.06,0.13	0.466
Gender (female is reference category)	-2.64	-4.87, -0.40	**0.021**
SBP target at baseline	-2.31	-3.89, -0.73	**0.004**
HbA1C value at baseline	-0.66	-2.37, 1.06	0.454
Vascular disease ever (PVD, CVD, IHD)	-1.44	-3.66, 0.79	0.206
Drug treatment ever (ACE, ARB, Dual Block)	0.02	-4.46, 4.50	0.993
Proteinuria at baseline (PCR>15)	0.173	-1.99, 2.33	0.875
Baseline eGFR	1.05	0.99, 1.11	**<0.001**
Constant	-3.18	-11.26, 4.89	0.440

The annual decline in the reference population (White) is -1.93 ml/min
The annual decline in Black patients is -2.12 ml/min
The annual decline in south Asian patients is -1.85 ml/min

Table 4: Number of patients developing end stage kidney failure and total mortality

Characteristic	*White*	*Black*	*South Asian*	*P value Black vs White*	*P value South Asian vs White*	*P Value Black vs SA*
Proportion with end stage kidney failure (%)	32.4	44.0	38.9	0.115	0.291	0.466
Number of Deaths (%)	16.2	20.0	18.8	0.516	0.599	0.829

References

1- Byrne C, Ford D, Gilg J, et al. UK ESRD Incident Rates in 2008: national and centre-specific analyses. UK Renal registry report 2009.

2- Crook ED, Patel SR. Diabetic nephropathy in African-american patients. Cuur Diab Rep 2004;4(6):455-46.

3- Cappuccio FP, Cook DG, Atkinson RW, et al . Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in south London. Heart 1997 78(6):555-563.

4- Burden AC, McNally PG, Feehally J, et al. Increased incidence stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med 9:641–645, 1992.

5- Feehally J, Burden AC, Mayberry JF, et al. Disease variations in Asians in Leicester.Q J Med86:263–269, 1993.

6- Karter A, Ferrara A, Liu J, et al. Ethnic Disparities in Diabetic Complications in an Insured Population. Nephrol Dial Transplant. 2006; 21(8):2178-83.

7- Roderick PJ, Raleigh VS,Hallam L, et al. The need and demand for renal replacement therapy amongst ethnic minorities in England. J Epi-demiol Comm Health 1996;50:334-9.

8- Friedman EA. Diabetic nephropathy in blacks. Transplant Proc 1993;25:2431.

9- Cruickshank JK. Diabetes: contrasts between peoples of black (West Afri can), Indian and white European origin. In: Cruickshank JK, Beevers DG,eds. Ethnic factors in health and disease. London: Wright, 1989.

10- Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends 1997;28:122–7.

11- Shaw P, Baboe F, van Es L, et al. South-Asian type 2 diabetic patients have

higher incidence and faster progression of renal disease compared with Dutch-European diabetic patients. Diabetes Care 2006; 29 (6): 1383-1385.

12- Salifu M, Shah S, Iqbal M et al. Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. Am J Nephrol 2009;30:261-267.

13- Earle KK, Porter KA, Ostberg J, et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001;16(2):286-90.

14- Koppiker N, Feehally J, Raymond N, et al. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. Diabet Med. 1998;15(1):60-5.

15- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association and the Royal College of General Practitioners. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. London: Royal College of Physicians; 2006.

16- Duru O, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the kidney early evaluation program (KEEP). Am J Kidney Dis 2008;51:192-8.

17- Davis TM. Ethnic diversity in type 2 diabetes. Diabet Med. 2008;25 Suppl 2:52-6.

18- Dreyer G, Hull S, Aitken Z, et al. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM (2009) 102 (4): 261-269.

19- Kanaya AM, Adler N, Moffet H, et al. Heterogeneity of Diabetes Outcomes Among Asians and Pacific Islanders in the U.S.The Diabetes Study of Northern California (DISTANCE). Diabetes care 2011; 34(4): 930-937.

20- Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med1999; 341: 1127–1133

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ editions and any other BMJPGL products and sublicences to exploit all subsidiary rights, as set out in our licence.

All authors listed have contributed sufficiently to the project to be included as authors. Dr Mohiuddin and Dr Ali contributed equally as first authors. To the best of our knowledge, no conflict of interest, financial or other, exists.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other peer-reviewed media.

Mr. Richard Sands
Managing Editor, BMJ Open
rsands@bmjgroup.com

Dear Mr Richard Sands,

Re: Manuscript ID bmjopen-2012-001855 entitled "The impact of ethnicity on the progression of diabetic nephropathy: A prospective observational study."

Thank you very much for giving us a chance to resubmit our manuscript after significant revision in the light of very helpful reviewer's comments. We have addressed all the points raised by the reviewers and we believe as a result the quality of manuscript has improved greatly. We are addressing every question point by point in this covering letter and referring to section where these changes are made.

Reviewer: R S Bhopal,
Bruce and John Usher Professor of Public Health University of Edinburgh UK

Competing interests - None.

Comments on: The impact of ethnicity etc by Ali et al

Title
Can ethnicity have an impact? Is it not association rather than impact?

We agree. It is an association. We have changed the title accordingly.

Design/Abstract
Is the design not of a cohort of patients? And, is it not retrospective? That is the way it looks to me.

This study was conceived around 2001. We developed an appropriate electronic data base to capture relevant information longitudinally to address the question posed. We believe it is justified to call this study a prospective observational study.

The abstract is rendered close to unreadable by the abbreviations.

There is an over-emphasis on p-values. The eGFR value in SA's (44) is not similar to blacks (39) and higher than Caucasians (38). Rather blacks and Caucasians are similar.

Abbreviations are removed from the abstract. Wording of the text is now made reader friendly for general readership with no specialist interest in Renal Medicine

Introduction
The abbreviations are a problem. Contrary to the text, blood pressure and hypertension are well known to be less common in South Asians – see systematic review by Agyemang et al (J Hypertension 2002). This is only one example of the fact the authors are not familiar with current literature. Another is the "3.5 times higher mortality in South Asians with diabetes" referring to a 1997 paper by Raleigh. The old and highly selected citations are unhelpful and misleading. The terminology for ethnic groups used – especially Caucasians – has been discarded in the UK since the

1991 census, and the problems of lumping South Asians into one group are also well known in the UK setting. Some considerably work is needed to get up to date.

We are very thankful to Dr Bhopal for his kind suggestions. We have removed where possible all the remarks with conflicting evidence and in general made the focus of introduction and discussion around the question addressed in this manuscript i.e. rate of progression of diabetic chronic kidney disease rather prevalence of hypertension in south Asian.

Methods/ethics
How was ethnic group ascertained?

Ethnicity was self-assigned by the patients (see page 3 paragraph 3)

How are patients referred into this centre and from where?

Patients are referred by general practices from the three primary care trusts: Newham, Tower Hamlets and City & Hackney. (see page 3 paragraph 1)

Was ethical approval sought and achieved and if not, why not?

Ethical approval was sought but was not required because of observational nature of the study utilizing routinely collected anonymised data. (see pages 3-last line and first line page 4)

The source of all data reported needs to be given in methods e.g. on PVD, CVD etc.

This is now addressed in detail on page 4 first paragraph.

How are censored data handled in these models?

This has been clarified on page 3-material and methods section: Third paragraph, line 6. Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009.

Results
In small studies like this one, observations of no difference need to be made with more care than here e.g. it is clear that PCR is higher in South Asians. If the p-value is not significant it just tells us the study is too small. This certainly applies to most outcomes. The authors have clearly not followed the move away from p-values to emphasis an effect sizes and confidence intervals and it seems unusual to find tables of p-values in this era when they have been so heavily criticised.

The analysis of entire data has been revised as per your and Dr Colin M Fischbacher suggestions. Figures are removed and instead 4 tables used with 95% CI and appropriate p values to address you questions. Clearly in the light of new analysis south Asian ethnicity is no longer an independent predictor of rate of progression diabetic chronic disease. Discussion is revised in the light of latest results (see pages-4-6, data coding, descriptive analysis, statistical methods and results with table1-4)

Discussion
The authors are right to focus on quantitative outcomes for which the statistical power of the study is higher than for binary outcomes. If the entire paper was focused on eGFR it might cohere better

and be more reliable. The authors should set their findings in the population context including studies showing ethnic variation in community samples e.g. higher proteinuria in South Asians (Fischbacher et al, Diabetic Medicine 2003). The big question is – why is eGFR higher and that needs detailed research moving away from reporting associations with a few variable, and starting with a hypothesis.

We have practically rewritten the discussions and most of the above mentioned concerned are now addressed. Notably comment has been made about early referral of south Asians on page 8 second paragraph as *"Primary care physicians may be more likely to refer south Asians with early diabetic kidney disease compared to Whites, reflecting concern that diabetic kidney disease in south Asians is more difficult to control and is associated with a faster rate of decline".*

Overall
I think this manuscript needs further thought and reworking before it is ready for publication. Nonetheless, these data are rare and I hope the authors will persevere.

We appreciate your encouragement about us persevering and thank you for helpful comments. Certainly manuscript has improved greatly as a result.

Reviewer: Dr Colin M Fischbacher,
Consultant in Public Health Medicine
Information Services Division (ISD),
NHS National Services
Scotland

I have no competing interests to declare.

This is an interesting, large and worthwhile study with important research questions which are clearly set out. The study design is entirely appropriate to the question. The main weakness is the analysis, which needs to be described more clearly, reported more fully and possibly developed further using more appropriate methods.

Thank you very much for your comments and recommendations. We have taken on board all of them. See below.

It would be helpful to have more details of the setting; the participating hospitals and clinics and their catchment area should be briefly mentioned and it would be good to have some indication (even if anecdotal) of what proportion of cases of diabetic nephropathy would have been referred to the clinics conducting this study.

This issue is now clarified on page 3-material and methods section: first paragraph. Reference 18 is our own. It is the only renal clinic for these three boroughs and gets all renal referrals from this catchment area.

The terminology may be confusing for the non-specialist. The cohort is defined in the text as having diabetic nephropathy but in the abstract as having diabetic chronic kidney disease. These two obviously overlap but it might be clearer to use just one term throughout.

We have done so. We have preferred diabetic chronic disease.

The authors have chosen to include both type 1 and type 2 diabetes which obviously has the advantage of increasing the numbers of participants available for analysis, particularly for the "Caucasian" group. However I wonder whether this is at the cost of grouping together conditions with different clinical characteristics in terms of renal outcomes. If they feel that the differences between the two groups are sufficiently minor to combine them the authors might provide some justification for this decision in the discussion section. The alternative would be to exclude those with type 1 diabetes.

You have made valid point. In real life only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80 mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro- and micro-vascular chronic complications of diabetes (20). We added this in the perceived weakness section of the study Page 9.

20. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med1999; 341: 1127–1133

Ideally ethnicity should be self-defined but this information may not be available. It would be helpful to know how ethnic group was assigned in this study - whether based on the judgement of those providing medical care, inspection of names or direct questions to the participants. There is some minor inconsistency in the terms used - eg "Afro-Caribbean" in table 1 and "Black" in table 3 - and this should be clarified.

This important point has been discussed in detail on page Material and methods 3 paragraph page 3 and reads *as "Ethnicity was self-assigned by the patient. Patients were grouped according to the ethnic categories of the 2001 census. For the purpose of this study patients of Indian, Bangladeshi and Pakistani ethnicity were analysed together as the South Asian subgroup. Patients of African and Caribbean ethnicity were grouped together to form the Black subgroup, though we recognize that these groupings may conceal underlying heterogeneity".*

It would be helpful to know when the participants were recruited to the study and whether recruitment continued during the whole follow-up period (2000-2009).

Please see Material and methods 3 paragraph page 3 reads as "*Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009".*

Some variables were collected at baseline and it would be helpful to know whether these were all collected at the first clinic visit or perhaps within the first month or other period after first presentation.

See page 4 first paragraph and reads "*Baseline variables were collected at the first clinic visit and subsequently updated at every clinic visit".*

The methods state that the outcome variable (change in eGFR) was calculated by subtracting the baseline from the final eGFR and dividing by follow-up time. This is not an ideal method as it gives undue weight to the first and last observations and discards information from the intervening observations. A preferable method would be to estimate the average rate of decline using linear regression. That average rate of decline (the beta co-efficient from a linear model) could then be used as the outcome variable.

The description of the multivariate analysis appears to describe four models: unadjusted, a first model, a second fully adjusted model and a final adjusted model. However table 4 shows results for only two models and it was not clear to me which ones these were. This point should be clarified. I would recommend a footnote to table 4 describing the variables included in each model - in my view this makes it easier for the reader to follow.

Logistic regression is mentioned in the methods section but I wasn't sure where these results were reported.

All above points are now addressed by reanalysis of whole data set per your recommendations. Please see Descriptive analysis, Statistical methods and Results section. Please see pages 5-6. and Tables 1 to 4. Figures have been sacrificed.

It doesn't make sense to compare the proportion in each CKD category separately (as shown in table 1) as they depend on each other - more in one category means less in another one. One approach would be to use a chi-squared test to test whether the difference in distribution across categories was different between ethnic groups - a separate p value could be shown for each ethnic group compared with the "Caucasians".

We agree with you about CKD category comment and taken it out from table 1.

The methods section should define all the conditions described in table 1 - for example the definitions of IHD, CVD, PVD and retinopathy used in the study should be briefly defined.

It is now provided on page 4 first paragraph and reads as *"The study variables were defined as follows; ischaemic heart disease (IHD) included patients who were had a documented history of angina, myocardial infarction or cardiac revascularization. Diabetic retinopathy included patients who had been formally assessed by the diabetic ophthalmology clinic. Peripheral vascular disease (PVD) included patients with a history of intermittent claudication or documented vascular disease on an angiogram, and cerebrovascular disease (CVD) included patients with a past history of transient or persistent vascular neurological deficit ".*

The references are on the whole relevant and up to date. The 2004 Health Survey for England provides more up to date and precise information on the risk of diabetes and hypertension among ethnic minorities than do some of the studies cited. The authors should distinguish between studies of US ethnic minorities and European or UK studies. The definitions of ethnicity in different countries are often different - for example the study by Chandie Shaw (reference 11) uses the term "South Asian" to denote Dutch Surinamese, a very different group from the "South Asians" in the present study or from the Pacific "Asians" in reference 20. It should probably not be assumed that findings in US Blacks can be automatically be extrapolated to UK Afro-Caribbean populations, though these studies are certainly of interest for the discussion. The study by Crook (reference 14) does not include any ethnic comparison and so may be of less relevance.

These issues have been rectified now in discussion section which is re-written. Please see page 7 and first paragraph.

The results should indicate what proportion of subjects had missing data and how many were lost to follow-up.

This information is now provided on page 6 first paragraph and reads as *"Twenty seven patients were excluded because 10 presented with ESKF and 17 patients had no ethnicity data. Less than 10% of the patients had missing data, which was attributed to missing clinics and less than 5% were lost to follow up due to death or relocation".*

There appears to be some repetition in the results section with the same points being made at the end of the second and the third paragraphs. I wondered whether the third paragraph should have come before the second one?

This has been rectified. Please page 6 Primary end point and secondary end points:

It would be helpful to make a clear distinction in the results between baseline data and data collected during follow-up.

Please see Statistical methods and tables 2 and 3 : self explanatory. Page 5

Blood pressure among South Asians was said to be lower at baseline - though I think this applied only to systolic BP.

This has been rectified and taken on board Dr Bhopal's suggestion. See Table 1.

Results for "proteinuria" (defined earlier as PCR>15) are mentioned in the results section but not shown in table 1 - I wonder whether this was an oversight?

Baseline PCR is said to be similar in the three groups but table 1 shows it to be notably higher among South Asians. The difference is obviously not statistically significant but I think I would be less confident about stating that PCR is truly similar.

PCR in table 1 clearly has a skewed distribution and would be better presented as a median and interquartile range, as was done in table 2.

This is now provided in Table 1. PCR > 15 issue has been clarified also on page 4 paragraph 2 and reads *as* *"Protein creatinine ratio (PCR) was only calculated for patients who had positive proteins on a urine dipstick, and thus individuals with no PCR data were considered to have a value less 15. This was based on a separate unit practice development observation on all dipstick negative urine samples in diabetic patients when analysed had PCR < 15"*

The statistical tests in table 1 address the question of whether the variation across the three ethnic groups is greater than would be expected by chance. Small p values however give no indication of which group is different. I wondered whether the authors had considered presenting p values for the Caucasian/Afro-Caribbean comparison separately from the South Asian/Caucasian comparison?

This has been rectified. Please see Table 1 and explanation in results section page 6 and first paragraph which reads as *"The south Asian group was the youngest, with a shorter duration of diabetes and lower baseline blood pressure in comparison to Whites. Black groups have the shortest duration of diabetes but higher baseline systolic and diastolic blood pressure. Baseline*

eGFR was highest for south Asian groups and lowest for White groups. Mean HbA1C did not differ between ethnic groups, while baseline proteinuria was highest for south Asian groups followed by White and Black groups. Prevalence of IHD was highest for south Asian patients. Prevalence of other co-morbidities, smoking, and drug prescription did not differ by ethnic group".

I don't think the authors have justified their conclusion that the high rate of decline in eGFR in the Afro-Caribbean group is related to hypertension. Perhaps this could be justified if more information was provided about the models in table 4. I would want to know how much higher the rate of decline was before and after adjustment for hypertension.

Adjusted linear regression analysis has addressed this question. Please see Table 3. Blood pressure, gender and degree of renal impairment at presentation were the only independent predictors of progression.

The authors state at the end of the introduction that one of the primary outcomes was a composite of RRT and death. However no results are presented on this outcome. The authors should say whether this analysis was done and not presented, or whether it was not carried out.
It would be helpful to have some comments on the figures as part of the results section.

Table 4 and secondary end points section on page 6 provided.

The table and figure titles should say what data are presented rather than commenting on the results - for example for table 4 I would suggest something along the lines of "Association between baseline and follow-up variables and decline in eGFR: estimates from linear regression models".

The title of table 1 makes it clear that it relates exclusively to baseline characteristics so I think that it is not necessary to include the word "baseline" in the description of any of the variables. Figures should be given to the same precision throughout - for example for current smokers (last line of table 1) "13" for South Asians is less precise than "13.6" for Afro-Caribbeans and should be given as "13.0".
In table 1 p values are not given for duration of follow up or serum creatinine. This should be corrected or clarified. (Duration of follow-up is not a baseline characteristic and might be better in table 2.) The authors should check that this duration is normally distributed - otherwise median duration might be better reported. The range of values for follow-up would also be of interest.

It was not clear to me whether the values in table 2 relate to baseline or follow-up results.

Figures are removed and 4 tables carry all the relevant information. Accompanying legends address your concerns.

In table 3 reporting mortality as a percentage of each cohort does not take account of either differences in follow-up time between groups or of censoring as a result of loss to follow-up. Further, presenting mortality unadjusted for age may be of limited value when the South Asians are clearly younger. The same points apply to the percentage requiring renal replacement therapy, though here censoring by death also affects an appreciable number of participants and needs to be taken into account. The options here might be to report age/sex standardised mortality rates based on person-years at risk, or better still, to use survival methods if suitable statistical advice is available.

Please see Table 4. We have stuck with crude prevalences of ESKF and total mortality as it was a secondary point and reasons behind was to see if differences in these numbers if present may affect primary end point i.e. rate of progression of renal failure. Reassuringly it was not the case.

Table 4 needs some expansion to present the results of the multivariate analysis. In table 4a, the results should show the difference in eGFR decline (the beta co-efficient from linear regression) with a 95% confidence interval and optionally a p value. (For example for South Asian ethnicity the decline might be given as 0.8 (95% CI 0.6, 0.9); meaning that the decline was 0.8 higher than that in the Caucasian group.) Table 4a should show all the variables examined in univariate analysis and not just the significant ones. The same points apply to table 4b, where it should also be clear what adjustments were made. Presenting the parameter estimate for Afro-Caribbeans in table 4b would make clear the change in the estimate resulting from adjustment for hypertension, and might support the authors' point in their conclusions which I discussed earlier.

Tables 2 and 3 and accompanying text in statistical methods addresses your valid concerns.

As mentioned above, I think the discussion needs to be clearer about the countries and ethnic groups included in the various studies in the literature. It is noteworthy that both UK studies mentioned (Earle and Koppiker) had very much smaller numbers than the present study and it might be worth giving the numbers in the text to make this point clear.

Done. Please see page 7 first paragraph.

The discussion section should include a paragraph on the strengths and weaknesses of this study. The large sample size and the paucity of previous UK research in this area appear to be important strengths while uncertainty about the extent to which the cases represent the source population might be a weakness.

Provided on page 9 as Strengths and weakness section and reads as
"Strengths of this study include the large number of cases, the completeness of ethnicity and clinical data recording and the prolonged period of follow up. The communities from which these patients are drawn include some of the most socially deprived and multi-ethnic populations in England, hence our results will be of interest to commissioning organisations throughout the UK. Weaknesses include combining ethnic subgroups into three broad categories, which may mask differences in treatment or progression. We are also unable to identify differences in referral thresholds and patterns by the GP practices in the localities. Other perceived weakness of the study could be combining diabetic patients with type 1 and 2 for analysis. However, in real life setting only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred because of variable period of undiagnosed type 2 diabetes mellitus. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80 mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro and micro-vascular chronic complications of diabetes 20"

The final sentence of the discussion might claim too much and I think could be better expressed.

Conclusions are rewritten in the light of new analysis. Please page 9 last paragraph which reads as
"This study clearly demonstrates that there is no interaction between ethnicity and the rate of progression of chronic kidney disease in patients with diabetes mellitus. Furthermore the prevalence of renal replacement therapy indicating end stage kidney failure, and mortality was also similar between the three groups".

I assume that ethical approval was not needed for this study, but a sentence on ethical approval should be included to make this clear.

This issue has been clarified on page 3 last line and first line on page 4. It reads *as* *"Ethical approval was sought, but not required, due to the observational nature of the study utilizing routinely collected, anonymised patient data".*

This is an important study which it would be good to see published. The analysis is not straightforward and if the authors have access to expert statistical advice it might greatly improve the value of the study.

Thank you once again for your critic and very helpful and constructive suggestion.

Regards

Professor M. M. Yaqoob MD FRCP PhD.

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

[1*]O. Ali — Core medical trainee

[1*]A. Mohiuddin — Senior clinical fellow

[2]R. Mathur — Research Fellow

[1]G. Dreyer — Specialist registrar in Nephrology

[2] S. Hull — Reader in Primary Care Development

[1]M.M Yaqoob — Professor of Nephrology

[1] Department of Nephrology, Royal London Hospital, London.

2 Department of Primary Care and Public Health, Queen Mary, University of London

*Dr Mohiuddin and Dr Ali contributed equally.

[*]Corresponding author

Professor M.M.Yaqoob.

Department of Nephrology

Royal London Hospital

Whitechapel road

London E1 1BB

Email: m.m.yaqoob@qmul.ac.uk

Word count: 2659 excluding tables and references

Keywords: Diabetic chronic kidney disease, end stage kidney failure, blood pressure, proteinuria.

Abstract:

Objective: To compare the rate of progression of diabetic chronic kidney disease in different ethnic groups.

Design: Prospective longitudinal observational study.

Participants: All new patients attending a tertiary renal unit in east London with diabetic chronic kidney disease between 2000 and 2007 and followed up till 2009 were included. Patients presenting with acute end stage kidney failure were excluded.

Main outcome measures: The primary outcome was annual decline in estimated glomerular filtration rate (eGFR) in different ethnic groups. Secondary end points were the number of patients developing end stage kidney failure and total mortality during the study period.

Results: 329 patients (age 60 years ± 11.9, 208 men) were studied comprising 149 south Asian, 105 White and 75 Black patients. Mean follow up was over 6 years and similar in all 3 groups. South Asians were younger and had a higher baseline eGFR, but both systolic and diastolic blood pressure was higher in blacks ($p<0.05$). Baseline proteinuria was highest for south Asian groups followed by White and Black groups. Adjusted linear regression analysis showed that an annual decline in eGFR was not significantly different between the three groups. The number of patients developing end stage kidney failure and total mortality was similar between the three groups. Angiotensin converting enzyme or angiotensin receptor blockers use, and glycated haemoglobin (HbA1C) were similar at baseline and through out the study period.

Conclusion: We conclude that ethnicity is not an independent factor in the rate of progression renal failure in patients with diabetic chronic kidney disease.

Introduction:

Diabetic chronic kidney disease (DCKD) is one of the leading cause of end-stage kidney failure (ESKF), accounting for 21% of all such cases in the UK[1]. Suboptimal glycaemic and blood pressure control, development of albuminuria and family history are important risk factors for the development of chronic kidney disease in diabetic patients. There is a higher prevalence of diabetes mellitus (DM) and ESKF in black and south Asian populations with prevalence ratios for DM of 2.7 and 3.8 respectively[2, 3, 4,5,6]. Diabetic chronic kidney disease and end stage kidney failure are significantly more common in south Asian populations with a reported relative risk of up to 14 compared to Whites[4]. Similarly, a number of studies have demonstrated a higher prevalence of diabetic chronic kidney disease and end stage kidney failure in Black populations[7,8,9]. One such study suggests a relative risk of 5.8 in south Asians and 6.5 in Blacks[7]. Mortality is also 3.5 times higher in south Asian and Black populations with diabetes compared to Whites in England and Wales[10]. The higher incidence of ESKF in south Asian and Black populations may be related to higher incidence and poorer control of diabetes and hypertension. However, it may also be related to faster progression of diabetic chronic kidney disease in ethnic minority populations. There are conflicting reports on progression of diabetic chronic kidney disease in these population subgroups. Higher rates of kidney function decline have been reported in some studies while others have failed to show this trend[11-14,19].

Most studies comparing progression of diabetic chronic kidney disease in ethnically diverse populations have either been small or had short duration of follow up. The renal clinic at the Royal London Hospital in east London serves an ethnically diverse population in a large urban centre. The aim of our study is firstly to determine whether the rate of kidney function decline differs by ethnic group after controlling for demographic characteristics and clinical parameters known to be associated with progression of chronic kidney disease, and secondly, to examine the number of patients developing ESKF and total mortality by ethnicity.

Materials and Methods:

Population

The study was conducted at the Royal London hospital, which serves as a tertiary referral centre for three primary care trusts in east London; Newham, Tower Hamlets and City & Hackney, with a combined GP registered population of 885,625 at the end of 2011. The prevalence of CKD among diabetics, based on a local study, is 18%[18].

All adult patients above the age of 18 years with biopsy proven or clinical diagnosis of diabetic chronic kidney disease (where all secondary causes were excluded) attending our kidney outpatient clinic were included in the study. Any other diagnosis of chronic kidney disease, and those presenting acutely with ESKF were excluded from the study.

Ethnicity was self-assigned by the patient. Patients were grouped according to the ethnic categories of the 2001 census. For the purpose of this study patients of Indian, Bangladeshi and Pakistani ethnicity were analysed together as the South Asian subgroup. Patients of African and Caribbean ethnicity were grouped together to form the Black subgroup, though we recognize that these groupings may conceal underlying heterogeneity. Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009.

Clinical data collection

Data was captured electronically using an in-house renal information technology programme (File maker pro) at every clinic visit. This included blood pressure measured in sitting position using cuffs appropriate for individual and all clinical events and changes in medication. Ethical approval was sought, but not required, due to the observational nature of the study utilizing routinely collected, anonymised patient data.

Baseline variables were collected at the first clinic visit and subsequently updated at every clinic visit. The study variables were defined as follows; ischaemic heart disease (IHD) included patients who were had a documented history of angina, myocardial infarction or cardiac revascularization. Diabetic retinopathy included patients who had been formally assessed by the diabetic ophthalmology clinic. Peripheral vascular disease (PVD) included patients with a history of intermittent claudication or documented vascular disease on an angiogram, and cerebrovascular disease (CVD) included patients with a past history of transient or persistent vascular neurological deficit.

Estimated glomerular filtration rate (eGFR) was calculated based on the 4 variable MDRD equation which includes a correction for black ethnicity. Serum creatinine was measured using Roche Modular Platform automated analyser. Proteinuria was determined using protein creatinine ratio (Roche Modular Platform automated analyser). Protein creatinine ratio (PCR) was only calculated for patients who had positive proteins on a urine dipstick, and thus individuals with no PCR data were considered to have a value less 15. This was based on a separate unit practice development observation on all dipstick negative urine samples in diabetic patients when analysed had PCR < 15. Glycated haemoglobin (HbA1C) was used to assess glycaemic control (BioRad Turbo 2 automated analyser). Data on systolic and diastolic blood pressure, HbA1C, proteinuria and eGFR were collected every 6 months.

Data coding

Data was cleaned, coded, and analysed using Stata 10. Baseline variables were created for: Average eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), PCR and HbA1c value. PCR was considered both as a linear variable and a binary variable (presence or absence of proteinuria at baseline defined as PCR>15). Medications were coded a constant variable (ever present vs never present) for angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or dual blockade.

Descriptive analysis

Bivariate statistics outlining the population breakdown by ethnicity were conducted. Average length of follow up was calculated for white, black, and south Asian groups. Significant differences in the mean baseline value for numerical variables were estimated using linear regression. Logistic regression was used to examine ethnic differences in the distribution of categorical variables.

Statistical Methods

Unadjusted and adjusted linear regression models were used to determine whether the annual change in eGFR differed by ethnic group. For this analysis, the eGFR values collected every 6 months were collapsed together to form annual averages. To investigate whether the annual decline in eGFR was modified by ethnicity, an interaction term between years of follow up and ethnic group was utilized. The adjusted analysis controlled for age at baseline, gender, presence or absence of vascular disease (defined as any prior diagnosis of CVD, PVD, or IHD), presence or absence of drug treatment (defined as any prior prescription of ACEi, ARBs, or dual blockade), presence or absence of proteinuria at baseline (defined as a baseline PCR value of greater than 15), and baseline eGFR. In addition, the analysis interaction terms to examine the effect of blood pressure and HbA1C being controlled to target in each year of follow-up. The BP target was set at <= 130/80 mmHg and the HbA1C target was <=7.5%.

Results

Population

Out of a total of 356 eligible patients a total of 329 patients with more than 6 years follow up were included. Twenty seven patients were excluded because 10 presented with ESKF and 17 patients had no ethnicity data. Less than 10% of the patients had

missing data, which was attributed to missing clinics and less than 5% were lost to follow up due to death or relocation. The baseline characteristics are shown in table1.

The south Asian group was the youngest, with a shorter duration of diabetes and lower baseline blood pressure in comparison to Whites. Black groups have the shortest duration of diabetes but higher baseline systolic and diastolic blood pressure. Baseline eGFR was highest for south Asian groups and lowest for White groups. Mean HbA1C did not differ between ethnic groups, while baseline proteinuria was highest for south Asian groups followed by White and Black groups. Prevalence of IHD was highest for south Asian patients. Prevalence of other co-morbidities, smoking, and drug prescription did not differ by ethnic group.

Primary end point *(Annual decline in eGFR):*

The overall annual decrease in eGFR was -1.69 in the total population. In the unadjusted linear regression analysis the annual decline in eGFR in white, black and south Asian groups was -1.78, -2.07 and – 1.45 respectively. There was no significant difference in the rate of decline in eGFR between the three groups (Table 2).

Furthermore the adjusted linear regression analysis indicated no significant differences in the annual change in eGFR between the ethnic groups over the entire study period. However the analysis showed that control of blood pressure, gender and degree of renal impairment at baseline were significant predictors of progression (Table 3).

Secondary end points:

The number of patients developing ESKF and total mortality was similar between the three groups (Table 4).

Discussion:

In this single centre longitudinal prospective observational study of patients with diabetic chronic kidney disease the overall annual decrease in eGFR was -1.69 in all three groups. No differences in the rate of progression by ethnic group were evidenced. To date, this is the largest study of its kind in the literature. Higher rates of chronic kidney disease (CKD) progression in south Asians have been reported before by Shaw et al and Earle et al[11,13]. However patients in both studies had significantly smaller numbers than our study and their patients had early CKD at baseline compared with our population who had moderately severe renal impairment at presentation which was an independent predictor of progression of renal failure. One small study (39 patients) in the United Kingdom by Koppiker et al, suggested no difference in the rate of progression between Whites and south Asians[14]. However complete data was available in only 36 patients. Another study in the United States, Salifu et al[12] also suggested that there was no significant difference in progression of diabetic kidney disease between Black and White populations with equivalent diabetic control. Our results are in agreement with these studies by demonstrating lack of interaction between ethnicity and the rate of decline in kidney function.

Blood pressure and glycaemic control are important risk factors for progression of diabetic chronic kidney disease. Generally blood pressure control is more difficult to achieve among Black populations and may contribute towards a faster rate of kidney function decline. One study showed that there was no significant difference in rate of kidney function decline after adjusting for the effects of glycaemic control in Black populations compared with Whites, while others have shown significant difference despite equivalent BP and glycaemic control. A difference in the use of antihypertensive medication including renin angiotensin blocking medication (RAAS) has also been suggested[14,16,17]. In this study there was no significant difference in glycaemic control or the use of renin angiotensin blocking medications in the three groups. However, Blacks

had a significantly higher baseline systolic, diastolic and above target blood pressure. In our previous study we observed a higher prevalence of BP>150/90 in Blacks in a community based cohort with mild CKD[18], a result which is confirmed by this study in a hospital based cohort of patients with DCKD. Although, in this study there was no significant difference in the decline of kidney function between the ethnic groups, the adjusted analysis showed that the lack of control of blood pressure below the target of 130/80 mmHg was independently associated with rapid decline of eGFR underscoring the importance of optimal blood pressure management as a key modifiable risk factor. Moreover, as expected gender and severity of renal impairment were the other significant predictors of progression of diabetic kidney disease (Table 3).

There was relatively a high mortality rate and prevalence of ESKF requiring renal replacement therapy in the entire cohort (Table 4). This may be explained by the high-risk population as shown by high prevalence of overt vascular disease and moderately severe renal impairment at presentation and long duration of follow up. However, there was no significant difference in total mortality and prevalence of end stage kidney disease between the different ethnic groups (Table 4). It is important to note however, that south Asians had a higher baseline eGFR, and this could be explained in part, by ethnic differences in referral patterns to our centre. Primary care physicians may be more likely to refer south Asians with early diabetic kidney disease compared to Whites, reflecting concern that diabetic kidney disease in south Asians is more difficult to control and is associated with a faster rate of decline.

Current national chronic kidney disease (CKD) guidelines do not include ethnicity as a risk factor for CKD[15]. Therefore the recommendation for the management of CKD in general and DCKD in particular for patients from different ethnic minority groups is similar to that for the white population. The results of this study suggest that there is no need for different set of guidelines for different ethnic groups at present and efforts should be directed at determining the reasons behind sub-optimal blood pressure

targets in certain ethnic groups.

Strengths and weaknesses of the study

Strengths of this study include the large number of cases, the completeness of ethnicity and clinical data recording and the prolonged period of follow up. The communities from which these patients are drawn include some of the most socially deprived and multi-ethnic populations in England, hence our results will be of interest to commissioning organisations throughout the UK.

Weaknesses include combining ethnic subgroups into three broad categories, which may mask differences in treatment or progression. We are also unable to identify differences in referral thresholds and patterns by the GP practices in the localities. Other perceived weakness of the study could be combining diabetic patients with type 1 and 2 for analysis. However, in real life setting only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred because of variable period of undiagnosed type 2 diabetes mellitus. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro and micro-vascular chronic complications of diabetes [20].

Conclusion

This study clearly demonstrates that there is no interaction between ethnicity and the rate of progression of chronic kidney disease in patients with diabetes mellitus. Furthermore the prevalence of renal replacement therapy indicating end stage kidney failure, and mortality was also similar between the three groups.

Tables

Legend for tables

Table 1: Baseline characteristics of study participants by ethnic group

Table 2. Unadjusted regression for annual change in eGFR

Table 3: Adjusted linear regression

Table 4: Number of patients developing end stage kidney failure and total mortality

Table 1: Baseline characteristics of study participants by ethnic group

Characteristic	White	Black	South Asian	P value
N	*105*	*75*	*149*	
Baseline Measures				
Mean age	61.3±12.6	62.4±11.3	57.8±11.4)	0.005
Male (%)	61.5	66.2	65.8	0.741
T2DM (%)	85	100	98	<0.001
Duration of diabetes (years)	18.3±11.6	13.4±7.1	14.0±12.9	0.013
Duration of follow up (years)	6.0±2.3	5.0±2.7	5.6±2.4	0.045
Diabetic retinopathy (%)	84	81	76	0.110
Mean eGFR	38.1±19	39.0±21	44.3±21	0.039
Mean Systolic BP	146.6±26	158.3±23	136.6±24	<0.001
Systolic BP >130 mmHG (%)	78.1	86.7	61.7	<0.001
Mean Diastolic BP	76±11	83±15	75±11	0.002
Diastolic BP >80 mmHG (%)	46.7	53.3	37.6	0.066
Mean HBA1c	8.5±1.8	8.8±2.2	8.7±1.9	0.445
HBA1c >7.5% (%)	67.6	69.3	71.1	0.833
PCR>15 mg/mmol (%)	58.2	47.5	64.4	<0.001
Constant Measures				
IHD (%)	28.6	21.3	38.9	0.020
PVD (%)	15.2	10.7	12.1	0.626
CVD (%)	10.5	8.0	10.7	0.799
Statin use (%)	83.8	80.0	80.4	0.742
ACE use (%)	72.4	70.7	73.7	0.894
ARB use (%)	34.3	40.0	41.2	0.519
Dual Blockade (%)	14.3	17.3	20.1	0.483
Current smoker (%)	18.6	13.6	13.1	0.609

*Mean values ± standard deviation

Table 2. Unadjusted regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change***	***95% CI***	***P value***
Overall pop	*-1.69*	*-1.87, -1.53*	*<0.001*
- Slope in White	-1.78	-2.06, -1.49	--
-Additional decline in Black population	-0.31	-0.78, 0.152	0.189
-Additional decline in south Asian population	0.32	-0.06, 0.07	0.099

The annual decline in White patients is -1.78 ml/min
The annual decline in Black patients is -2.07 ml/min
The annual decline in south Asian patients is -1.45 ml/min

Table 3: Adjusted linear regression

Predictor Variables	***Annual Change***	***95% CI***	***P value***
- Years of follow up (Slope in reference pop)	-1.93	-2.31, -1.56	<0.001
- Black * time (Black additional slope)	-0.19	-0.68, 0.30	0.438
- SA * time (South Asian additional slope)	0.08	-0.31, 0.48	0.676
Time varying variables			
BP<=130/80 * time	0.62	0.27, 0.98	**<0.001**
hbA1C <=7.5 * time	0.03	-0.33, 0.39	0.883
Constant variables			
Ethnicity (white is reference category)			
- Black ethnicity	-1.67	-4.97, 1.64	0.322
- SA ethnicity	-0.51	-3.25, 2.23	0.716
Age	0.03	-0.06,0.13	0.466
Gender (female is reference category)	-2.64	-4.87, -0.40	**0.021**
SBP target at baseline	-2.31	-3.89, -0.73	**0.004**
HbA1C value at baseline	-0.66	-2.37, 1.06	0.454
Vascular disease ever (PVD, CVD, IHD)	-1.44	-3.66, 0.79	0.206
Drug treatment ever (ACE, ARB, Dual Block)	0.02	-4.46, 4.50	0.993
Proteinuria at baseline (PCR>15)	0.173	-1.99, 2.33	0.875
Baseline eGFR	1.05	0.99, 1.11	**<0.001**
Constant	-3.18	-11.26, 4.89	0.440

The annual decline in the reference population (White) is -1.93 ml/min
The annual decline in Black patients is -2.12 ml/min
The annual decline in south Asian patients is -1.85 ml/min

Table 4: Number of patients developing end stage kidney failure and total mortality

Characteristic	*White*	*Black*	*South Asian*	*P value Black vs White*	*P value South Asian vs White*	*P Value Black vs SA*
Proportion with end stage kidney failure (%)	32.4	44.0	38.9	0.115	0.291	0.466
Number of Deaths (%)	16.2	20.0	18.8	0.516	0.599	0.829

References

1- Byrne C, Ford D, Gilg J, et al. UK ESRD Incident Rates in 2008: national and centre-specific analyses. UK Renal registry report 2009.

2- Crook ED, Patel SR. Diabetic nephropathy in African-american patients. Cuur Diab Rep 2004;4(6):455-46.

3- Cappuccio FP, Cook DG, Atkinson RW, et al . Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in south London. Heart 1997 78(6):555-563.

4- Burden AC, McNally PG, Feehally J, et al. Increased incidence stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med 9:641–645, 1992.

5- Feehally J, Burden AC, Mayberry JF, et al. Disease variations in Asians in Leicester.Q J Med86:263–269, 1993.

6- Karter A, Ferrara A, Liu J, et al. Ethnic Disparities in Diabetic Complications in an Insured Population. Nephrol Dial Transplant. 2006; 21(8):2178-83.

7- Roderick PJ, Raleigh VS,Hallam L, et al. The need and demand for renal replacement therapy amongst ethnic minorities in England. J Epi-demiol Comm Health 1996;50:334-9.

8- Friedman EA. Diabetic nephropathy in blacks. Transplant Proc 1993;25:2431.

9- Cruickshank JK. Diabetes: contrasts between peoples of black (West Afri can), Indian and white European origin. In: Cruickshank JK, Beevers DG,eds. Ethnic factors in health and disease. London: Wright, 1989.

10- Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends 1997;28:122–7.

11- Shaw P, Baboe F, van Es L, et al. South-Asian type 2 diabetic patients have

higher incidence and faster progression of renal disease compared with Dutch-European diabetic patients. Diabetes Care 2006; 29 (6): 1383-1385.

12- Salifu M, Shah S, Iqbal M et al. Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. Am J Nephrol 2009;30:261-267.

13- Earle KK, Porter KA, Ostberg J, et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001;16(2):286-90.

14- Koppiker N, Feehally J, Raymond N, et al. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. Diabet Med. 1998;15(1):60-5.

15- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association and the Royal College of General Practitioners. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. London: Royal College of Physicians; 2006.

16- Duru O, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the kidney early evaluation program (KEEP). Am J Kidney Dis 2008;51:192-8.

17- Davis TM. Ethnic diversity in type 2 diabetes. Diabet Med. 2008;25 Suppl 2:52-6.

18- Dreyer G, Hull S, Aitken Z, et al. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM (2009) 102 (4): 261-269.

19- Kanaya AM, Adler N, Moffet H, et al. Heterogeneity of Diabetes Outcomes Among Asians and Pacific Islanders in the U.S.The Diabetes Study of Northern California (DISTANCE). Diabetes care 2011; 34(4): 930-937.

20- Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med1999; 341: 1127–1133

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001855.R2
Article Type:	Research
Date Submitted by the Author:	16-Jan-2013
Complete List of Authors:	Ali, Omer; Royal london hospital, Nephrology Mohiuddin, Atif; Royal London Hospital, Nephrology Mathur, Rohini; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Dreyer, Gavin; Royal London Hospital, Nephrology Hull, Sally; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Yaqoob, Magdi; Royal London Hospital, Nephrology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Diabetes and endocrinology, Renal medicine
Keywords:	Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Chronic renal failure < NEPHROLOGY, End stage renal failure < NEPHROLOGY, Nephrology < INTERNAL MEDICINE

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

[1*]O. Ali Core medical trainee

[1*]A. Mohiuddin Senior clinical fellow

[2]R. Mathur Research Fellow

[1]G. Dreyer Specialist registrar in Nephrology

[2] S. Hull Reader in Primary Care Development

[1]M.M Yaqoob Professor of Nephrology

[1] Department of Nephrology, Royal London Hospital, London.

2 Department of Primary Care and Public Health, Queen Mary, University of London

*Dr Mohiuddin and Dr Ali contributed equally.

[*]Corresponding author

Professor M.M.Yaqoob.

Department of Nephrology

Royal London Hospital

Whitechapel road

London E1 1BB

Email: m.m.yaqoob@qmul.ac.uk

Word count: 2817 excluding tables and references

Keywords: Diabetic chronic kidney disease, end stage kidney failure, blood pressure, proteinuria.

Abstract:

Objective: To compare the rate of progression of diabetic chronic kidney disease in different ethnic groups.

Design: Prospective longitudinal observational study.

Participants: All new patients attending a tertiary renal unit in east London with diabetic chronic kidney disease between 2000 and 2007 and followed up till 2009 were included. Patients presenting with acute end stage kidney failure were excluded.

Main outcome measures: The primary outcome was annual decline in estimated glomerular filtration rate (eGFR) in different ethnic groups. Secondary end points were the number of patients developing end stage kidney failure and total mortality during the study period.

Results: 329 patients (age 60 years ± 11.9, 208 men) were studied comprising 149 south Asian, 105 White and 75 Black patients. Mean follow up was 6.0±2.3, 5.0±2.7 5.6±2.4 for White, black and south Asian patients respectively. South Asian patients were younger and had a higher baseline eGFR, but both systolic and diastolic blood pressure was higher in Black patients ($p<0.05$). Baseline proteinuria was highest for the south Asian group followed by White and Black groups. Adjusted linear regression analysis showed that an annual decline in eGFR was not significantly different between the three groups. The number of patients developing end stage kidney failure and total mortality were also not significantly different between the three groups. Angiotensin converting enzyme or angiotensin receptor blockers use, and glycated haemoglobin (HbA1C) were similar at baseline and through out the study period.

Conclusion: We conclude that ethnicity is not an independent factor in the rate of progression renal failure in patients with diabetic chronic kidney disease.

Introduction:

Diabetic chronic kidney disease (DCKD) is one of the leading cause of end-stage kidney failure (ESKF), accounting for 21% of all such cases in the UK[1]. Suboptimal glycaemic and blood pressure control, development of albuminuria and family history are important risk factors for the development of chronic kidney disease in diabetic patients.

There is a higher prevalence of diabetes mellitus (DM) in black and south Asian populations. The prevalence of diabetes among Black Caribbean and Indian men has been reported to be approximately 10% compared with 4.3% in whites[2]. A recent study conducted in one of the most ethnically diverse cities in the United Kingdom (UK) where the incidence of renal replacement therapy (RRT) for south Asian and Black groups was reported to be respectively, 1.88 and 2.16 times greater than for White patients[3]. Therefore, it is not surprising that a higher proportion of patients on RRT comes from ethnic minority groups compared to the UK white population (17.8% vs 11%)[4].

Mortality is also 3.5 times higher in south Asian and Black populations with diabetes compared to Whites in England and Wales[5]. The higher incidence of ESKF in south Asian and Black populations may be related to higher incidence and poorer control of diabetes and hypertension. However, it may also be related to faster progression of diabetic chronic kidney disease in ethnic minority populations. There are conflicting reports on progression of diabetic chronic kidney disease in these population subgroups. Higher rates of kidney function decline have been reported in some studies while others have failed to show this trend[6-9,]

Most studies comparing progression of diabetic chronic kidney disease in ethnically diverse populations have either been small or had a short duration of follow up. The renal clinic at the Royal London Hospital in east London serves an ethnically diverse population in a large urban centre. The aim of our study is firstly to determine whether

the rate of kidney function decline differs by ethnic group after controlling for demographic characteristics and clinical parameters known to be associated with progression of chronic kidney disease, and secondly, to examine the number of patients developing ESKF and total mortality by ethnicity.

Materials and Methods:

Population

The study was conducted at the Royal London hospital, which serves as a tertiary referral centre for three primary care trusts in east London; Newham, Tower Hamlets and City & Hackney, with a combined GP registered population of 885,625 at the end of 2011. The prevalence of CKD among diabetics, based on a local study, is 18%[18].

All adult patients above the age of 18 years with biopsy proven or clinical diagnosis of diabetic chronic kidney disease (where all secondary causes were excluded) attending our kidney outpatient clinic were included in the study. Any other diagnosis of chronic kidney disease, and those presenting acutely with ESKF were excluded from the study.

Ethnicity was self-assigned by the patient. Patients were grouped according to the ethnic categories of the 2001 census. For the purpose of this study patients of Indian, Bangladeshi and Pakistani ethnicity were analysed together as the South Asian subgroup. Patients of African and Caribbean ethnicity were grouped together to form the Black subgroup, though we recognize that these groupings may conceal underlying heterogeneity. Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009.

Clinical data collection

Data was captured electronically using an in-house renal information technology programme (File maker pro) at every clinic visit. This included blood pressure measured in sitting position using cuffs appropriate for individual and all clinical events and changes in medication. Ethical approval was sought, but not required, due to the observational nature of the study utilizing routinely collected, anonymised patient data.

Baseline variables were collected at the first clinic visit and subsequently updated at every clinic visit. The study variables were defined as follows; ischaemic heart disease (IHD) included patients who were had a documented history of angina, myocardial infarction or cardiac revascularization. Diabetic retinopathy included patients who had been diagnosed with the condition by the diabetic ophthalmology clinic. Peripheral vascular disease (PVD) included patients with a history of intermittent claudication or documented vascular disease on an angiogram, and cerebrovascular disease (CVD) included patients with a past history of transient or persistent vascular neurological deficit.

Estimated glomerular filtration rate (eGFR) was calculated based on the 4 variable MDRD equation which includes a correction for black ethnicity. Serum creatinine was measured using Roche Modular Platform automated analyser. Proteinuria was determined using protein creatinine ratio (Roche Modular Platform automated analyser). Protein creatinine ratio (PCR) was only calculated for patients who had positive proteins on a urine dipstick, and thus individuals with no PCR data were considered to have a value less 15. This was based on a separate unit practice development observation on all dipstick negative urine samples in diabetic patients when analysed had PCR < 15 (personal communication). Glycated haemoglobin (HbA1C) was used to assess glycaemic control (BioRad Turbo 2 automated analyser). Data on systolic and diastolic blood pressure, HbA1C, proteinuria and eGFR were collected every 6 months.

Data coding

Data was cleaned, coded, and analysed using Stata 10. Baseline variables were created for: Average eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), PCR and HbA1c value. PCR was considered both as a linear variable and a binary variable (presence or absence of proteinuria at baseline defined as PCR>15). Medications were coded a constant variable (ever present vs never present) for angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or dual blockade.

Descriptive analysis

Bivariate statistics outlining the population breakdown by ethnicity were conducted. Analysis of Variance (ANOVA) was used to examine ethnic differences in the means of continuous variables, while chi-squared tests were used to examine differences ethnic differences for categorical variables.

Statistical Methods

Unadjusted and adjusted linear regression models were used to determine whether the annual change in eGFR differed by ethnic group. For this analysis, the eGFR values collected every 6 months were collapsed together to form annual averages. To investigate whether the annual decline in eGFR was modified by ethnicity, an interaction term between years of follow up and ethnic group was utilized. The adjusted analysis controlled for age at baseline, gender, presence or absence of vascular disease (defined as any prior diagnosis of CVD, PVD, or IHD), presence or absence of drug treatment (defined as any prior prescription of ACEi, ARBs, or dual blockade), presence or absence of proteinuria at baseline (defined as a baseline PCR value of greater than 15), and baseline eGFR. In addition, the analysis included interaction terms to examine the effect of blood pressure and HbA1C being controlled to target in each year of follow-up. The BP target was set at <= 130/80 mmHg and the HbA1C target was <=7.5%.

Analysis of Variance (ANOVA) was used to examine ethnic differences in the distribution of continuous variables, while chi-squared tests were used for categorical variables. Finally, survival analysis using cox regression was used to estimate ethnic differences in the risk of death adjusting for age and gender.

Results

Population

Out of a total of 356 eligible patients a total of 329 patients with more than 6 years follow up were included. Twenty seven patients were excluded because 10 presented with ESKF and 17 patients had no ethnicity data. Less than 10% of the patients had missing data, which was attributed to missing clinics and less than 5% were lost to follow up due to death or relocation. The baseline characteristics are shown in table1.

The south Asian group was the youngest, with a shorter duration of diabetes and lower baseline blood pressure in comparison to Whites. Black groups have the shortest duration of diabetes but higher baseline systolic and diastolic blood pressure. Baseline eGFR was highest for south Asian groups and lowest for White groups. Mean HbA1C did not differ between ethnic groups, while baseline proteinuria was highest for south Asian groups followed by White and Black groups. Prevalence of IHD was highest for south Asian patients. Prevalence of other co-morbidities, smoking, and drug prescription was not significantly different between the three groups.

Primary end point *(Annual decline in eGFR):*

The overall annual decrease in eGFR was -1.69 in the total population. In the unadjusted linear regression analysis the annual decline in eGFR in white, black and south Asian groups was -1.78, -2.07 and – 1.45 respectively. There was no significant difference in the rate of decline in eGFR between the three groups (Table 2).

Furthermore the adjusted linear regression analysis indicated no significant differences in the annual change in eGFR between the ethnic groups over the entire study period. However the analysis showed that control of blood pressure, gender and degree of renal impairment at baseline were significant predictors of progression (Table 3).

Secondary end points:

By the end of the observation period, 125 individuals had developed ESKF, 32 individuals had died, and 172 individuals were censored. The crude proportions of ESKF were 32%, 44% and 38% in the White, Black, and South Asian groups respectively and were not statistically different (p=0.272). After adjusting for age and gender, the survival analysis indicated no significant difference by ethnicity in the risk of death (Table 4).

Discussion:

In this single centre longitudinal prospective observational study of patients with diabetic chronic kidney disease, the average annual decrease in eGFR in the whole population was -1.69 ml/min/1.73^2. No significant differences in the rate of progression by ethnic group were evidenced. To date, this is the largest study of its kind in the literature.

Burden et al. have reported previously that south Asians with diabetes are 13 times more likely to develop ESKF than their White counterparts, suggesting a faster progression of chronic kidney disease (CKD)[7]. A study carried out in the UK, which supports this hypothesis, found that the proportion of patients doubling their creatinine was significantly higher in south Asians compared to whites[8]. However this study had significantly fewer patients than our study and their patients had early CKD at baseline compared with our population who had moderately severe renal impairment at

presentation, which was an independent predictor of progression of renal failure. In contrast, another small study (39 patients) in the UK by Koppiker et al., has suggested no difference in the rate of progression between Whites and south Asians[9]. However complete data was available for only 36 patients. Similarly a study in the United States, has also reported no significant differences in progression of diabetic kidney disease between Black and White populations with equivalent diabetic control[6]. Our results are broadly in agreement with these studies by demonstrating lack of interaction between ethnicity and the rate of decline in kidney function, though Black patients had a modest additional unadjusted annual decline of 0.31 ml/min/1.73[2].

Blood pressure and glycaemic control are important risk factors for progression of diabetic chronic kidney disease. Generally blood pressure control is more difficult to achieve among Black populations and may contribute towards a faster rate of kidney function decline. One study showed that there was no significant difference in rate of kidney function decline after adjusting for the effects of glycaemic control in Black populations compared with Whites, while others have shown significant difference despite equivalent BP and glycaemic control. A difference in the use of antihypertensive medication including renin angiotensin blocking medication (RAAS) has also been suggested[9,-11]. In this study there was no significant difference in glycaemic control or the use of renin angiotensin blocking medications in the three groups. However, Black patients had a significantly higher baseline systolic, diastolic and above target blood pressure. In our previous study we observed a higher prevalence of BP>150/90 in Blacks in a community based cohort with mild CKD[12], a result which is confirmed by this study in a hospital based cohort of patients with DCKD. Although, in this study there was no significant difference in the decline of kidney function between the ethnic groups, the adjusted analysis showed that the lack of control of blood pressure below the target of 130/80 mmHg was independently associated with rapid decline of eGFR underscoring the importance of optimal blood pressure management as a key modifiable risk factor. Moreover, as expected gender and severity of renal impairment

were the other significant predictors of progression of diabetic kidney disease (Table 3).

There was no significant difference in total mortality (Table 4) and prevalence of end stage kidney failure between the different ethnic groups, however the study was not powered to address this question adequately and will require a large cohort study to confirm these findings. It is important to note however, that south Asians had a higher baseline eGFR, and this could be explained in part, by ethnic differences in referral patterns to our center. Primary care physicians may be more likely to refer south Asians with early diabetic kidney disease compared to Whites, reflecting concern that diabetic kidney disease in south Asians is more difficult to control and is associated with a faster rate of decline.

Current national chronic kidney disease (CKD) guidelines do not include ethnicity as a risk factor for CKD[13]. Therefore the recommendation for the management of CKD in general and DCKD in particular for patients from different ethnic minority groups is similar to that for the white population. The results of this study suggest that there is no need for different set of guidelines for different ethnic groups at present and efforts should be directed at determining the reasons behind sub-optimal blood pressure targets in certain ethnic groups.

Strengths and weaknesses of the study

Strengths of this study include the large number of cases, the completeness of ethnicity and clinical data recording and the prolonged period of follow up. The communities from which these patients are drawn include some of the most socially deprived and multi-ethnic populations in England, hence our results will be of interest to commissioning organisations throughout the UK.

Weaknesses include combining ethnic subgroups into three broad categories, which may mask differences in treatment or progression. We are also unable to identify

differences in referral thresholds and patterns by the GP practices in the localities. Other perceived weakness of the study could be combining diabetic patients with type 1 and 2 for analysis. However, in real life setting only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred because of variable period of undiagnosed type 2 diabetes mellitus. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro and micro-vascular chronic complications of diabetes [14].

Conclusion

This study clearly demonstrates that there is no interaction between ethnicity and the rate of progression of chronic kidney disease in patients with diabetes mellitus. Furthermore the prevalence of renal replacement therapy indicating end stage kidney failure, and mortality was also similar between the three groups.

Tables

Legend for tables

Table 1: Baseline characteristics of study participants by ethnic group

Table 2: Unadjusted linear regression for annual change in eGFR (n=329)

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Table 4: Ethnic differences in risk of death using cox regression

Table 1: Baseline characteristics of study participants by ethnic group

Characteristic	White	Black	South Asian	P value
N	*105*	*75*	*149*	
Baseline Measures*				
Mean age	61.3±12.6	62.4±11.3	57.8±11.4)	0.005
Male (%)	61.5	66.2	65.8	0.741
T2DM (%)	85	100	98	<0.001
Duration of diabetes (years)	18.3±11.6	13.4±7.1	14.0±12.9	0.013
Duration of follow up (years)	6.0±2.3	5.0±2.7	5.6±2.4	0.05
Diabetic retinopathy (%)	84	81	76	0.110
Mean eGFR ml/min/1.73^2	38.1±19	39.0±21	44.3±21	0.039
Mean Systolic BP mmHG	146.6±26	158.3±23	136.6±24	<0.001
Systolic BP >130 mmHG (%)	78.1	86.7	61.7	<0.001
Mean Diastolic BP mmHG	76±11	83±15	75±11	0.002
Diastolic BP >80 (%)	46.7	53.3	37.6	0.066
Mean HBA1c %	8.5±1.8	8.8±2.2	8.7±1.9	0.445
HBA1c >7.5% (%)	67.6	69.3	71.1	0.833
PCR>15 mg/mmol (%)	58.2	47.5	64.4	<0.001
Constant Measures				
IHD (%)	28.6	21.3	38.9	0.020
PVD (%)	15.2	10.7	12.1	0.626
CVD (%)	10.5	8.0	10.7	0.799
Statin use (%)	83.8	80.0	80.4	0.742
ACE use (%)	72.4	70.7	73.7	0.894
ARB use (%)	34.3	40.0	41.2	0.519
Dual Blockade (%)	14.3	17.3	20.1	0.483
Current smoker (%)	18.6	13.6	13.1	0.609
Outcome Measures				
End stage Kidney Failure (%)	32.4	44.0	38.9	0.272
Death (%)	10.5	12.0	8.1	0.612

*Mean values ± standard deviation

Table 2: Unadjusted regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change in ml/min/1.73²***	***95% CI***	***P value***
Overall pop	*-1.69*	*-1.87, -1.53*	*<0.001*
- Slope in White	-1.78	-2.06, -1.49	--
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black population	-0.31	-0.78, 0.152	0.189
-Additional decline in south Asian population	0.32	-0.06, 0.07	0.099

The annual decline in White patients is -1.78 ml/min
The annual decline in Black patients is -2.07 ml/min
The annual decline in south Asian patients is -1.45 ml/min

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change in ml/min/1.73²***	***95% CI***	***P value***
- Years of follow up (Slope in reference pop)	-1.93	-2.31, -1.56	<0.001
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black Population	-0.19	-0.68, 0.30	0.438
-Additional decline in South Asian Population	0.08	-0.31, 0.48	0.676
Time varying variables			
BP<=130/80 * time	0.62	0.27, 0.98	**<0.001**
hbA1C <=7.5 * time	0.03	-0.33, 0.39	0.883
Constant variables			
Ethnicity (white is reference category)			
- Black ethnicity	-1.67	-4.97, 1.64	0.322
- SA ethnicity	-0.51	-3.25, 2.23	0.716
Age	0.03	-0.06,0.13	0.466
Gender (female is reference category)	-2.64	-4.87, -0.40	**0.021**
SBP target at baseline	-2.31	-3.89, -0.73	**0.004**
HbA1C value at baseline	-0.66	-2.37, 1.06	0.454
Vascular disease ever (PVD, CVD, IHD)	-1.44	-3.66, 0.79	0.206
Drug treatment ever (ACE, ARB, Dual Block)	0.02	-4.46, 4.50	0.993
Proteinuria at baseline (PCR>15)	0.173	-1.99, 2.33	0.875
Baseline eGFR	1.05	0.99, 1.11	**<0.001**
Constant	-3.18	-11.26, 4.89	0.440

The annual decline in the reference population (White) is -1.93 ml/min
The annual decline in Black patients is -2.12 ml/min
The annual decline in south Asian patients is -1.85 ml/min

Table 4: Ethnic differences in risk of death rate using cox regression

Ethnic group	*Hazard Ratio*	*95% CI*	*P value*
- White (ref)	1	--	--
- Black	1.01	0.63-2.57	0.982
- South Asian	1.17	0.68-2.32	0.718

*adjusted for age and gender

References

1- Byrne C, Ford D, Gilg J, et al. UK ESRD Incident Rates in 2008: national and centre-specific analyses. UK Renal registry report 2009.

2- Health Survey of England 2004 .http://www.ic.nhs.uk/pubs/hse04ethnic.

3 - Lambie M, Richards N, Smith S. Ethnicity, age and incidence rates for renal replacement therapy in Birmingham, UK: 1990-2004. Nephrol Dial Transplant. 2008 23:3983-3987

4- Ansell DFJ, Feest TG, UK Renal Registry Report. 2007. http://www.renalreg.com

5- Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends 1997;28:122–7.

6- Salifu M, Shah S, Iqbal M et al. Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. Am J Nephrol 2009;30:261-267.

7- Burden AC, McNally PG, Feehally J etal. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med 1992;9:641-645.

8- Earle KK, Porter KA, Ostberg J, et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001;16(2):286-90.

9- Koppiker N, Feehally J, Raymond N, et al. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. Diabet Med. 1998;15(1):60-5.

10- Duru O, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the kidney early evaluation program (KEEP). Am J Kidney Dis 2008;51:192-8.

11- Davis TM. Ethnic diversity in type 2 diabetes. Diabet Med. 2008;25 Suppl

2:52-6.

12- Dreyer G, Hull S, Aitken Z, et al. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM (2009) 102 (4): 261-269.

13- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association and the Royal College of General Practitioners. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. London: Royal College of Physicians; 2006.

14- Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med1999; 341: 1127–1133.

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

[1*]O. Ali Core medical trainee

[1*]A. Mohiuddin Senior clinical fellow

[2]R. Mathur Research Fellow

[1]G. Dreyer Specialist registrar in Nephrology

[2] S. Hull Reader in Primary Care Development

[1]M.M Yaqoob Professor of Nephrology

[1] Department of Nephrology, Royal London Hospital, London.

2 Department of Primary Care and Public Health, Queen Mary, University of London

*Dr Mohiuddin and Dr Ali contributed equally.

[*]Corresponding author

Professor M.M.Yaqoob.

Department of Nephrology

Royal London Hospital

Whitechapel road

London E1 1BB

Email: m.m.yaqoob@qmul.ac.uk

Word count: 2817 excluding tables and references

Keywords: Diabetic chronic kidney disease, end stage kidney failure, blood pressure, proteinuria.

Abstract:

Objective: To compare the rate of progression of diabetic chronic kidney disease in different ethnic groups.

Design: Prospective longitudinal observational study.

Participants: All new patients attending a tertiary renal unit in east London with diabetic chronic kidney disease between 2000 and 2007 and followed up till 2009 were included. Patients presenting with acute end stage kidney failure were excluded.

Main outcome measures: The primary outcome was annual decline in estimated glomerular filtration rate (eGFR) in different ethnic groups. Secondary end points were the number of patients developing end stage kidney failure and total mortality during the study period.

Results: 329 patients (age 60 years ± 11.9, 208 men) were studied comprising 149 south Asian, 105 White and 75 Black patients. Mean follow up was 6.0±2.3, 5.0±2.7 5.6±2.4 for White, black and south Asian patients respectively. South Asian patients were younger and had a higher baseline eGFR, but both systolic and diastolic blood pressure was higher in Black patients ($p<0.05$). Baseline proteinuria was highest for the south Asian group followed by White and Black groups. Adjusted linear regression analysis showed that an annual decline in eGFR was not significantly different between the three groups. The number of patients developing end stage kidney failure and total mortality were also not significantly different between the three groups. Angiotensin converting enzyme or angiotensin receptor blockers use, and glycated haemoglobin (HbA1C) were similar at baseline and through out the study period.

Conclusion: We conclude that ethnicity is not an independent factor in the rate of progression renal failure in patients with diabetic chronic kidney disease.

Introduction:

Diabetic chronic kidney disease (DCKD) is one of the leading cause of end-stage kidney failure (ESKF), accounting for 21% of all such cases in the UK[1]. Suboptimal glycaemic and blood pressure control, development of albuminuria and family history are important risk factors for the development of chronic kidney disease in diabetic patients.

There is a higher prevalence of diabetes mellitus (DM) in black and south Asian populations. The prevalence of diabetes among Black Caribbean and Indian men has been reported to be approximately 10% compared with 4.3% in whites[2]. A recent study conducted in one of the most ethnically diverse cities in the United Kingdom (UK) where the incidence of renal replacement therapy (RRT) for south Asian and Black groups was reported to be respectively, 1.88 and 2.16 times greater than for White patients[3]. Therefore, it is not surprising that a higher proportion of patients on RRT comes from ethnic minority groups compared to the UK white population (17.8% vs 11%)[4].

Mortality is also 3.5 times higher in south Asian and Black populations with diabetes compared to Whites in England and Wales[5]. The higher incidence of ESKF in south Asian and Black populations may be related to higher incidence and poorer control of diabetes and hypertension. However, it may also be related to faster progression of diabetic chronic kidney disease in ethnic minority populations. There are conflicting reports on progression of diabetic chronic kidney disease in these population subgroups. Higher rates of kidney function decline have been reported in some studies while others have failed to show this trend[6-9,]

Most studies comparing progression of diabetic chronic kidney disease in ethnically diverse populations have either been small or had a short duration of follow up. The renal clinic at the Royal London Hospital in east London serves an ethnically diverse population in a large urban centre. The aim of our study is firstly to determine whether

the rate of kidney function decline differs by ethnic group after controlling for demographic characteristics and clinical parameters known to be associated with progression of chronic kidney disease, and secondly, to examine the number of patients developing ESKF and total mortality by ethnicity.

Materials and Methods:

Population

The study was conducted at the Royal London hospital, which serves as a tertiary referral centre for three primary care trusts in east London; Newham, Tower Hamlets and City & Hackney, with a combined GP registered population of 885,625 at the end of 2011. The prevalence of CKD among diabetics, based on a local study, is 18%[18].

All adult patients above the age of 18 years with biopsy proven or clinical diagnosis of diabetic chronic kidney disease (where all secondary causes were excluded) attending our kidney outpatient clinic were included in the study. Any other diagnosis of chronic kidney disease, and those presenting acutely with ESKF were excluded from the study.

Ethnicity was self-assigned by the patient. Patients were grouped according to the ethnic categories of the 2001 census. For the purpose of this study patients of Indian, Bangladeshi and Pakistani ethnicity were analysed together as the South Asian subgroup. Patients of African and Caribbean ethnicity were grouped together to form the Black subgroup, though we recognize that these groupings may conceal underlying heterogeneity. Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009.

Clinical data collection

Data was captured electronically using an in-house renal information technology programme (File maker pro) at every clinic visit. This included blood pressure measured in sitting position using cuffs appropriate for individual and all clinical events and changes in medication. Ethical approval was sought, but not required, due to the observational nature of the study utilizing routinely collected, anonymised patient data.

Baseline variables were collected at the first clinic visit and subsequently updated at every clinic visit. The study variables were defined as follows; ischaemic heart disease (IHD) included patients who were had a documented history of angina, myocardial infarction or cardiac revascularization. Diabetic retinopathy included patients who had been diagnosed with the condition by the diabetic ophthalmology clinic. Peripheral vascular disease (PVD) included patients with a history of intermittent claudication or documented vascular disease on an angiogram, and cerebrovascular disease (CVD) included patients with a past history of transient or persistent vascular neurological deficit.

Estimated glomerular filtration rate (eGFR) was calculated based on the 4 variable MDRD equation which includes a correction for black ethnicity. Serum creatinine was measured using Roche Modular Platform automated analyser. Proteinuria was determined using protein creatinine ratio (Roche Modular Platform automated analyser). Protein creatinine ratio (PCR) was only calculated for patients who had positive proteins on a urine dipstick, and thus individuals with no PCR data were considered to have a value less 15. This was based on a separate unit practice development observation on all dipstick negative urine samples in diabetic patients when analysed had PCR < 15 (personal communication). Glycated haemoglobin (HbA1C) was used to assess glycaemic control (BioRad Turbo 2 automated analyser). Data on systolic and diastolic blood pressure, HbA1C, proteinuria and eGFR were collected every 6 months.

Data coding

Data was cleaned, coded, and analysed using Stata 10. Baseline variables were created for: Average eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), PCR and HbA1c value. PCR was considered both as a linear variable and a binary variable (presence or absence of proteinuria at baseline defined as PCR>15). Medications were coded a constant variable (ever present vs never present) for angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or dual blockade.

Descriptive analysis

Bivariate statistics outlining the population breakdown by ethnicity were conducted. Analysis of Variance (ANOVA) was used to examine ethnic differences in the means of continuous variables, while chi-squared tests were used to examine differences ethnic differences for categorical variables.

Statistical Methods

Unadjusted and adjusted linear regression models were used to determine whether the annual change in eGFR differed by ethnic group. For this analysis, the eGFR values collected every 6 months were collapsed together to form annual averages. To investigate whether the annual decline in eGFR was modified by ethnicity, an interaction term between years of follow up and ethnic group was utilized. The adjusted analysis controlled for age at baseline, gender, presence or absence of vascular disease (defined as any prior diagnosis of CVD, PVD, or IHD), presence or absence of drug treatment (defined as any prior prescription of ACEi, ARBs, or dual blockade), presence or absence of proteinuria at baseline (defined as a baseline PCR value of greater than 15), and baseline eGFR. In addition, the analysis included interaction terms to examine the effect of blood pressure and HbA1C being controlled to target in each year of follow-up. The BP target was set at <= 130/80 mmHg and the HbA1C target was <=7.5%.

Analysis of Variance (ANOVA) was used to examine ethnic differences in the distribution of continuous variables, while chi-squared tests were used for categorical variables. Finally, survival analysis using cox regression was used to estimate ethnic differences in the risk of death adjusting for age and gender.

Results

Population

Out of a total of 356 eligible patients a total of 329 patients with more than 6 years follow up were included. Twenty seven patients were excluded because 10 presented with ESKF and 17 patients had no ethnicity data. Less than 10% of the patients had missing data, which was attributed to missing clinics and less than 5% were lost to follow up due to death or relocation. The baseline characteristics are shown in table1.

The south Asian group was the youngest, with a shorter duration of diabetes and lower baseline blood pressure in comparison to Whites. Black groups have the shortest duration of diabetes but higher baseline systolic and diastolic blood pressure. Baseline eGFR was highest for south Asian groups and lowest for White groups. Mean HbA1C did not differ between ethnic groups, while baseline proteinuria was highest for south Asian groups followed by White and Black groups. Prevalence of IHD was highest for south Asian patients. Prevalence of other co-morbidities, smoking, and drug prescription was not significantly different between the three groups.

Primary end point *(Annual decline in eGFR):*

The overall annual decrease in eGFR was -1.69 in the total population. In the unadjusted linear regression analysis the annual decline in eGFR in white, black and south Asian groups was -1.78, -2.07 and – 1.45 respectively. There was no significant difference in the rate of decline in eGFR between the three groups (Table 2).

Furthermore the adjusted linear regression analysis indicated no significant differences in the annual change in eGFR between the ethnic groups over the entire study period. However the analysis showed that control of blood pressure, gender and degree of renal impairment at baseline were significant predictors of progression (Table 3).

Secondary end points:

By the end of the observation period, 125 individuals had developed ESKF, 32 individuals had died, and 172 individuals were censored. The crude proportions of ESKF were 32%, 44% and 38% in the White, Black, and South Asian groups respectively and were not statistically different (p=0.272). After adjusting for age and gender, the survival analysis indicated no significant difference by ethnicity in the risk of death (Table 4).

Discussion:

In this single centre longitudinal prospective observational study of patients with diabetic chronic kidney disease, the average annual decrease in eGFR in the whole population was -1.69 ml/min/1.73^2. No significant differences in the rate of progression by ethnic group were evidenced. To date, this is the largest study of its kind in the literature.

Burden et al. have reported previously that south Asians with diabetes are 13 times more likely to develop ESKF than their White counterparts, suggesting a faster progression of chronic kidney disease (CKD)[7]. A study carried out in the UK, which supports this hypothesis, found that the proportion of patients doubling their creatinine was significantly higher in south Asians compared to whites[8]. However this study had significantly fewer patients than our study and their patients had early CKD at baseline compared with our population who had moderately severe renal impairment at

presentation, which was an independent predictor of progression of renal failure. In contrast, another small study (39 patients) in the UK by Koppiker et al., has suggested no difference in the rate of progression between Whites and south Asians[9]. However complete data was available for only 36 patients. Similarly a study in the United States, has also reported no significant differences in progression of diabetic kidney disease between Black and White populations with equivalent diabetic control[6]. Our results are broadly in agreement with these studies by demonstrating lack of interaction between ethnicity and the rate of decline in kidney function, though Black patients had a modest additional unadjusted annual decline of 0.31 ml/min/1.73[2].

Blood pressure and glycaemic control are important risk factors for progression of diabetic chronic kidney disease. Generally blood pressure control is more difficult to achieve among Black populations and may contribute towards a faster rate of kidney function decline. One study showed that there was no significant difference in rate of kidney function decline after adjusting for the effects of glycaemic control in Black populations compared with Whites, while others have shown significant difference despite equivalent BP and glycaemic control. A difference in the use of antihypertensive medication including renin angiotensin blocking medication (RAAS) has also been suggested[9,-11]. In this study there was no significant difference in glycaemic control or the use of renin angiotensin blocking medications in the three groups. However, Black patients had a significantly higher baseline systolic, diastolic and above target blood pressure. In our previous study we observed a higher prevalence of BP>150/90 in Blacks in a community based cohort with mild CKD[12], a result which is confirmed by this study in a hospital based cohort of patients with DCKD. Although, in this study there was no significant difference in the decline of kidney function between the ethnic groups, the adjusted analysis showed that the lack of control of blood pressure below the target of 130/80 mmHg was independently associated with rapid decline of eGFR underscoring the importance of optimal blood pressure management as a key modifiable risk factor. Moreover, as expected gender and severity of renal impairment

were the other significant predictors of progression of diabetic kidney disease (Table 3).

There was no significant difference in total mortality (Table 4) and prevalence of end stage kidney failure between the different ethnic groups, however the study was not powered to address this question adequately and will require a large cohort study to confirm these findings. It is important to note however, that south Asians had a higher baseline eGFR, and this could be explained in part, by ethnic differences in referral patterns to our center. Primary care physicians may be more likely to refer south Asians with early diabetic kidney disease compared to Whites, reflecting concern that diabetic kidney disease in south Asians is more difficult to control and is associated with a faster rate of decline.

Current national chronic kidney disease (CKD) guidelines do not include ethnicity as a risk factor for CKD[13]. Therefore the recommendation for the management of CKD in general and DCKD in particular for patients from different ethnic minority groups is similar to that for the white population. The results of this study suggest that there is no need for different set of guidelines for different ethnic groups at present and efforts should be directed at determining the reasons behind sub-optimal blood pressure targets in certain ethnic groups.

Strengths and weaknesses of the study

Strengths of this study include the large number of cases, the completeness of ethnicity and clinical data recording and the prolonged period of follow up. The communities from which these patients are drawn include some of the most socially deprived and multi-ethnic populations in England, hence our results will be of interest to commissioning organisations throughout the UK.

Weaknesses include combining ethnic subgroups into three broad categories, which may mask differences in treatment or progression. We are also unable to identify

differences in referral thresholds and patterns by the GP practices in the localities. Other perceived weakness of the study could be combining diabetic patients with type 1 and 2 for analysis. However, in real life setting only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred because of variable period of undiagnosed type 2 diabetes mellitus. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro and micro-vascular chronic complications of diabetes [14].

Conclusion

This study clearly demonstrates that there is no interaction between ethnicity and the rate of progression of chronic kidney disease in patients with diabetes mellitus. Furthermore the prevalence of renal replacement therapy indicating end stage kidney failure, and mortality was also similar between the three groups.

Tables

Legend for tables

Table 1: Baseline characteristics of study participants by ethnic group

Table 2: Unadjusted linear regression for annual change in eGFR (n=329)

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Table 4: Ethnic differences in risk of death using cox regression

Table 1: Baseline characteristics of study participants by ethnic group

Characteristic	White	Black	South Asian	P value
N	*105*	*75*	*149*	
Baseline Measures*				
Mean age	61.3±12.6	62.4±11.3	57.8±11.4)	0.005
Male (%)	61.5	66.2	65.8	0.741
T2DM (%)	85	100	98	<0.001
Duration of diabetes (years)	18.3±11.6	13.4±7.1	14.0±12.9	0.013
Duration of follow up (years)	6.0±2.3	5.0±2.7	5.6±2.4	0.05
Diabetic retinopathy (%)	84	81	76	0.110
Mean eGFR ml/min/1.73^2	38.1±19	39.0±21	44.3±21	0.039
Mean Systolic BP mmHG	146.6±26	158.3±23	136.6±24	<0.001
Systolic BP >130 mmHG (%)	78.1	86.7	61.7	<0.001
Mean Diastolic BP mmHG	76±11	83±15	75±11	0.002
Diastolic BP >80 (%)	46.7	53.3	37.6	0.066
Mean HBA1c %	8.5±1.8	8.8±2.2	8.7±1.9	0.445
HBA1c >7.5% (%)	67.6	69.3	71.1	0.833
PCR>15 mg/mmol (%)	58.2	47.5	64.4	<0.001
Constant Measures				
IHD (%)	28.6	21.3	38.9	0.020
PVD (%)	15.2	10.7	12.1	0.626
CVD (%)	10.5	8.0	10.7	0.799
Statin use (%)	83.8	80.0	80.4	0.742
ACE use (%)	72.4	70.7	73.7	0.894
ARB use (%)	34.3	40.0	41.2	0.519
Dual Blockade (%)	14.3	17.3	20.1	0.483
Current smoker (%)	18.6	13.6	13.1	0.609
Outcome Measures				
End stage Kidney Failure (%)	32.4	44.0	38.9	0.272
Death (%)	10.5	12.0	8.1	0.612

*Mean values ± standard deviation

Table 2: Unadjusted regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change in ml/min/1.73²***	***95% CI***	***P value***
Overall pop	*-1.69*	*-1.87, -1.53*	*<0.001*
- Slope in White	-1.78	-2.06, -1.49	--
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black population	-0.31	-0.78, 0.152	0.189
-Additional decline in south Asian population	0.32	-0.06, 0.07	0.099

The annual decline in White patients is -1.78 ml/min
The annual decline in Black patients is -2.07 ml/min
The annual decline in south Asian patients is -1.45 ml/min

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Predictor Variables	*Annual Change in ml/min/1.73²*	*95% CI*	*P value*
- Years of follow up (Slope in reference pop)	-1.93	-2.31, -1.56	<0.001
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black Population	-0.19	-0.68, 0.30	0.438
-Additional decline in South Asian Population	0.08	-0.31, 0.48	0.676
Time varying variables			
BP<=130/80 * time	0.62	0.27, 0.98	**<0.001**
hbA1C <=7.5 * time	0.03	-0.33, 0.39	0.883
Constant variables			
Ethnicity (white is reference category)			
- Black ethnicity	-1.67	-4.97, 1.64	0.322
- SA ethnicity	-0.51	-3.25, 2.23	0.716
Age	0.03	-0.06,0.13	0.466
Gender (female is reference category)	-2.64	-4.87, -0.40	**0.021**
SBP target at baseline	-2.31	-3.89, -0.73	**0.004**
HbA1C value at baseline	-0.66	-2.37, 1.06	0.454
Vascular disease ever (PVD, CVD, IHD)	-1.44	-3.66, 0.79	0.206
Drug treatment ever (ACE, ARB, Dual Block)	0.02	-4.46, 4.50	0.993
Proteinuria at baseline (PCR>15)	0.173	-1.99, 2.33	0.875
Baseline eGFR	1.05	0.99, 1.11	**<0.001**
Constant	-3.18	-11.26, 4.89	0.440

The annual decline in the reference population (White) is -1.93 ml/min
The annual decline in Black patients is -2.12 ml/min
The annual decline in south Asian patients is -1.85 ml/min

Table 4: Ethnic differences in risk of death rate using cox regression

Ethnic group	*Hazard Ratio*	*95% CI*	*P value*
- White (ref)	1	--	--
- Black	1.01	0.63-2.57	0.982
- South Asian	1.17	0.68-2.32	0.718

*adjusted for age and gender

References

1- Byrne C, Ford D, Gilg J, et al. UK ESRD Incident Rates in 2008: national and centre-specific analyses. UK Renal registry report 2009.

2- Health Survey of England 2004 .http://www.ic.nhs.uk/pubs/hse04ethnic.

3 - Lambie M, Richards N, Smith S. Ethnicity, age and incidence rates for renal replacement therapy in Birmingham, UK: 1990-2004. Nephrol Dial Transplant. 2008 23:3983-3987

4- Ansell DFJ, Feest TG, UK Renal Registry Report. 2007. http://www.renalreg.com

5- Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends 1997;28:122–7.

6- Salifu M, Shah S, Iqbal M et al. Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. Am J Nephrol 2009;30:261-267.

7- Burden AC, McNally PG, Feehally J etal. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med 1992;9:641-645.

8- Earle KK, Porter KA, Ostberg J, et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001;16(2):286-90.

9- Koppiker N, Feehally J, Raymond N, et al. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. Diabet Med. 1998;15(1):60-5.

10- Duru O, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the kidney early evaluation program (KEEP). Am J Kidney Dis 2008;51:192-8.

11- Davis TM. Ethnic diversity in type 2 diabetes. Diabet Med. 2008;25 Suppl

2:52-6.

12- Dreyer G, Hull S, Aitken Z, et al. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM (2009) 102 (4): 261-269.

13- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association and the Royal College of General Practitioners. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. London: Royal College of Physicians; 2006.

14- Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med1999; 341: 1127–1133.

Reviewers comments

As discussed in my previous review, the authors have not made a clear distinction in their discussion between studies of UK South Asians and those of "South Asians" in other countries. For example (and as mentioned in my previous review) the "South Asians" in the study by Shaw (reference 11) are Dutch Surinamese while the "Asians" in the paper by Kanaya (reference 19) include Filipinos and Japanese. These groups may not be comparable to UK South Asians. Similarly it is almost certainly not reasonable to treat US Black Americans as identical to UK Africans or Afro-Caribbeans. As a minimum, the text should make clear which studies are UK based and which are from the US. **(these issues have been addressed)**

The authors have used linear regression to describe changes in eGFR. This is reasonable if the decline is really linear (ie straight line). The methods section should confirm that steps were taken to check linearity (this could be done, for example, by using the "linktest" command in Stata or testing the significance of the addition of "year squared" as a predictor in the linear model)**.(the linktest command is not available for panel data. The addition of an interaction between ethnicity and "year squared" to the linear model already containing an interaction between ethnicity and year is shown to be non-significant (p=0.313 for the main effect of "year squared")**

The methods section still mentions the use of logistic regression though I could not find any corresponding results **(Though Logistic regression was used initially to examine ethnic differences in p.values for Table 1, this has now been changed to ANOVA for continuous variables and Chi-squared test for categorical variables).**

When power is limited there are difficulties about describing differences between groups which are not statistically significant. For example on page 6 it is not strictly true to say that prevalence of smoking did not differ by ethnic group when smoking prevalence among South Asians was about a third lower than that in the "White" group. The "non-significant" p value indicates that the difference could not be estimated precisely (because of limited power), but it also means that a fairly large difference cannot be ruled out with any certainty. It might be better to say that the prevalence of smoking was not significantly different. The same problem applies to the statement at the start of the discussion that "No differences in the rate of progression by ethnic group were evidenced." It might be reasonable to say that "No significant differences . . were evidenced" but again this leaves open the question of how big a difference could be excluded by the authors' data. The lower confidence interval in table 2 show that the annual decline could be up to 0.78ml/min greater in the Black population, which seems substantial to me (though this is really a clinical judgement that I would leave to the authors to justify). I think it would be more reasonable to say that any additional decline in the Black group is likely to be modest (0.31 ml/min) but that the confidence limits make the estimate very imprecise. For South Asians the 95% confidence limits in table 2 are not plausible as they do not include the point estimate - I suspect a typo here. **(changed as per your suggestion)**

In table 3 the Black and South Asian "additional slope" figures do not correspond with those in table 2. This may be because they are from an adjusted model, but I think it may also be because these are coefficients for the interaction. Depending on how time was coded here the interpretation is that the difference between Whites and Blacks increases by 0.19ml/min each year. It would be helpful to clarify this point. **(Correct- Table 2 shows the coefficient for interaction in the unadjusted model. Table 2 shoes the coefficient for interaction in the adjusted model- the wording in both tables has been clarified)**

In table 4, the comparison of the proportion of participants from each ethnic group who died by the end of follow up does not seem to take account of different individual lengths of follow up. It would be usual to do this by dividing the number of deaths by the number of person-years of follow-up in each ethnic group. This still does not take account of differences in age (or other risk factors) between groups. Possible analytic options here would include age standardisation, Poisson or Cox regression, but as the other reviewer notes, power to detect differences in mortality will be limited. **(Cox regression have been used to determine the hazard ratios for rates of death by ethnic group. The cox regression models reported hazard ratios for differences by ethnicity and are adjusted for age and gender.)**

Minor issues

I suggest it would be preferable to give the exact mean follow up in the abstract (or the median if the distribution of follow up times is skewed). (done)

I would suggest that the sentence in the methods section: "Diabetic retinopathy included patients who had been formally assessed by the diabetic ophthalmology clinic" might be clearer if worded as "Diabetic retinopathy included patients who had been diagnosed with the condition by the diabetic ophthalmology clinic" (done)

The sentence in the methods "This was based on a separate unit practice development observation . . ." was not clear to me. If this is a report it needs a reference or if unpublished data it might be shown as a personal communication. (done)

I think the word "included" is missing after "analysis" in this sentence in the methods section: "In addition, the analysis interaction terms to examine the effect of blood pressure and HbA1c being controlled to target . . . "
(done)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001855.R3
Article Type:	Research
Date Submitted by the Author:	05-Feb-2013
Complete List of Authors:	Ali, Omer; Royal london hospital, Nephrology Mohiuddin, Atif; Royal London Hospital, Nephrology Mathur, Rohini; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Dreyer, Gavin; Royal London Hospital, Nephrology Hull, Sally; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Yaqoob, Magdi; Royal London Hospital, Nephrology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Diabetes and endocrinology, Renal medicine
Keywords:	Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Chronic renal failure < NEPHROLOGY, End stage renal failure < NEPHROLOGY, Nephrology < INTERNAL MEDICINE

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

[1*]O. Ali Core medical trainee

[1*]A. Mohiuddin Senior clinical fellow

[2]R. Mathur Research Fellow

[1]G. Dreyer Specialist registrar in Nephrology

[2] S. Hull Reader in Primary Care Development

[1]M.M Yaqoob Professor of Nephrology

[1] Department of Nephrology, Royal London Hospital, London.

2 Department of Primary Care and Public Health, Queen Mary, University of London

*Dr Mohiuddin and Dr Ali contributed equally.

[*]Corresponding author

Professor M.M.Yaqoob.

Department of Nephrology

Royal London Hospital

Whitechapel road

London E1 1BB

Email: m.m.yaqoob@qmul.ac.uk

Word count: 2863 excluding tables and references

Keywords: Diabetic chronic kidney disease, end stage kidney failure, blood pressure, proteinuria.

Abstract:

Objective: To compare the rate of progression of diabetic chronic kidney disease in different ethnic groups.

Design: Prospective longitudinal observational study.

Participants: All new patients attending a tertiary renal unit in east London with diabetic chronic kidney disease between 2000 and 2007 and followed up till 2009 were included. Patients presenting with acute end stage kidney failure were excluded.

Main outcome measures: The primary outcome was annual decline in estimated glomerular filtration rate (eGFR) in different ethnic groups. Secondary end points were the number of patients developing end stage kidney failure and total mortality during the study period.

Results: 329 patients (age 60 years ± 11.9, 208 men) were studied comprising 149 south Asian, 105 White and 75 Black patients. Mean follow up was 6.0±2.3, 5.0±2.7 5.6±2.4 years for White, black and south Asian patients respectively. South Asian patients were younger and had a higher baseline eGFR, but both systolic and diastolic blood pressure was higher in Black patients ($p<0.05$). Baseline proteinuria was highest for the south Asian group followed by White and Black groups. Adjusted linear regression analysis showed that an annual decline in eGFR was not significantly different between the three groups. The number of patients developing end stage kidney failure and total mortality were also not significantly different between the three groups. Angiotensin converting enzyme or angiotensin receptor blockers use, and glycated haemoglobin (HbA1C) were similar at baseline and through out the study period.

Conclusion: We conclude that ethnicity is not an independent factor in the rate of progression renal failure in patients with diabetic chronic kidney disease.

Introduction:

Diabetic chronic kidney disease (DCKD) is one of the leading cause of end-stage kidney failure (ESKF), accounting for 21% of all such cases in the UK[1]. Suboptimal glycaemic and blood pressure control, development of albuminuria and family history are important risk factors for the development of chronic kidney disease in diabetic patients.

There is a higher prevalence of diabetes mellitus (DM) in black and south Asian populations. The prevalence of diabetes among Black Caribbean and Indian men has been reported to be approximately 10% compared with 4.3% in whites[2]. A recent study conducted in one of the most ethnically diverse cities in the United Kingdom (UK) where the incidence of renal replacement therapy (RRT) for south Asian and Black groups was reported to be respectively, 1.88 and 2.16 times greater than for White patients[3]. Therefore, it is not surprising that a higher proportion of patients on RRT comes from ethnic minority groups compared to the UK white population (17.8% vs 11%)[4].

Mortality is also 3.5 times higher in south Asian and Black populations with diabetes compared to Whites in England and Wales[5]. The higher incidence of ESKF in south Asian and Black populations may be related to higher incidence and poorer control of diabetes and hypertension. However, it may also be related to faster progression of diabetic chronic kidney disease in ethnic minority populations. There are conflicting reports on progression of diabetic chronic kidney disease in these population subgroups. Higher rates of kidney function decline have been reported in some studies while others have failed to show this trend[6-9,]

Most studies comparing progression of diabetic chronic kidney disease in ethnically diverse populations have either been small or had a short duration of follow up. The renal clinic at the Royal London Hospital in east London serves an ethnically diverse

population in a large urban centre. The aim of our study is firstly to determine whether the rate of kidney function decline differs by ethnic group after controlling for demographic characteristics and clinical parameters known to be associated with progression of chronic kidney disease, and secondly, to examine the number of patients developing ESKF and total mortality by ethnicity.

Materials and Methods:

Population

The study was conducted at the Royal London hospital, which serves as a tertiary referral centre for three primary care trusts in east London; Newham, Tower Hamlets and City & Hackney, with a combined GP registered population of 885,625 at the end of 2011. The prevalence of CKD among patients with diabetes, based on a local study, is 18%[12].

All adult patients above the age of 18 years with biopsy proven or clinical diagnosis of diabetic chronic kidney disease (where all secondary causes were excluded) attending our kidney outpatient clinic were included in the study. Any other diagnosis of chronic kidney disease, and those presenting acutely with ESKF were excluded from the study.

Ethnicity was self-assigned by the patient. Patients were grouped according to the ethnic categories of the 2001 census. For the purpose of this study patients of Indian, Bangladeshi and Pakistani ethnicity were analysed together as the South Asian subgroup. Patients of African and Caribbean ethnicity were grouped together to form the Black subgroup, though we recognize that these groupings may conceal underlying heterogeneity. Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009.

Clinical data collection

Data was captured electronically using an in-house renal information technology programme (File maker pro) at every clinic visit. This included blood pressure measured in sitting position using cuffs appropriate for individual and all clinical events and changes in medication. Ethical approval was sought, but not required, due to the observational nature of the study utilizing routinely collected, anonymised patient data.

Baseline variables were collected at the first clinic visit and subsequently updated at every clinic visit. The study variables were defined as follows; ischaemic heart disease (IHD) included patients who were had a documented history of angina, myocardial infarction or cardiac revascularization. Diabetic retinopathy included patients who had been diagnosed with the condition by the diabetic ophthalmology clinic. Peripheral vascular disease (PVD) included patients with a history of intermittent claudication or documented vascular disease on an angiogram, and cerebrovascular disease (CVD) included patients with a past history of transient or persistent vascular neurological deficit.

Estimated glomerular filtration rate (eGFR) was calculated based on the 4 variable MDRD equation which includes a correction for black ethnicity. Serum creatinine was measured using Roche Modular Platform automated analyser. Proteinuria was determined using protein creatinine ratio (Roche Modular Platform automated analyser). Protein creatinine ratio (PCR) was only calculated for patients who had positive proteins on a urine dipstick, and thus individuals with no PCR data were considered to have a value less 15. This was based on a separate unit practice development observation on all dipstick negative urine samples in diabetic patients when analysed had PCR < 15 (personal communication). Glycated haemoglobin (HbA1C) was used to assess glycaemic control (BioRad Turbo 2 automated analyser). Data on systolic and diastolic blood pressure, HbA1C, proteinuria and eGFR were

collected every 6 months.

Data coding

Data was cleaned, coded, and analysed using Stata 10. Baseline variables were created for: Average eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), PCR and HbA1c value. PCR was considered both as a linear variable and a binary variable (presence or absence of proteinuria at baseline defined as PCR>15). Medications were coded a constant variable (ever present vs never present) for angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or dual blockade.

Descriptive analysis

Bivariate statistics outlining the population breakdown by ethnicity were conducted. Analysis of Variance (ANOVA) was used to examine ethnic differences in the means of continuous variables, while chi-squared tests were used to examine differences ethnic differences for categorical variables.

Statistical Methods

Unadjusted and adjusted linear regression models were used to determine whether the annual change in eGFR differed by ethnic group. For this analysis, the eGFR values collected every 6 months were collapsed together to form annual averages.

To investigate whether the annual decline in eGFR was modified by ethnicity, an interaction term between years of follow up and ethnic group was utilized. The addition of an interaction term between ethnicity and "year squared" to the linear model already containing an interaction between ethnicity and year was shown to be non-significant, thus suggesting for us to proceed with a model examining linear annual change in eGFR.

The adjusted analysis controlled for age at baseline, gender, presence or absence of vascular disease (defined as any prior diagnosis of CVD, PVD, or IHD), presence or

absence of drug treatment (defined as any prior prescription of ACEi, ARBs, or dual blockade), presence or absence of proteinuria at baseline (defined as a baseline PCR value of greater than 15), and baseline eGFR. In addition, the analysis included interaction terms to examine the effect of blood pressure and HbA1C being controlled to target in each year of follow-up. The BP target was set at <= 130/80 mmHg and the HbA1C target was <=7.5%.

Analysis of Variance (ANOVA) was used to examine ethnic differences in the distribution of continuous variables, while chi-squared tests were used for categorical variables. Finally, survival analysis using Cox regression was used to estimate ethnic differences in the risk of death adjusting for age and gender.

Results

Population

Out of a total of 356 eligible patients a total of 329 patients with more than 6 years follow up were included. Twenty seven patients were excluded because 10 presented with ESKF and 17 patients had no ethnicity data. Less than 10% of the patients had missing data, which was attributed to missing clinics and less than 5% were lost to follow up due to death or relocation. The baseline characteristics are shown in table1.

The south Asian group was the youngest, with a shorter duration of diabetes and lower baseline blood pressure in comparison to Whites. Black groups have the shortest duration of diabetes but higher baseline systolic and diastolic blood pressure. Baseline eGFR was highest for south Asian groups and lowest for White groups. Mean HbA1C did not differ between ethnic groups, while baseline proteinuria was highest for south Asian groups followed by White and Black groups. Prevalence of IHD was highest for south Asian patients. Prevalence of other co-morbidities, smoking, and drug prescription was not significantly different between the three groups.

Primary end point *(Annual decline in eGFR):*

The overall annual decrease in eGFR was -1.69 in the total population. In the unadjusted linear regression analysis the annual decline in eGFR in white, black and south Asian groups was -1.78, -2.02 and – 1.51 respectively. There was no significant difference in the rate of decline in eGFR between the three groups (Table 2).

Furthermore the adjusted linear regression analysis indicated no significant differences in the annual change in eGFR between the ethnic groups over the entire study period. However the analysis showed that control of blood pressure, gender and degree of renal impairment at baseline were significant predictors of progression (Table 3).

Secondary end points:

By the end of the observation period, 125 individuals had developed ESKF, 32 individuals had died, and 172 individuals were censored. The crude proportions of ESKF were 32%, 44% and 38% in the White, Black, and South Asian groups respectively and were not statistically different (p=0.272). After adjusting for age and gender, the survival analysis indicated no significant difference by ethnicity in the risk of death (Table 4).

Discussion:

In this single centre longitudinal prospective observational study of patients with diabetic chronic kidney disease, the average annual decrease in eGFR in the whole population was -1.69 ml/min/1.73^2. No significant differences in the rate of progression by ethnic group were evidenced. To date, this is the largest study of its kind in the literature.

Burden et al. have reported previously that south Asians with diabetes are 13 times more likely to develop ESKF than their White counterparts, suggesting a faster progression of chronic kidney disease (CKD)[7]. A study carried out in the UK, which supports this hypothesis, found that the proportion of patients doubling their creatinine was significantly higher in south Asians compared to whites[8]. However this study had significantly fewer patients than our study and their patients had early CKD at baseline compared with our population who had moderately severe renal impairment at presentation, which was an independent predictor of progression of renal failure. In contrast, another small study (39 patients) in the UK by Koppiker et al., has suggested no difference in the rate of progression between Whites and south Asians[9]. However complete data was available for only 36 patients. Similarly a study in the United States, has also reported no significant differences in progression of diabetic kidney disease between Black and White populations with equivalent diabetic control[6]. Our results are broadly in agreement with these studies by demonstrating lack of interaction between ethnicity and the rate of decline in kidney function, though Black patients had a modest additional unadjusted annual decline of 0.31 ml/min/1.73^2.

Blood pressure and glycaemic control are important risk factors for progression of diabetic chronic kidney disease. Generally blood pressure control is more difficult to achieve among Black populations and may contribute towards a faster rate of kidney function decline. One study showed that there was no significant difference in rate of kidney function decline after adjusting for the effects of glycaemic control in Black populations compared with Whites, while others have shown significant difference despite equivalent BP and glycaemic control. A difference in the use of antihypertensive medication including renin angiotensin blocking medication (RAAS) has also been suggested[9,-11]. In this study there was no significant difference in glycaemic control or the use of renin angiotensin blocking medications in the three groups. However, Black patients had a significantly higher baseline systolic, diastolic and above target blood pressure. In our previous study we observed a higher prevalence of BP>150/90 in

Blacks in a community based cohort with mild CKD[12], a result which is confirmed by this study in a hospital based cohort of patients with DCKD. Although, in this study there was no significant difference in the decline of kidney function between the ethnic groups, the adjusted analysis showed that the lack of control of blood pressure below the target of 130/80 mmHg was independently associated with rapid decline of eGFR underscoring the importance of optimal blood pressure management as a key modifiable risk factor. Moreover, as expected gender and severity of renal impairment were the other significant predictors of progression of diabetic kidney disease (Table 3).

There was no significant difference in total mortality (Table 4) and prevalence of end stage kidney failure between the different ethnic groups, however the study was not powered to address this question adequately and will require a large cohort study to confirm these findings. It is important to note however, that south Asians had a higher baseline eGFR, and this could be explained in part, by ethnic differences in referral patterns to our center. Primary care physicians may be more likely to refer south Asians with early diabetic kidney disease compared to Whites, reflecting concern that diabetic kidney disease in south Asians is more difficult to control and is associated with a faster rate of decline.

Current national chronic kidney disease (CKD) guidelines do not include ethnicity as a risk factor for CKD[13]. Therefore the recommendation for the management of CKD in general and DCKD in particular for patients from different ethnic minority groups is similar to that for the white population. The results of this study suggest that there is no need for different set of guidelines for different ethnic groups at present and efforts should be directed at determining the reasons behind sub-optimal blood pressure targets in certain ethnic groups.

Strengths and weaknesses of the study

Strengths of this study include the large number of cases, the completeness of ethnicity and clinical data recording and the prolonged period of follow up. The communities from which these patients are drawn include some of the most socially deprived and multi-ethnic populations in England, hence our results will be of interest to commissioning organisations throughout the UK.

Weaknesses include combining ethnic subgroups into three broad categories, which may mask differences in treatment or progression. We are also unable to identify differences in referral thresholds and patterns by the GP practices in the localities. Other perceived weakness of the study could be combining diabetic patients with type 1 and 2 for analysis. However, in real life setting only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred because of variable period of undiagnosed type 2 diabetes mellitus. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro and micro-vascular chronic complications of diabetes [14].

Conclusion

This study demonstrates that there is no significant interaction between ethnicity and the rate of progression of chronic kidney disease in patients with diabetes mellitus. Furthermore the prevalence of renal replacement therapy indicating end stage kidney failure, and mortality was also similar between the three groups.

Tables

Legend for tables

Table 1: Baseline characteristics of study participants by ethnic group

Table 2: Unadjusted linear regression for annual change in eGFR (n=329)

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Table 4: Ethnic differences in risk of death using Cox regression

Table 1: Baseline characteristics of study participants by ethnic group

Characteristic	White	Black	South Asian	P value
N	*105*	*75*	*149*	
Baseline Measures*				
Mean age	61.3±12.6	62.4±11.3	57.8±11.4)	0.005
Male (%)	61.5	66.2	65.8	0.741
T2DM (%)	85	100	98	<0.001
Duration of diabetes (years)	18.3±11.6	13.4±7.1	14.0±12.9	0.013
Duration of follow up (years)	6.0±2.3	5.0±2.7	5.6±2.4	0.05
Diabetic retinopathy (%)	84	81	76	0.110
Mean eGFR ml/min/1.73^2	38.1±19	39.0±21	44.3±21	0.039
Mean Systolic BP mmHG	146.6±26	158.3±23	136.6±24	<0.001
Systolic BP >130 mmHG (%)	78.1	86.7	61.7	<0.001
Mean Diastolic BP mmHG	76±11	83±15	75±11	0.002
Diastolic BP >80 (%)	46.7	53.3	37.6	0.066
Mean HBA1c %	8.5±1.8	8.8±2.2	8.7±1.9	0.445
HBA1c >7.5% (%)	67.6	69.3	71.1	0.833
PCR>15 mg/mmol (%)	58.2	47.5	64.4	<0.001
Constant Measures				
IHD (%)	28.6	21.3	38.9	0.020
PVD (%)	15.2	10.7	12.1	0.626
CVD (%)	10.5	8.0	10.7	0.799
Statin use (%)	83.8	80.0	80.4	0.742
ACE use (%)	72.4	70.7	73.7	0.894
ARB use (%)	34.3	40.0	41.2	0.519
Dual Blockade (%)	14.3	17.3	20.1	0.483
Current smoker (%)	18.6	13.6	13.1	0.609
Outcome Measures				
End stage Kidney Failure (%)	32.4	44.0	38.9	0.272
Death (%)	10.5	12.0	8.1	0.612

*Mean values ± standard deviation

Table 2: Unadjusted regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change in ml/min/1.73²***	***95% CI***	***P value***
Overall pop	*-1.69*	*-1.84, -1.53*	*<0.001*
- Slope in White	-1.71	-1.98, -1.44	<0.001
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black population	-0.31	-0.75, 0.13	0.161
-Additional decline in south Asian population	0.19	-0.16, 0.55	0.285

The annual decline in White patients is -1.71 ml/min/*1.73²*
The annual decline in Black patients is -2.02 ml/min/*1.73²*
The annual decline in south Asian patients is -1.51ml/min/*1.73²*

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Predictor Variables	*Annual Change in ml/min/1.73²*	*95% CI*	*P value*
- Years of follow up (Slope in reference pop)	-1.93	-2.31, -1.56	<0.001
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black Population	-0.19	-0.68, 0.30	0.438
-Additional decline in South Asian Population	0.08	-0.31, 0.48	0.676
Time varying variables			
BP<=130/80 mmHg * time in years	0.62	0.27, 0.98	**<0.001**
HbA1C <=7.5% * time in years	0.03	-0.33, 0.39	0.883
Constant variables			
Ethnicity (white is reference category)			
- Black ethnicity	-1.67	-4.97, 1.64	0.322
- SA ethnicity	-0.51	-3.25, 2.23	0.716
Age	0.03	-0.06,0.13	0.466
Gender (female is reference category)	-2.64	-4.87, -0.40	**0.021**
SBP target at baseline	-2.31	-3.89, -0.73	**0.004**
HbA1C value at baseline	-0.66	-2.37, 1.06	0.454
Vascular disease ever (PVD, CVD, IHD)	-1.44	-3.66, 0.79	0.206
Drug treatment ever (ACE, ARB, Dual Block)	0.02	-4.46, 4.50	0.993
Proteinuria at baseline (PCR>15)	0.173	-1.99, 2.33	0.875
Baseline eGFR	1.05	0.99, 1.11	**<0.001**
Constant	-3.18	-11.26, 4.89	0.440

The annual decline in the reference population (White) is -1.93 ml/min
The annual decline in Black patients is -2.12 ml/min
The annual decline in south Asian patients is -1.85 ml/min

Table 4: Ethnic differences in risk of death rate using Cox regression

Ethnic group	*Hazard Ratio*	*95% CI*	*P value*
- White (ref)	1	--	--
- Black	1.01	0.63-2.57	0.982
- South Asian	1.17	0.68-2.32	0.718

*adjusted for age and gender

References

1- Byrne C, Ford D, Gilg J, et al. UK ESRD Incident Rates in 2008: national and centre-specific analyses. UK Renal registry report 2009.

2- Health Survey of England 2004 .http://www.ic.nhs.uk/pubs/hse04ethnic.

3 - Lambie M, Richards N, Smith S. Ethnicity, age and incidence rates for renal replacement therapy in Birmingham, UK: 1990-2004. Nephrol Dial Transplant. 2008 23:3983-3987

4- Ansell DFJ, Feest TG, UK Renal Registry Report. 2007. http://www.renalreg.com

5- Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends 1997;28:122–7.

6- Salifu M, Shah S, Iqbal M et al. Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. Am J Nephrol 2009;30:261-267.

7- Burden AC, McNally PG, Feehally J etal. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med 1992;9:641-645.

8- Earle KK, Porter KA, Ostberg J, et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001;16(2):286-90.

9- Koppiker N, Feehally J, Raymond N, et al. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. Diabet Med. 1998;15(1):60-5.

10- Duru O, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the kidney early evaluation program (KEEP). Am J Kidney Dis 2008;51:192-8.

11- Davis TM. Ethnic diversity in type 2 diabetes. Diabet Med. 2008;25 Suppl

2:52-6.

12- Dreyer G, Hull S, Aitken Z, et al. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM (2009) 102 (4): 261-269.

13- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association and the Royal College of General Practitioners. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. London: Royal College of Physicians; 2006.

14- Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med1999; 341: 1127–1133.

Rate of Progression of diabetic chronic kidney disease in different ethnic groups.

[1*]O. Ali Core medical trainee

[1*]A. Mohiuddin Senior clinical fellow

[2]R. Mathur Research Fellow

[1]G. Dreyer Specialist registrar in Nephrology

[2] S. Hull Reader in Primary Care Development

[1]M.M Yaqoob Professor of Nephrology

[1] Department of Nephrology, Royal London Hospital, London.

2 Department of Primary Care and Public Health, Queen Mary, University of London

*Dr Mohiuddin and Dr Ali contributed equally.

[*]Corresponding author

Professor M.M.Yaqoob.

Department of Nephrology

Royal London Hospital

Whitechapel road

London E1 1BB

Email: m.m.yaqoob@qmul.ac.uk

Word count: 2863 excluding tables and references

Keywords: Diabetic chronic kidney disease, end stage kidney failure, blood pressure, proteinuria.

Abstract:

Objective: To compare the rate of progression of diabetic chronic kidney disease in different ethnic groups.

Design: Prospective longitudinal observational study.

Participants: All new patients attending a tertiary renal unit in east London with diabetic chronic kidney disease between 2000 and 2007 and followed up till 2009 were included. Patients presenting with acute end stage kidney failure were excluded.

Main outcome measures: The primary outcome was annual decline in estimated glomerular filtration rate (eGFR) in different ethnic groups. Secondary end points were the number of patients developing end stage kidney failure and total mortality during the study period.

Results: 329 patients (age 60 years ± 11.9, 208 men) were studied comprising 149 south Asian, 105 White and 75 Black patients. Mean follow up was 6.0±2.3, 5.0±2.7 5.6±2.4 years for White, black and south Asian patients respectively. South Asian patients were younger and had a higher baseline eGFR, but both systolic and diastolic blood pressure was higher in Black patients ($p<0.05$). Baseline proteinuria was highest for the south Asian group followed by White and Black groups. Adjusted linear regression analysis showed that an annual decline in eGFR was not significantly different between the three groups. The number of patients developing end stage kidney failure and total mortality were also not significantly different between the three groups. Angiotensin converting enzyme or angiotensin receptor blockers use, and glycated haemoglobin (HbA1C) were similar at baseline and through out the study period.

Conclusion: We conclude that ethnicity is not an independent factor in the rate of progression renal failure in patients with diabetic chronic kidney disease.

Introduction:

Diabetic chronic kidney disease (DCKD) is one of the leading cause of end-stage kidney failure (ESKF), accounting for 21% of all such cases in the UK[1]. Suboptimal glycaemic and blood pressure control, development of albuminuria and family history are important risk factors for the development of chronic kidney disease in diabetic patients.

There is a higher prevalence of diabetes mellitus (DM) in black and south Asian populations. The prevalence of diabetes among Black Caribbean and Indian men has been reported to be approximately 10% compared with 4.3% in whites[2]. A recent study conducted in one of the most ethnically diverse cities in the United Kingdom (UK) where the incidence of renal replacement therapy (RRT) for south Asian and Black groups was reported to be respectively, 1.88 and 2.16 times greater than for White patients[3]. Therefore, it is not surprising that a higher proportion of patients on RRT comes from ethnic minority groups compared to the UK white population (17.8% vs 11%)[4].

Mortality is also 3.5 times higher in south Asian and Black populations with diabetes compared to Whites in England and Wales[5]. The higher incidence of ESKF in south Asian and Black populations may be related to higher incidence and poorer control of diabetes and hypertension. However, it may also be related to faster progression of diabetic chronic kidney disease in ethnic minority populations. There are conflicting reports on progression of diabetic chronic kidney disease in these population subgroups. Higher rates of kidney function decline have been reported in some studies while others have failed to show this trend[6-9,]

Most studies comparing progression of diabetic chronic kidney disease in ethnically diverse populations have either been small or had a short duration of follow up. The renal clinic at the Royal London Hospital in east London serves an ethnically diverse

population in a large urban centre. The aim of our study is firstly to determine whether the rate of kidney function decline differs by ethnic group after controlling for demographic characteristics and clinical parameters known to be associated with progression of chronic kidney disease, and secondly, to examine the number of patients developing ESKF and total mortality by ethnicity.

Materials and Methods:

Population

The study was conducted at the Royal London hospital, which serves as a tertiary referral centre for three primary care trusts in east London; Newham, Tower Hamlets and City & Hackney, with a combined GP registered population of 885,625 at the end of 2011. The prevalence of CKD among patients with diabetes, based on a local study, is 18%[12].

All adult patients above the age of 18 years with biopsy proven or clinical diagnosis of diabetic chronic kidney disease (where all secondary causes were excluded) attending our kidney outpatient clinic were included in the study. Any other diagnosis of chronic kidney disease, and those presenting acutely with ESKF were excluded from the study.

Ethnicity was self-assigned by the patient. Patients were grouped according to the ethnic categories of the 2001 census. For the purpose of this study patients of Indian, Bangladeshi and Pakistani ethnicity were analysed together as the South Asian subgroup. Patients of African and Caribbean ethnicity were grouped together to form the Black subgroup, though we recognize that these groupings may conceal underlying heterogeneity. Participants were recruited to the study from 2000 until 2007 and followed up prospectively until 2009. Patients left the study if they moved away, died, were started on dialysis or transplanted. The follow-up for remaining patients was censored at the end of 2009.

Clinical data collection

Data was captured electronically using an in-house renal information technology programme (File maker pro) at every clinic visit. This included blood pressure measured in sitting position using cuffs appropriate for individual and all clinical events and changes in medication. Ethical approval was sought, but not required, due to the observational nature of the study utilizing routinely collected, anonymised patient data.

Baseline variables were collected at the first clinic visit and subsequently updated at every clinic visit. The study variables were defined as follows; ischaemic heart disease (IHD) included patients who were had a documented history of angina, myocardial infarction or cardiac revascularization. Diabetic retinopathy included patients who had been diagnosed with the condition by the diabetic ophthalmology clinic. Peripheral vascular disease (PVD) included patients with a history of intermittent claudication or documented vascular disease on an angiogram, and cerebrovascular disease (CVD) included patients with a past history of transient or persistent vascular neurological deficit.

Estimated glomerular filtration rate (eGFR) was calculated based on the 4 variable MDRD equation which includes a correction for black ethnicity. Serum creatinine was measured using Roche Modular Platform automated analyser. Proteinuria was determined using protein creatinine ratio (Roche Modular Platform automated analyser). Protein creatinine ratio (PCR) was only calculated for patients who had positive proteins on a urine dipstick, and thus individuals with no PCR data were considered to have a value less 15. This was based on a separate unit practice development observation on all dipstick negative urine samples in diabetic patients when analysed had PCR < 15 (personal communication). Glycated haemoglobin (HbA1C) was used to assess glycaemic control (BioRad Turbo 2 automated analyser). Data on systolic and diastolic blood pressure, HbA1C, proteinuria and eGFR were

collected every 6 months.

Data coding

Data was cleaned, coded, and analysed using Stata 10. Baseline variables were created for: Average eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), PCR and HbA1c value. PCR was considered both as a linear variable and a binary variable (presence or absence of proteinuria at baseline defined as PCR>15). Medications were coded a constant variable (ever present vs never present) for angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or dual blockade.

Descriptive analysis

Bivariate statistics outlining the population breakdown by ethnicity were conducted. Analysis of Variance (ANOVA) was used to examine ethnic differences in the means of continuous variables, while chi-squared tests were used to examine differences ethnic differences for categorical variables.

Statistical Methods

Unadjusted and adjusted linear regression models were used to determine whether the annual change in eGFR differed by ethnic group. For this analysis, the eGFR values collected every 6 months were collapsed together to form annual averages.

To investigate whether the annual decline in eGFR was modified by ethnicity, an interaction term between years of follow up and ethnic group was utilized. The addition of an interaction term between ethnicity and "year squared" to the linear model already containing an interaction between ethnicity and year was shown to be non-significant, thus suggesting for us to proceed with a model examining linear annual change in eGFR.

The adjusted analysis controlled for age at baseline, gender, presence or absence of vascular disease (defined as any prior diagnosis of CVD, PVD, or IHD), presence or

absence of drug treatment (defined as any prior prescription of ACEi, ARBs, or dual blockade), presence or absence of proteinuria at baseline (defined as a baseline PCR value of greater than 15), and baseline eGFR. In addition, the analysis included interaction terms to examine the effect of blood pressure and HbA1C being controlled to target in each year of follow-up. The BP target was set at <= 130/80 mmHg and the HbA1C target was <=7.5%.

Analysis of Variance (ANOVA) was used to examine ethnic differences in the distribution of continuous variables, while chi-squared tests were used for categorical variables. Finally, survival analysis using Cox regression was used to estimate ethnic differences in the risk of death adjusting for age and gender.

Results

Population

Out of a total of 356 eligible patients a total of 329 patients with more than 6 years follow up were included. Twenty seven patients were excluded because 10 presented with ESKF and 17 patients had no ethnicity data. Less than 10% of the patients had missing data, which was attributed to missing clinics and less than 5% were lost to follow up due to death or relocation. The baseline characteristics are shown in table1.

The south Asian group was the youngest, with a shorter duration of diabetes and lower baseline blood pressure in comparison to Whites. Black groups have the shortest duration of diabetes but higher baseline systolic and diastolic blood pressure. Baseline eGFR was highest for south Asian groups and lowest for White groups. Mean HbA1C did not differ between ethnic groups, while baseline proteinuria was highest for south Asian groups followed by White and Black groups. Prevalence of IHD was highest for south Asian patients. Prevalence of other co-morbidities, smoking, and drug prescription was not significantly different between the three groups.

Primary end point *(Annual decline in eGFR):*

The overall annual decrease in eGFR was -1.69 in the total population. In the unadjusted linear regression analysis the annual decline in eGFR in white, black and south Asian groups was -1.78, -2.02 and – 1.51 respectively. There was no significant difference in the rate of decline in eGFR between the three groups (Table 2).

Furthermore the adjusted linear regression analysis indicated no significant differences in the annual change in eGFR between the ethnic groups over the entire study period. However the analysis showed that control of blood pressure, gender and degree of renal impairment at baseline were significant predictors of progression (Table 3).

Secondary end points:

By the end of the observation period, 125 individuals had developed ESKF, 32 individuals had died, and 172 individuals were censored. The crude proportions of ESKF were 32%, 44% and 38% in the White, Black, and South Asian groups respectively and were not statistically different (p=0.272). After adjusting for age and gender, the survival analysis indicated no significant difference by ethnicity in the risk of death (Table 4).

Discussion:

In this single centre longitudinal prospective observational study of patients with diabetic chronic kidney disease, the average annual decrease in eGFR in the whole population was -1.69 ml/min/1.73^2. No significant differences in the rate of progression by ethnic group were evidenced. To date, this is the largest study of its kind in the literature.

Burden et al. have reported previously that south Asians with diabetes are 13 times more likely to develop ESKF than their White counterparts, suggesting a faster progression of chronic kidney disease (CKD)[7]. A study carried out in the UK, which supports this hypothesis, found that the proportion of patients doubling their creatinine was significantly higher in south Asians compared to whites[8]. However this study had significantly fewer patients than our study and their patients had early CKD at baseline compared with our population who had moderately severe renal impairment at presentation, which was an independent predictor of progression of renal failure. In contrast, another small study (39 patients) in the UK by Koppiker et al., has suggested no difference in the rate of progression between Whites and south Asians[9]. However complete data was available for only 36 patients. Similarly a study in the United States, has also reported no significant differences in progression of diabetic kidney disease between Black and White populations with equivalent diabetic control[6]. Our results are broadly in agreement with these studies by demonstrating lack of interaction between ethnicity and the rate of decline in kidney function, though Black patients had a modest additional unadjusted annual decline of 0.31 ml/min/1.73^2.

Blood pressure and glycaemic control are important risk factors for progression of diabetic chronic kidney disease. Generally blood pressure control is more difficult to achieve among Black populations and may contribute towards a faster rate of kidney function decline. One study showed that there was no significant difference in rate of kidney function decline after adjusting for the effects of glycaemic control in Black populations compared with Whites, while others have shown significant difference despite equivalent BP and glycaemic control. A difference in the use of antihypertensive medication including renin angiotensin blocking medication (RAAS) has also been suggested[9,-11]. In this study there was no significant difference in glycaemic control or the use of renin angiotensin blocking medications in the three groups. However, Black patients had a significantly higher baseline systolic, diastolic and above target blood pressure. In our previous study we observed a higher prevalence of BP>150/90 in

Blacks in a community based cohort with mild CKD[12], a result which is confirmed by this study in a hospital based cohort of patients with DCKD. Although, in this study there was no significant difference in the decline of kidney function between the ethnic groups, the adjusted analysis showed that the lack of control of blood pressure below the target of 130/80 mmHg was independently associated with rapid decline of eGFR underscoring the importance of optimal blood pressure management as a key modifiable risk factor. Moreover, as expected gender and severity of renal impairment were the other significant predictors of progression of diabetic kidney disease (Table 3).

There was no significant difference in total mortality (Table 4) and prevalence of end stage kidney failure between the different ethnic groups, however the study was not powered to address this question adequately and will require a large cohort study to confirm these findings. It is important to note however, that south Asians had a higher baseline eGFR, and this could be explained in part, by ethnic differences in referral patterns to our center. Primary care physicians may be more likely to refer south Asians with early diabetic kidney disease compared to Whites, reflecting concern that diabetic kidney disease in south Asians is more difficult to control and is associated with a faster rate of decline.

Current national chronic kidney disease (CKD) guidelines do not include ethnicity as a risk factor for CKD[13]. Therefore the recommendation for the management of CKD in general and DCKD in particular for patients from different ethnic minority groups is similar to that for the white population. The results of this study suggest that there is no need for different set of guidelines for different ethnic groups at present and efforts should be directed at determining the reasons behind sub-optimal blood pressure targets in certain ethnic groups.

Strengths and weaknesses of the study

Strengths of this study include the large number of cases, the completeness of ethnicity and clinical data recording and the prolonged period of follow up. The communities from which these patients are drawn include some of the most socially deprived and multi-ethnic populations in England, hence our results will be of interest to commissioning organisations throughout the UK.

Weaknesses include combining ethnic subgroups into three broad categories, which may mask differences in treatment or progression. We are also unable to identify differences in referral thresholds and patterns by the GP practices in the localities. Other perceived weakness of the study could be combining diabetic patients with type 1 and 2 for analysis. However, in real life setting only differences in patients with chronic kidney disease with type 1 and type 2 are stages at which patients are referred because of variable period of undiagnosed type 2 diabetes mellitus. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro and micro-vascular chronic complications of diabetes [14].

Conclusion

This study demonstrates that there is no significant interaction between ethnicity and the rate of progression of chronic kidney disease in patients with diabetes mellitus. Furthermore the prevalence of renal replacement therapy indicating end stage kidney failure, and mortality was also similar between the three groups.

Tables

Legend for tables

Table 1: Baseline characteristics of study participants by ethnic group

Table 2: Unadjusted linear regression for annual change in eGFR (n=329)

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Table 4: Ethnic differences in risk of death using Cox regression

Table 1: Baseline characteristics of study participants by ethnic group

Characteristic	White	Black	South Asian	P value
N	*105*	*75*	*149*	
Baseline Measures*				
Mean age	61.3±12.6	62.4±11.3	57.8±11.4)	0.005
Male (%)	61.5	66.2	65.8	0.741
T2DM (%)	85	100	98	<0.001
Duration of diabetes (years)	18.3±11.6	13.4±7.1	14.0±12.9	0.013
Duration of follow up (years)	6.0±2.3	5.0±2.7	5.6±2.4	0.05
Diabetic retinopathy (%)	84	81	76	0.110
Mean eGFR ml/min/1.73^2	38.1±19	39.0±21	44.3±21	0.039
Mean Systolic BP mmHG	146.6±26	158.3±23	136.6±24	<0.001
Systolic BP >130 mmHG (%)	78.1	86.7	61.7	<0.001
Mean Diastolic BP mmHG	76±11	83±15	75±11	0.002
Diastolic BP >80 (%)	46.7	53.3	37.6	0.066
Mean HBA1c %	8.5±1.8	8.8±2.2	8.7±1.9	0.445
HBA1c >7.5% (%)	67.6	69.3	71.1	0.833
PCR>15 mg/mmol (%)	58.2	47.5	64.4	<0.001
Constant Measures				
IHD (%)	28.6	21.3	38.9	0.020
PVD (%)	15.2	10.7	12.1	0.626
CVD (%)	10.5	8.0	10.7	0.799
Statin use (%)	83.8	80.0	80.4	0.742
ACE use (%)	72.4	70.7	73.7	0.894
ARB use (%)	34.3	40.0	41.2	0.519
Dual Blockade (%)	14.3	17.3	20.1	0.483
Current smoker (%)	18.6	13.6	13.1	0.609
Outcome Measures				
End stage Kidney Failure (%)	32.4	44.0	38.9	0.272
Death (%)	10.5	12.0	8.1	0.612

*Mean values ± standard deviation

Table 2: Unadjusted regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change in ml/min/1.73²***	***95% CI***	***P value***
Overall pop	*-1.69*	*-1.84, -1.53*	*<0.001*
- Slope in White	-1.71	-1.98, -1.44	<0.001
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black population	-0.31	-0.75, 0.13	0.161
-Additional decline in south Asian population	0.19	-0.16, 0.55	0.285
The annual decline in White patients is -1.71 ml/min/*1.73²*			
The annual decline in Black patients is -2.02 ml/min/*1.73²*			
The annual decline in south Asian patients is -1.51ml/min/*1.73²*			

Table 3: Adjusted linear regression for annual change in eGFR (n=329)

Predictor Variables	***Annual Change in ml/min/1.73²***	***95% CI***	***P value***
- Years of follow up (Slope in reference pop)	-1.93	-2.31, -1.56	<0.001
Coefficients for ethnicity interaction (additional decline in ml/min/*1.73²* per year)			
-Additional decline in Black Population	-0.19	-0.68, 0.30	0.438
-Additional decline in South Asian Population	0.08	-0.31, 0.48	0.676
Time varying variables			
BP<=130/80 mmHg * time in years	0.62	0.27, 0.98	**<0.001**
HbA1C <=7.5% * time in years	0.03	-0.33, 0.39	0.883
Constant variables			
Ethnicity (white is reference category)			
- Black ethnicity	-1.67	-4.97, 1.64	0.322
- SA ethnicity	-0.51	-3.25, 2.23	0.716
Age	0.03	-0.06,0.13	0.466
Gender (female is reference category)	-2.64	-4.87, -0.40	**0.021**
SBP target at baseline	-2.31	-3.89, -0.73	**0.004**
HbA1C value at baseline	-0.66	-2.37, 1.06	0.454
Vascular disease ever (PVD, CVD, IHD)	-1.44	-3.66, 0.79	0.206
Drug treatment ever (ACE, ARB, Dual Block)	0.02	-4.46, 4.50	0.993
Proteinuria at baseline (PCR>15)	0.173	-1.99, 2.33	0.875
Baseline eGFR	1.05	0.99, 1.11	**<0.001**
Constant	-3.18	-11.26, 4.89	0.440
The annual decline in the reference population (White) is -1.93 ml/min			
The annual decline in Black patients is -2.12 ml/min			
The annual decline in south Asian patients is -1.85 ml/min			

Table 4: Ethnic differences in risk of death rate using Cox regression

Ethnic group	*Hazard Ratio*	*95% CI*	*P value*
- White (ref)	1	--	--
- Black	1.01	0.63-2.57	0.982
- South Asian	1.17	0.68-2.32	0.718

*adjusted for age and gender

References

1- Byrne C, Ford D, Gilg J, et al. UK ESRD Incident Rates in 2008: national and centre-specific analyses. UK Renal registry report 2009.

2- Health Survey of England 2004 .http://www.ic.nhs.uk/pubs/hse04ethnic.

3 - Lambie M, Richards N, Smith S. Ethnicity, age and incidence rates for renal replacement therapy in Birmingham, UK: 1990-2004. Nephrol Dial Transplant. 2008 23:3983-3987

4- Ansell DFJ, Feest TG, UK Renal Registry Report. 2007. http://www.renalreg.com

5- Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends 1997;28:122–7.

6- Salifu M, Shah S, Iqbal M et al. Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. Am J Nephrol 2009;30:261-267.

7- Burden AC, McNally PG, Feehally J etal. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med 1992;9:641-645.

8- Earle KK, Porter KA, Ostberg J, et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001;16(2):286-90.

9- Koppiker N, Feehally J, Raymond N, et al. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. Diabet Med. 1998;15(1):60-5.

10- Duru O, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the kidney early evaluation program (KEEP). Am J Kidney Dis 2008;51:192-8.

11- Davis TM. Ethnic diversity in type 2 diabetes. Diabet Med. 2008;25 Suppl

2:52-6.

12- Dreyer G, Hull S, Aitken Z, et al. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM (2009) 102 (4): 261-269.

13- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association and the Royal College of General Practitioners. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. London: Royal College of Physicians; 2006.

14- Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med1999; 341: 1127–1133.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.