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The impact of chronic kidney disease and cardiovascular comorbidity on mortality in a multi-ethnic population

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Abstract

Objective: To assess the impact of chronic kidney disease (CKD) and cardiovascular comorbidity on mortality in a multi-ethnic primary care population.

Design: Retrospective, observational cohort study.

Setting: Inner-city primary care trust in West Midlands, United Kingdom.

Participants: Individuals aged 40 years and older, of South Asian, black or white ethnicity, registered with a general practice and with their kidney function checked within the last 12 months.

Outcome Measure: All-cause mortality.

Results: Reduced estimated Glomerular Filtration Rate, higher albuminuria, older age, white ethnicity (versus South-Asian or black ethnicity) and increasing cardiovascular comorbidities were independent determinants of a higher mortality risk. In the multivariate model including comorbidities and kidney function, the hazard ratio for mortality for South Asians was 0.697 (95% confidence interval (CI) 0.56 – 0.868, p=0.001) and for blacks was 0.533 (95% CI 0.403 – 0.704, p<0.001) compared to whites.

Conclusions: The hazard ratio for death is lower for South Asian and black individuals compared to white individuals. This is, in part, independent of age, gender, socio-economic status, kidney function and comorbidities. Risk of death is higher in individuals with CKD and with a higher cumulative cardiovascular comorbidity.

Article summary

- Article focus
  - Retrospective, primary care based cohort study
  - Investigating relationship between ethnicity and cardiovascular comorbidity
  - Inner city population with high deprivation
- Key messages
  - Renal function (both eGFR and ACR) conveys prognostic significance
  - Cumulative comorbidity score can be used to risk stratify
  - Hazard ratio for death is lower for South Asian and black individuals compared to white individuals
- Strengths and limitations of this study
  - Sample size with inclusion of many practices
  - Ethnicity data well recorded (>80%)
  - Primary care based, looking at multiple cardiovascular comorbidities

Introduction

Chronic kidney disease (CKD) is a risk factor for increased mortality [1], with an increased risk of death associated with both declining excretory renal function and albuminuria [2-4]. CKD prevalence and the risk imparted by CKD may vary by ethnicity; for example, some studies indicate that CKD is more common in people of white ethnicity [5 6] but non-white ethnic groups have a faster progression to end-stage kidney disease [7 8]. Paradoxically, when treated with chronic dialysis treatment, people of non-white ethnicity have a lower mortality risk than people of white ethnicity [9 10]. An increased risk of death is also associated with other comorbidities, including hypertension, diabetes and cardiovascular disease (CVD) [11-16].

Whilst previous studies have indicated survival differences between ethnic groups [8 17-21], there has been limited reporting in these studies on the relative impact of comorbidities including kidney function on a population basis. This paucity of data reflects a shortfall in the availability of population based primary care databases linked to estimated Glomerular Filtration Rate (eGFR) and albuminuria reporting and traceable to mortality. Furthermore there is minimal comparative data on people of South Asian ethnicity; comparative studies usually report data on Chinese-Asians [5].

In the United Kingdom, there has been a systematic improvement in chronic disease recognition through a primary care pay for performance system, the Quality and Outcomes Framework (QOF) [22 23]. This system utilises chronic disease registers for the identification, monitoring and management of patients with known comorbidities; these disease registers can be combined with laboratory results and linked with demographic and mortality data to better identify determinants of outcomes.

We have therefore utilised chronic disease registers to perform a retrospective cohort study of the relationship between CKD, cardiovascular comorbidity and mortality within a deprived, inner-city multi-ethnic population. This study incorporated all stages of kidney function (except those with an eGFR below 15ml/min/1.73m^2) in patients with known CV comorbidities and focused on three ethnic groups: South Asian (including individuals of Bangladeshi, Indian and Pakistani descent), black (individuals from or who have ancestors from Africa or the Caribbean) and white.

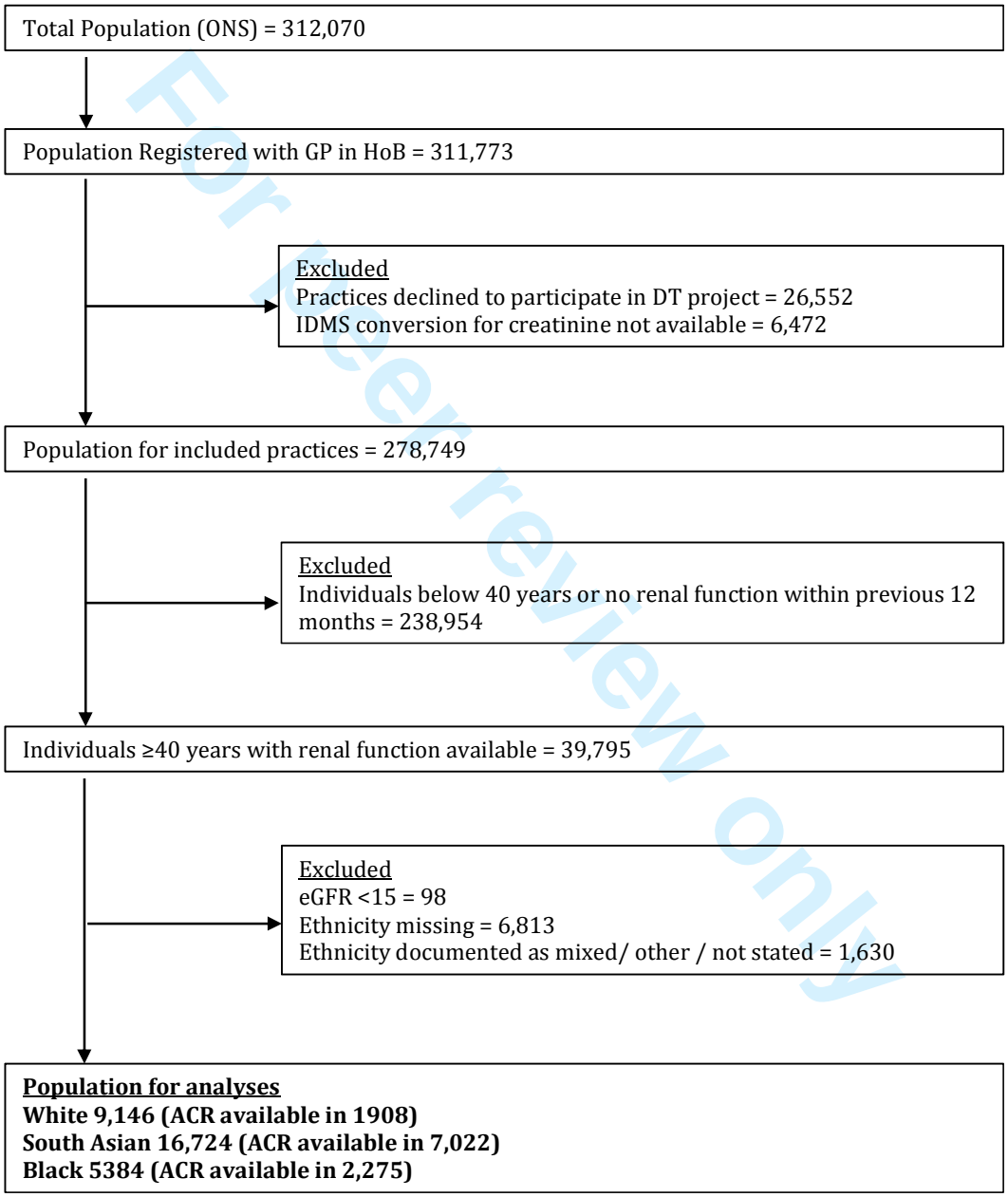
Methods

Ethics: The data was fully anonymised and was available as a component of an on-going clinical development programme. The responsible NHS R&D Consortium stated that this study did not require ethical submission to an NHS research ethics committee as it represented an evaluation of part an on-going primary care trust (PCT) programme. For PCT data extraction the PCT professional executive committee and GP locality leads provided approval for the programme, including evaluation and publication.

Cohort identification: The cohort was derived from Heart of Birmingham (Teaching) Primary Care Trust (HoB PCT) which had a registered population of 312,070 (September 2008). The majority of the

population (62%) were non-white [24]. Data were collected centrally, utilising software able to identify comorbidities through their classification on chronic disease registers **[Enhanced Healthcare Services, Essex, UK].** Complete sets of anonymised data were available for 63 out of 73 general practices within HoB PCT comprising a population of 285,221 and these were extracted from electronic downloads. **Figure 1** illustrates the selection process for inclusion in the study.

Figure 1. Flow Diagram indicating selection process for inclusion in the analyses



The inclusion criteria comprised individuals aged 40 years and over whom had kidney function testing performed within the previous 12 months. Data for the following variables were collected: age, gender, ethnicity (self-reported), current smoking status, socio-economic status (SES), eGFR and\or creatinine, urinary albumin:creatinine ratio (ACR) and vascular comorbidity (atrial fibrillation, chronic kidney disease, diabetes mellitus, heart failure, hypertension, ischaemic heart disease and stroke) as defined by a relevant clinical (Read) code specified by the UK pay for performance (QOF) business rules [25].

A standardised Isotope Dilution Mass Spectrometry (IDMS) eGFR was reported from one of three local biochemistry laboratories, however eGFR reporting was not universally recorded on primary care systems in 2008 and if this was not available the eGFR was calculated by utilising laboratory provided correction factors for the creatinine to generate IDMS traceable eGFR. One general practice in the catchment area was excluded as IDMS traceable creatinine was not available from a fourth laboratory that provided blood tests specifically for that catchment area.

Socio-economic status was assessed using the Index of Multiple Deprivation (IMD 2007 [26]); this utilises the postcode from an individual's address to identify the Lower Layer Super Output Area (LSOA) where the individual resides. Each of the 32,482 LSOAs in England are assigned a score and rank for the IMD 2007, with lower ranks corresponding to the most deprived areas. The Index of Multiple Deprivation has been validated as superior to traditional deprivation indexes such as the Townsend score [27], due to its use of multiple domains reflective of socioeconomic deprivation [28]. The IMD 2007 score incorporates seven areas of deprivation: income deprivation; employment deprivation; health deprivation and disability; education; skills and training deprivation; barriers to housing and services; living environment deprivation; and crime. For the analyses presented, deprivation was divided into national quintiles, with the most deprived quintile as the reference population (i.e. how mortality in less deprived quintiles compared to the most deprived quintile).

Mortality data was obtained from the Primary Care Mortality Database [29] , a resource developed by The NHS Information Centre in partnership with the Office for National Statistics (ONS). Data obtained from ONS records is linked to the general practice where the individual was registered and therefore allows data to be extracted for specific general practices (i.e. those within HoB PCT). Individuals included in this analysis were either still registered with a HoB PCT GP at the end of the follow up period or had died whilst still registered at the practice. The follow up period was from May 2008 until February 2011.

Statistical Analyses

All analyses were performed using PASW statistics 18 for Windows **[IBM, Chicago, Il, USA]**.

Measurements for kidney function were divided into categories; eGFR into six categories (15-29, 30-44, 45-59, 60-89, 90-119 and >120 ml/min) with the eGFR range between 90 and 119 ml/min as the reference population. Individuals with an eGFR <15 ml/min were excluded from the analysis. ACR was divided into five categories (<1.1 mg/mmol 'optimal', 1.1-2.99 'high normal', 3-29.99 'high', 30-199.99 'very high' and ≥200 'nephrotic') in line with the KDIGO consensus conference [30].

The relationship between age and mortality was not linear. Therefore, age was divided into six categories (50 years and under, 51-60, 61-70, 71-80, 81-90, greater than 90 years) with the youngest group serving as comparator.

Descriptive statistics are presented as mean with standard deviation or median with interquartile range depending on distribution. Continuous variables were compared using ANOVA (normal distribution) with post-hoc Bonferroni analysis or Kruskal-Wallis (non-parametric distribution) tests. Chi-squared tests were used to compare categorical variables.

Cox regression survival analysis was used to evaluate the association of ethnicity and mortality, both before and after adjusting for covariates. Data are presented using survival plots, hazard ratios (HRs) with 95% confidence intervals (95% CI) and p-values. Both univariate (unadjusted) and multivariate (adjusted) regression analyses are presented.

The association between comorbidity, ethnicity and mortality was assessed by univariate analyses for all risk factors and then presented as three models. Model 1 incorporates the number of identified vascular comorbidities (zero to seven), ethnicity, age, gender, smoking status and SES. Model 2 includes eGFR level with removal of CKD from the comorbidity score (possible scores therefore zero to six) in order to avoid the association between declining renal function and the likelihood of being on the CKD register. Model 3 added ACR to the variables in Model 2.

A complete case model was used in the analyses. All data were complete with the exception of ACR. Therefore data were analysed for all individuals identified (unadjusted, Model 1 and Model 2) and then repeated for individuals who had an ACR recorded (unadjusted and Models 1-3). An 'enter' technique was used for the regression analysis.

Results

Complete Cohort

At inception (May 2008) 31,254 individuals fulfilled inclusion criteria for analysis. People of South Asians ethnicity formed the largest ethnic group (16,724, 53.4%), followed by people of white ethnicity (9146, 29.3%) and black ethnicity (5384, 17.2%). Baseline characteristics of the study population are shown in **Table 1**. The age distribution differed between groups with South Asians significantly younger than the other two ethnic groups. There was no significant difference in gender between the three ethnic groups. Smoking was least common in the South Asian group. The majority of all three ethnic groups resided in the most deprived quintile, with a higher proportion of people of South Asian and black ethnicity in this quintile than people of white ethnicity.

Table 1: Baseline characteristics by ethnicity. Complete Cohort.

		All	White	South Asian	Black	p-value
Number	**n (%)**	31254 (100)	9146 (29.3)	16724 (53.4)	5384 (17.2)	
Age	**median (lower, upper quartile)**	59.0 (50.0,71.0)	65.0 (55.0, 75.0)	56.0 (49.0, 68.0)	61.0 (48.0, 73.0)	<0.001
	50 and under (%)	8421 (26.9)	1515 (16.6)	5124 (30.6)	1782 (33.1)	<0.001
	51-60 (%)	8017 (25.7)	1948 (21.3)	5170 (30.9)	899 (16.7)	
	61-70 (%)	6650 (21.3)	2459 (26.9)	3206 (19.2)	985 (18.3)	
	71-80 (%)	6006 (19.2)	2109 (23.1)	2568 (15.4)	1329 (24.7)	
	81-90 (%)	1974 (6.3)	1008 (11.0)	604 (3.6)	362 (6.7)	
	>90 (%)	186 (0.6)	107 (1.2)	52 (0.3)	27 (0.5)	
Gender	**female (%)**	15248 (48.8)	4384 (47.9)	8184 (48.9)	2680 (49.8)	0.085
Smoking	**n (%)**	5150 (16.5)	2285 (25.0)	1812 (10.8)	1053 (19.6)	<0.001
IMD Rank	**Quintile 1 (least deprived) (%)**	152 (0.5)	59 (0.6)	92 (0.6)	1 (0.0)	<0.001
	Quintile 2 (%)	316 (1.0)	132 (1.4)	173 (1.0)	11 (0.2)	
	Quintile 3(%)	3348 (10.7)	1860 (20.3)	1255 (7.5)	233 (4.3)	
	Quintile 4 (%)	5144 (16.5)	2243 (24.5)	2238 (13.4)	663 (12.3)	
	Quintile 5 (most deprived) (%)	22294 (71.3)	4852 (53.1)	12966 (77.5)	4476 (83.1)	
AF	**n (%)**	807 (2.6)	515 (5.6)	212 (1.3)	80 (1.5)	<0.001
CKD	**n (%)**	3648 (11.7)	1318 (14.4)	1691 (10.1)	639 (11.9)	<0.001
Diabetes	**n (%)**	9931 (31.8)	1771 (19.4)	6415 (38.4)	1745 (32.4)	<0.001
Heart Failure	**n (%)**	822 (2.6)	308 (3.4)	385 (2.3)	129 (2.4)	<0.001
Hypertension	**n (%)**	16505 (52.8)	5181 (56.6)	8063 (48.2)	3261 (60.6)	<0.001
IHD	**n (%)**	4226 (13.5)	1417 (15.5)	2386 (14.3)	423 (7.9)	<0.001
Stroke	**n (%)**	1476 (4.7)	570 (6.2)	673 (4.0)	233 (4.4)	<0.001
Comorbidities	**median (lower, upper quartile)**	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.075
	0 (%)	9879 (31.6)	2829 (30.9)	5459 (32.6)	1591 (29.6)	<0.001
	1 (%)	10707 (34.3)	3253 (35.6)	5524 (33)	1930 (35.8)	
	2 (%)	6845 (21.9)	1898 (20.8)	3694 (22.1)	1253 (23.3)	
	3 (%)	2667 (8.5)	785 (8.6)	1451 (8.7)	431 (8)	
	4 (%)	828 (2.6)	254 (2.8)	447 (2.7)	127 (2.4)	
	5 (%)	268 (0.9)	103 (1.1)	124 (0.7)	41 (0.8)	
	6 (%)	55 (0.2)	23 (0.3)	23 (0.1)	9 (0.2)	
	7 (%)	5 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)	
Creatinine	**mean (SD)**	87.0 (25.8)	88.2 (24.7)	84.6 (25.4)	92.3 (28)	<0.001
eGFR (ml/min)	**median (lower, upper quartile)**	80.2 (66.7, 94.3)	74.9 (62.3, 88.8)	81.3 (68.1, 95.3)	85.5 (72.3, 100.1)	<0.001
	>120 (%)	1473 (4.7)	264 (2.9)	802 (4.8)	407 (7.6)	<0.001
	90-120 (%)	8523 (27.3)	1842 (20.1)	4841 (28.9)	1840 (34.2)	
	60-89 (%)	16373 (52.4)	5077 (55.5)	8776 (52.5)	2520 (46.8)	
	45-59 (%)	3447 (11.0)	1389 (15.2)	1627 (9.7)	431 (8.0)	
	30-44 (%)	1134 (3.6)	466 (5.1)	517 (3.1)	151 (2.8)	
	15-29 (%)	304 (1.0)	108 (1.2)	161 (1.0)	35 (0.7)	
Died	**n (%)**	1435 (4.6)	681 (7.4)	541 (3.2)	213 (4.0)	<0.001

The number of vascular comorbidities was similar between groups, with 11-13% of each ethnic group having three or more comorbidities. The prevalence of different vascular comorbidities varied between groups: the white group had a lower reported prevalence of diabetes but a higher prevalence of CKD, atrial fibrillation, heart failure and stroke.

Median eGFR (corrected for ethnicity as appropriate) was 80.2 ml/min and was lowest in the white group (74.9 ml/min compared to 81.3 ml/min for South Asian individuals and 85.5 ml/min for those of black ethnicity; p<0.001). 21.5% of White, 13.8% of South Asian and 11.5% of Black individuals had an eGFR between 15 and 59 ml/min consistent with stage 3-4 CKD.

At the end of the study period a higher proportion of white individuals had died (7.4%) compared to the two other ethnic groups (South Asian 3.2%, Black 4.0%; p<0.001).

Albumin Creatinine Ratio Cohort

An ACR had been tested in 7022 (42.0%), 2275 (24.9%) and 1908 (20.9%) of South Asian, black and white individuals respectively. **Table 2** lists the baseline characteristics for this subgroup. The median ACR was 1.1 mg/mmol and was highest in the South Asian group (1.2 mg/mmol compared to 1.0 mg/mmol for both white and black individuals; p<0.001). There were similar trends to the whole cohort for age distribution, eGFR, smoking status, and deprivation.

Those with an ACR tested were more likely to have a greater vascular comorbid burden (18-20% having three or more comorbidities). A higher proportion of individuals of South Asian descent, male gender and with diabetes had their ACR tested.

In concordance to the whole group analyses, deaths in the ACR cohort were highest amongst white individuals (7.8%) compared to the South Asian (3.6%) and black individuals (3.7%) (p<0.001).

Univariate Analysis

The univariate (unadjusted) analysis for the complete cohort (**Table 3a**) demonstrated unadjusted HRs for death of 0.421 (95% CI 0.376 – 0.471, p<0.001) for people of South Asian ethnicity and 0.522 (95% CI 0.447 – 0.609, p<0.001) for people of black ethnicity compared to people of white ethnicity. The mortality rate increased exponentially with age and a higher HR was observed for male gender, current smokers and total number of comorbidities. No difference in mortality was found between deprivation quintiles. Using an eGFR of 90-119 ml/min as reference, a J-shaped relationship was observed with a higher risk of death seen for both higher and lower eGFR values. The HR for death increased progressively by stage of CKD with an eGFR <90 ml/min.

The univariate analysis was repeated for those individuals who had their ACR reported (**Table 3b**) with similar trends identified to the whole population analysis with the exception of no observed difference between individuals with an eGFR of ≥120 ml/min compared to 90-119 ml/min. A progressive increase in HR for death was seen with each increasing category for ACR.

Table 2: Baseline characteristics by ethnicity. ACR tested cohort.

		All	White	South Asian	Black	p-value
Number	**n (%)**	11205 (100)	1908 (17)	7022 (62.7)	2275 (20.3)	
Age (years)	**median (lower, upper quartile)**	59.0 (50.0, 71.0)	65.0 (55.0, 75.0)	57.0 (50.0, 68.0)	65.0 (49.0, 74.0)	<0.001
	50 and under (%)	1900 (25.9)	304 (15.9)	1961 (27.9)	635 (27.9)	<0.001
	51-60 (%)	3024 (27.0)	413 (21.6)	2239 (31.9)	372 (16.4)	
	61-70 (%)	2370 (21.2)	496 (26.0)	1423 (20.3)	451 (19.8)	
	71-80 (%)	2251 (20.1)	456 (23.9)	1152 (16.2)	643 (28.3)	
	81-90 (%)	611 (5.5)	222 (11.6)	226 (3.2)	163 (7.2)	
	>90 (%)	49 (0.4)	17 (0.9)	21 (0.3)	11 (0.5)	
Gender	**female (%)**	4348 (38.8)	682 (35.7)	2754 (39.2)	912 (40.1)	0.008
Smoking	**n (%)**	1869 (16.7)	518 (27.1)	872 (12.4)	479 (21.1)	<0.001
IMD Rank	**Quintile 1 (least deprived) (%)**	30 (0.3)	4 (0.2)	25 (0.4)	1 (0.0)	<0.001
	Quintile 2 (%)	84 (0.7)	19 (1.0)	60 (0.9)	5 (0.2)	
	Quintile 3(%)	712 (6.4)	233 (12.2)	540 (5.7)	78 (3.4)	
	Quintile 4 (%)	1458 (13.0)	339 (17.8)	876 (12.5)	243 (10.7)	
	Quintile 5 (most deprived) (%)	8921 (79.6)	1313 (68.8)	5660 (80.6)	1948 (85.6)	
AF	**n (%)**	233 (2.1)	113 (5.9)	91 (1.3)	29 (1.3)	<0.001
CKD	**n (%)**	1637 (14.6)	356 (18.7)	921 (13.1)	360 (15.8)	<0.001
Diabetes	**n (%)**	6828 (60.9)	990 (51.9)	4505 (62.4)	1333 (58.6)	<0.001
Heart Failure	**n (%)**	310 (2.8)	74 (3.9)	175 (2.5)	61 (2.7)	0.005
Hypertension	**n (%)**	6189 (55.2)	1092 (57.2)	3679 (52.4)	1418 (62.3)	<0.001
IHD	**n (%)**	1556 (13.9)	281 (14.7)	1071 (15.3)	201 (8.8)	<0.001
Stroke	**n (%)**	480 (4.3)	97 (5.1)	283 (4.0)	100 (4.4)	0.126
Comorbidities	**median (lower, upper quartile)**	1.0 (1.0, 2.0)	2.0 (1.0,2.0)	1.0 (1.0, 2.0)	2.0 (1.0,2.0)	0.818
	0 (%)	2510 (22.4)	472 (24.7)	1514 (21.6)	524 (23.0)	<0.001
	1 (%)	3139 (28.0)	466 (24.4)	2103 (29.9)	870 (25.1)	
	2 (%)	3438 (30.7)	574 (30.1)	2093 (29.8)	771 (33.9)	
	3 (%)	1481 (13.2)	261 (13.7)	928 (13.2)	292 (12.8)	
	4 (%)	448 (4.0)	79 (4.1)	284 (4.0)	85 (3.7)	
	5 (%)	154 (1.4)	46 (2.4)	83 (1.2)	25 (1.1)	
	6 (%)	32 (0.3)	10 (0.5)	15 (0.2)	7 (0.3)	
	7 (%)	3 (<0.1)	0 (<0.1)	2 (<0.1)	1 (<0.1)	
Creatinine	**mean (SD)**	89.1 (27.6)	91.8 (26.2)	86.2 (26.8)	95.8 (29.6)	<0.001
eGFR (ml/min)	**median (lower, upper quartile)**	81.1 (66.3, 95.9)	74.3 (59.7, 89.8)	82 (67.4, 89.8)	84.2 (70.0, 98.9)	<0.001
	>120 (%)	611 (5.5)	67 (3.5)	380 (5.4)	164 (7.2)	<0.001
	90-120 (%)	3234 (28.9)	404 (21.2)	2091 (29.8)	739 (32.5)	
	60-89 (%)	5451 (48.6)	953 (49.9)	3453 (49.2)	1045 (45.9)	
	45-59 (%)	1300 (11.6)	323 (16.9)	750 (10.7)	227 (10.0)	
	30-44 (%)	487 (4.3)	131 (6.9)	274 (3.9)	82 (3.6)	
	15-29 (%)	122 (1.1)	30 (1.6)	74 (1.1)	18 (0.8)	
ACR (mg/mmol)	**median (lower, upper quartile)**	1.1 (0.4, 3.4)	1.0 (1.4, 2.8)	1.2 (0.5, 3.8)	1.0 (0.3, 2.9)	<0.001
	Optimal (<1.1) (%)	5641 (50.3)	1026 (53.8)	3400 (48.4)	1214 (53.4)	<0.001
	High Normal (1.1-2.99) (%)	2485 (22.2)	426 (22.3)	1560 (22.2)	499 (21.9)	
	High (3.0-29.99) (%)	2594 (23.2)	402 (21.1)	1717 (24.4)	475 (20.9)	
	Very High (30 - 200) (%)	413 (3.7)	49 (2.6)	287 (4.1)	77 (3.4)	
	Nephrotic (>200) (%)	73 (0.7)	5 (0.3)	58 (0.8)	10 (0.4)	
Died	**n (%)**	484 (4.3)	149 (7.8)	250 (3.6)	85 (3.7)	<0.001

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Table 3: Cox Proportional Hazard Regression Analysis. Univariate (unadjusted) analyses

		Complete Cohort (3a)		ACR Tested Cohort (3b)	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	Reference population	(<0.001*)	Reference Population	(<0.001*)
	South Asian	0.421 (0.376 - 0.471)	<0.001	0.444 (0.362 - 0.545)	<0.001
	Black	0.522 (0.447 - 0.609)	<0.001	0.467 (0.357 - 0.611)	<0.001
Age (years)	**50 and under**	Reference population	(<0.001*)	Reference Population	(<0.001*)
	51-60	2.127 (1.553 - 2.914)	<0.001	1.757 (1.057 - 2.921)	0.03
	61-70	5.429 (4.078 - 7.228)	<0.001	4.646 (2.926 - 7.345)	<0.001
	71-80	12.971 (9.887 - 17.016)	<0.001	11.363 (7.376 - 17.505)	<0.001
	81-90	32.86 (29.952 - 43.275)	<0.001	24.725 (15.769 - 38.767)	<0.001
	>90	90.904 (65.097 - 126.943)	<0.001	82.731 (46.684 - 146.612)	<0.001
Gender	**Female as reference**	1.375 (1.238 - 1.529)	<0.001	1.401 (1.155 - 1.699)	0.001
Smoker	**Non-smoker as reference**	1.154 (1.009 - 1.317)	0.036	1.259 (1.006 - 1.574)	0.044
IMD Rank	**Quintile 1 (least deprived)**	0.860 (0.385 - 1.919)	0.713	<0.001 (<0.001 - >10^5)	0.939
	Quintile 2	0.822 (0.465 - 1.453)	0.501	<0.001 (<0.001 - >10^5)	0.897
	Quintile 3	1.002 (0.846 - 1.186)	0.983	1.151 (0.818 - 1.619)	0.419
	Quintile 4	0.925 (0.800 - 1.070)	0.297	0.774 (0.577 - 1.039)	0.088
	Quintile 5 (most deprived)	Reference population	(0.802*)	Reference Population	(0.42*)
AF		5.588 (4.757 - 6.565)	<0.001	6.123 (4.568 - 8.207)	<0.001
CKD		3.442 (3.074 - 3.854)	<0.001	3.498 (2.904 - 4.213)	<0.001
Diabetes		1.346 (1.209 - 1.498)	<0.001	1.939 (1.577 - 2.385)	<0.001
Heart Failure		7.622 (6.595 - 8.804)	<0.001	7.279 (5.681 - 9.327)	<0.001
Hypertension		2.079 (1.857 - 2.325)	<0.001	2.05 (1.681 - 2.499)	<0.001
IHD		2.796 (2.495 - 3.132)	<0.001	3.136 (2.592 - 3.795)	<0.001
Stroke		3.654 (3.154 - 4.233)	<0.001	3.709 (2.855 - 4.817)	<0.001
Comorbidities	**0**	Reference population	(<0.001*)	Reference population	(<0.001*)
	1	1.775 (1.487 - 2.118)	<0.001	1.630 (1.094 - 2.430)	0.016
	2	2.930 (2.458 - 3.493)	<0.001	2.917 (2.023 - 4.205)	<0.001
	3	5.486 (4.550 - 6.615)	<0.001	5.580 (3.837 - 8.113)	<0.001
	4	9.584 (7.691 - 11.942)	<0.001	9.855 (6.511 - 14.917)	<0.001
	5	17.591 (13.490 - 22.939)	<0.001	21.091 (13.479 - 33.001)	<0.001
	6	28.391 (18.411 - 43.782)	<0.001	33.673 (17.519 - 64.722)	<0.001
	7	11.873 (1.664 - 84.728)	0.014	29.402 (4.031 - 214.462)	0.001
eGFR (ml/min)	**>120**	1.492 (1.110 - 2.007)	0.008	1.072 (0.603 - 1.903)	0.813
	90-120	Reference population	(<0.001*)	Reference Population	(<0.001*)
	60-89	1.360 (1.162 - 1.591)	<0.001	1.504 (1.138 - 1.987)	0.04
	45-59	3.849 (3.239 - 4.573)	<0.001	4.255 (3.155 - 5.737)	<0.001
	30-44	6.590 (5.401 - 8.041)	<0.001	7.715 (5.564 - 10.699)	<0.001
	15-29	14.465 (11.341 - 18.450)	<0.001	15.054 (9.942 - 22.796)	<0.001
ACR (mg/mmol)	**Optimal (<1.1)**			Reference Population	(<0.001*)
	High Normal (1.1-2.99)			1.363 (1.038 - 1.788)	0.026
	High (3.0-29.99)			2.967 (2.381 - 3.697)	<0.001
	Very High (30 - 200)			6.253 (4.493 - 14.005)	<0.001
	Nephrotic (>200)			7.932 (4.493 - 14.005)	<0.001

* P-value for overall effect

Multivariate Analysis

Following adjustment for covariates the differences in ethnicity remained; people of South Asian and black ethnicities had a lower HR for death in all analyses.

Model 1 (complete cohort, incorporating the number of identified comorbidities, see **Supplementary Table I**) analysed the complete cohort and showed an adjusted HR for death of 0.673 (95% CI 0.595 – 0.761, p<0.001) for people of South Asian ethnicity and 0.592 (95% CI 0.504 – 0.696, p<0.001) for people of black ethnicity compared to people of white ethnicity. When the analysis was restricted to the cohort with ACR tests available the HR for death was 0.757 (95% CI 0.61 – 0.939, p=0.011) for people of South Asian ethnicity and 0.526 for people of black ethnicity (95% CI 0.4 – 0.692, p<0.001) compared to people of white ethnicity. For the complete cohort, mortality risk was lower in IMD quintiles 3 and 4 (compared to the most deprived quintile 5). No significant difference between IMD quintiles was identified in the ACR cohort. Increasing age (51 and over in complete cohort, 61 and over in ACR cohort), smoking status and male gender was significant in analyses for both cohorts. An increased HR for death was observed for two or more comorbidities, with the HR increasing as the number of comorbidities increased.

Kidney function (eGFR) was incorporated into Model 2 (with the removal of CKD from the comorbidity score, see **Supplementary Table I**) and in the complete cohort the HR for people of South-Asian ethnicity was 0.678 (95% CI 0.6 – 0.767 p<0.001) and for people of black ethnicity was 0.789 (95% CI 0.635 – 0.98, p=0.032) compared to people of white ethnicity. Similarly, when the analysis was restricted to the cohort of patients with ACR tests available people of South Asian and Black ethnicity had a lower proportion of deaths compared to people of white ethnicity with HRs of 0.614 (95% CI 0.522 – 0.722, p<0.001) and 0.575 (95% CI 0.435 – 0.759, p<0.001) respectively. In the complete cohort mortality risk was lower in the IMD quintile 4. More than two comorbidities were associated with an increasing HR and an increased HR of death compared to the reference eGFR range (90-119 ml/min) was seen with an eGFR ≥120 ml/min and ≥45 ml/min. An eGFR of 60-89 ml/min was associated with a lower HR. In the analysis of those with ACR tested, an eGFR <60 ml/min was associated with progressively higher HR by CKD stage.

In model 3 (all vascular comorbidities except CKD and the addition of eGFR and ACR, **Table 4**) the HR for death for people of South Asian ethnicity was 0.697 (95% CI 0.56 – 0.868, p=0.001) and for people of black ethnicity was 0.533 (95% CI 0.403 – 0.704, p<0.001) compared to people of white ethnicity **(Figure 2)**. Older age, male gender, being a current smoker and increasing comorbidity (two or more) were associated with an increased HR of death **(Figure 3)**. An ACR of 'high' or greater (i.e. ≥3.0 mg/mmol) and an eGFR <45 ml/min was also associated with an increased HR for death. No significant differences in HRs were observed between deprivation quintiles.

Table 4: Cox Proportional Hazard Regression Analysis. Multivariate (adjusted) analyses. Model 3.

		ACR Tested Cohort	
		Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	Reference Population	(<0.001*)
	South Asian	0.697 (0.56 - 0.868)	0.001
	Black	0.533 (0.403 - 0.704)	<0.001
Age (years)	**50 and under**	Reference Population	(<0.001*)
	51-60	1.519 (0.907 - 2.546)	0.112
	61-70	3.521 (2.17 - 5.712)	<0.001
	71-80	7.381 (4.61 - 11.818)	<0.001
	81-90	15.721 (9.534 - 25.922)	<0.001
	>90	51.641 (27.889 - 95.621)	<0.001
Gender	**Female as reference**	1.782 (1.46 - 2.176)	<0.001
Smoker	**Non-smoker as reference**	1.886 (1.488 - 2.392)	<0.001
IMD Rank	**Quintile 1 (least deprived)**	<0.001 (<0.001 - >10^5)	0.952
	Quintile 2	<0.001 (<0.001 - >10^5)	0.913
	Quintile 3	0.978 (0.68 - 1.387)	0.902
	Quintile 4	0.788 (0.585 - 1.062)	0.118
	Quintile 5 (most deprived)	Reference Population	0.65*
Comorbidities	**0**	Reference population	(<0.001*)
	1	1.371 (0.932 - 2.016)	0.109
	2	1.486 (1.019 - 2.166)	0.039
	3	2.29 (1.53 - 3.428)	<0.001
	4	3.153 (2.002 - 4.964)	<0.001
	5	5.141 (2.869 - 9.212)	<0.001
	6	10.54 (2.52 - 44.084)	0.001
eGFR (ml/min)	**>120**	1.396 (0.782 - 2.492)	0.26
	90-120	Reference Population	(<0.001*)
	60-89	0.907 (0.982 - 1.207)	0.505
	45-59	1.282 (0.932 - 1.763)	0.126
	30-44	1.566 (1.095 - 2.239)	0.014
	15-29	2.073 (1.315 - 3.268)	0.002
ACR (mg/mmol)	**Optimal (<1.1)**	Reference Population	(<0.001*)
	High Normal (1.1-2.99)	1.032 (0.784 - 1.359)	0.821
	High (3.0-29.99)	1.837 (1.464 - 2.305)	<0.001
	Very High (30 - 200)	2.956 (2.132 - 4.099)	<0.001
	Nephrotic (>200)	3.838 (2.108 - 6.985)	<0.001

* P-value for overall effect

Figure 2. Cox Regression Survival Plot. Differences between ethnicities in Model 3 (comorbidities, eGFR and ACR)

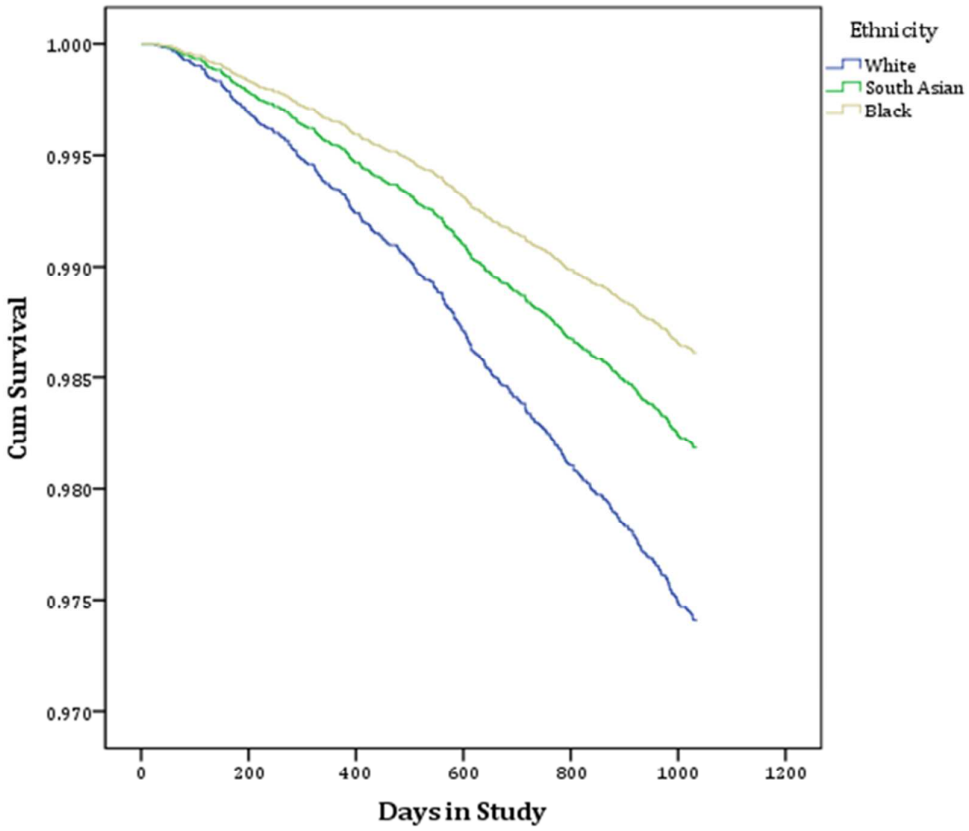
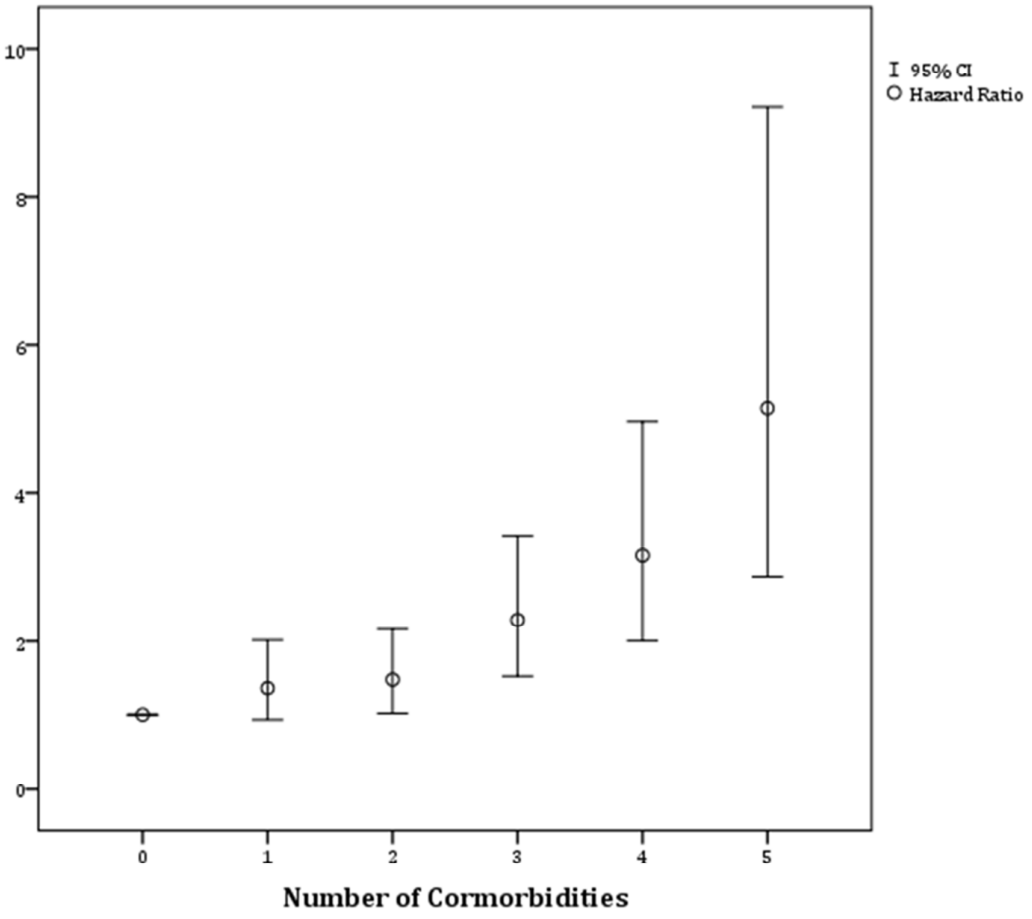


Figure 3. Hazard ratio (HR) for death by number of comorbidities. Multivariate (adjusted) analysis: Model 3



HR not illustrated for 6 comorbidities; HR 10.54 (95% CI 2.52 - 44.084)

Discussion

This study utilised routinely available clinical and laboratory data, including kidney function assessed by eGFR and ACR, from a large primary care population. We included in the analysis detailed socio-economic status (SES) and, importantly, studied three ethnic groups, South-Asian, black and white. Prior to this research, there has been uncertainty about the impact of ethnicity and SES on clinical outcomes in people with significant comorbidities including CKD. The comprehensive nature of the dataset coupled with the ability to utilise the Primary Care Mortality Database has allowed us to assess the relative impact of these factors on survival.

We found that previous associations between lower eGFR and higher ACR and increased mortality applied to this population. Furthermore, these associations remained significant when adjusted for ethnicity, age, gender, cardiovascular risk factors and SES. These results add weight to the risk stratification benefit of measuring ACR has in high risk groups.

A strong cumulative impact of comorbidity on CKD and ethnicity was shown. Whereas traditional comorbidity scores such as the Charlson Comorbidity Index [31] are difficult to calculate accurately in a large primary care setting, our study demonstrates that a simple cumulative score can be used to risk stratify. A similar approach, but also including non-cardiovascular risk factors has recently been described [32]. Our study demonstrates that routinely collected clinical data can be utilised to quantify risk. Potential implications for this include identifying (and targeting) those at the highest risk.

SES was measured by the IMD 2007 score; a cumulative deprivation index score incorporating seven areas of deprivation which has been validated as superior to other deprivation scores [28]. One notable finding is that we did not demonstrate any association between mortality when corrected for all other factors including comorbidity and ethnicity. This is not consistent with a number of other studies, which have shown that there is an independent relationship between SES and mortality and this applies across disease states and ethnic groups [33-36]. Whilst we studied a health care system that is free at the point of care, limiting possible health access issues, the majority of individuals were from the most deprived national quintile. We therefore re-ran the analyses dividing the cohort into equal quintiles. All analyses continue to indicate the effect of ethnicity and the importance of cardiovascular comorbidity and renal function. The univariate analysis (**Supplementary Table II**) and the most comprehensive multivariate analysis (Model 3, (**Supplementary Table III**) did not show any differences between most and least deprived quintiles.

One of the seven areas included in the IMD is health deprivation, raising the possibility of an inbuilt relationship between and deprivation and health even before analyses are undertaken. The possible implication of this was investigated by Adams and White [37] who analysed data having removed the health domain from IMD 2004 and found that its removal had little, practical, effect. This suggests the presence of the health domain is unlikely to influence our result.

We found that the risk of death was lower for people of South Asian and black ethnicity compared to people of white ethnicity, and this remained in all analyses (adjusted and unadjusted) performed. Previous studies comparing the outcomes of different ethnic groups have been limited in their generalizability. They have either looked at disease specific mortality [8 18 20 21] or have been based in populations that do not have access to free comprehensive healthcare. The finding that differences in mortality risk between ethnic groups is independent of age, gender, SES, kidney function and comorbidities requires further work. There may be other external factors which can explain this risk or factors related to genetic diversity which may require genome wide studies to elucidate.

A major strength in this study is the sample size, which included sixty-two practices of varying list size and number of practitioners. Ethnicity was documented in over 80% of the population studied; this is, much higher than normally found in primary care records [38]. Renal function was described in terms of eGFR and ACR, the latter becoming of increased prominence in the stratification of cardiovascular risk.

Our analyses have used data from primary care coding and recording systems, which formed part of the electronic downloads. There is a relative paucity of published literature regarding the correct identification of people onto the correct risk registers [39 40]. Surrogate measures of accuracy of the data include previous studies looking at gaming for QOF points (falsely classifying people with conditions they do not have thereby increasing revenue) or exception reporting (excluding individuals who have not had the appropriate monitoring completed) suggest that both these are rare [23 41 42].

Not all individuals had their ACR measured and the percentage varied between ethnic groups, one of the limitations of retrospective, population-based analyses. A higher number of males and individuals with diabetes or of South Asian descent had an ACR performed. However, similar trends for mortality were observed for age distribution, eGFR, smoking status and deprivation, suggesting generalizability of results.

In summary, we have shown the determinants of mortality were multifactorial in a high risk population and that ethnicity should be considered as a non-traditional risk factor for mortality; the HR for death was lower for South Asian and black individuals compared to white individuals which was, in part, independent of age, gender, SES, renal function and comorbidities. Furthermore, a simple cumulative comorbidity system may have prognostic utility. Renal function (eGFR and ACR) provides additional information and gender, age and smoking status remain significant risk factors for mortality.

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none

Competing Interests

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Contributorship

Mark Jesky: study design, data analysis, preparation of manuscript
Amanda Lambert: study design, data acquisition and analysis, review of manuscript
AC Felix Burden: study design, data acquisition, review of manuscript
Paul Cockwell: study design, data analysis, preparation and review of manuscript

Data sharing

No other data will be available.

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Supplementary Tables

Supplementary Table I: Cox Proportional Hazard Regression Analysis. National IMD quintiles. Multivariate (adjusted) analyses

		Model 1				Model 2			
		Complete Cohort		ACR Tested Cohort		Complete Cohort		ACR Tested Cohort	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	Reference population	(<0.001*)	Reference Population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)
	South Asian	0.673 (0.595 - 0.761)	<0.001	0.757 (0.61 - 0.939)	0.011	0.678 (0.6 - 0.767)	<0.001	0.789 (0.635 - 0.98)	0.032
	Black	0.592 (0.504 - 0.696)	<0.001	0.526 (0.4 - 0.692)	<0.001	0.614 (0.522 - 0.722)	<0.001	0.575 (0.435 - 0.759)	<0.001
Age (years)	**50 and under**	Reference population	(<0.001*)	Reference Population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)
	51-60	1.958 (1.425 - 2.691)	<0.001	1.538 (0.919 - 2.573)	0.101	2.09 (1.52 - 2.874)	<0.001	1.571 (0.937 - 2.632)	0.086
	61-70	4.512 (3.358 - 6.062)	<0.001	3.634 (2.252 - 5.867)	<0.001	4.918 (3.651 - 6.625)	<0.001	3.697 (2.278 - 6.002)	<0.001
	71-80	10.075 (7.568 - 13.412)	<0.001	8.124 (5.122 - 12.887)	<0.001	10.904 (8.153 - 14.582)	<0.001	7.95 (4.962 - 12.738)	<0.001
	81-90	23.973 (17.839 - 32.217)	<0.001	17.018 (10.444 - 27.73)	<0.001	25.203 (18.626 - 34.104)	<0.001	16.155 (9.79 - 26.659)	<0.001
	>90	68.62 (48.166 - 97.759)	<0.001	61.221 (33.372 - 112.31)	<0.001	68.189 (47.554 - 97.777)	<0.001	52.695 (28.401 - 97.77)	<0.001
Gender	**Female as reference**	1.451 (1.303 - 1.616)	<0.001	1.806 (1.48 - 2.203)	<0.001	1.447 (1.298 - 1.612)	<0.001	1.819 (1.491 - 2.22)	<0.001
Smoker	**Non-smoker as reference**	1.722 (1.495 - 1.983)	<0.001	1.986 (1.567 - 2.517)	<0.001	1.692 (1.469 - 1.95)	<0.001	1.959 (1.546 - 2.483)	<0.001
IMD Rank	**Quintile 1 (least deprived)**	1.081 (0.484 - 2.416)	0.849	<0.001 (<0.001 - >10^5)	0.951	1.115 (0.499 - 2.494)	0.79	<0.001 (<0.001 - >10^5)	0.951
	Quintile 2	0.906 (0.512 - 1.603)	0.734	<0.001 (<0.001 - >10^5)	0.916	0.896 (0.506 - 1.587)	0.707	<0.001 (<0.001 - >10^5)	0.917
	Quintile 3	0.821 (0.689 - 0.979)	0.028	0.979 (0.692 - 1.387)	0.907	0.841 (0.705 - 1.003)	0.054	0.984 (0.694 - 1.395)	0.929
	Quintile 4	0.733 (0.63 - 0.852)	<0.001	0.753 (0.559 - 1.015)	0.062	0.737 (0.634 - 0.857)	<0.001	0.776 (0.576 - 1.046)	0.096
	Quintile 5 (most deprived)	Reference population	(0.001*)	Reference Population	(0.478*)	Reference population	(0.002*)	Reference population	(0.592*)
Comorbidities	**0**	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)
	1	1.045 (0.87 - 1.254)	0.64	1.394 (0.926 - 2.098)	0.112	1.024 (0.863 - 1.215)	0.788	1.459 (0.993 - 2.145)	0.055
	2	1.262 (1.049 - 1.52)	0.014	1.831 (1.242 - 2.701)	0.002	1.208 (1.099 - 1.445)	0.039	1.698 (1.166 - 2.471)	0.006
	3	1.824 (1.495 - 2.226)	<0.001	2.551 (1.706 - 3.814)	<0.001	2.118 (1.739 - 2.58)	<0.001	2.719 (1.823 - 4.055)	<0.001
	4	2.722 (2.157 - 3.435)	<0.001	3.866 (2.479 - 6.031)	<0.001	2.643 (2.055 - 3.399)	<0.001	3.713 (2.362 - 5.838)	<0.001
	5	3.892 (2.949 - 5.136)	<0.001	6.247 (3.880 - 10.057)	<0.001	3.641 (2.518 - 5.265)	<0.001	6.203 (3.461 - 11.118)	<0.001
	6	6.535 (4.202 - 10.162)	<0.001	10.83 (5.527 - 21.219)	<0.001	5.069 (1.615 - 15.909)	0.005	10.017 (2.395 - 41.898)	0.002
	7	3.085 (0.431 - 22.084)	0.262	8.972 (1.217 - 66.15)	0.031				
eGFR (ml/min)	**>120**					2.02 (1.5 - 2.721)	<0.001	1.466 (0.822 - 2.616)	0.195
	90-120					Reference population	(<0.001*)	Reference population	(<0.001*)
	60-89					0.82 (0.699 - 0.962)	0.015	0.936 (0.704 - 1.245)	0.649
	45-59					1.102 (0.917 - 1.324)	0.301	1.395 (1.014 - 1.918)	0.041
	30-44					1.342 (1.084 - 1.662)	0.007	1.947 (1.367 - 2.775)	<0.001
	15-29					2.929 (2.267 - 3.784)	<0.001	3.256 (2.095 - 5.059)	<0.001

* P-value for overall effect

Impact of CKD and comorbidity on mortality in a multi-ethnic population.
Jesky et al.
Supplementary Tables

Supplementary Table II: Cox Proportional Hazard Regression Analysis. Population specific IMD quintiles. Univariate (unadjusted) analyses

		Complete Cohort (2a)		ACR Tested Cohort (2b)	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
HoB IMD Rank	**Quintile 1 (least deprived)**	0.942 (0.798 - 1.111)	0.476	0.831 (0.6 - 1.152)	0.268
	Quintile 2	0.947 (0.806 - 1.113)	0.507	0.943 (0.725 - 1.227)	0.664
	Quintile 3	0.895 (0.761 - 1.054)	0.183	0.71 (0.537 - 0.938)	0.016
	Quintile 4	0.923 (0.786 - 1.084)	0.33	0.908 (0.701 - 1.179)	0.465
	Quintile 5 (most deprived)	Reference Population	(0.75*)	Reference Population	(0.154*)

* P-value for overall effect

Impact of CKD and comorbidity on mortality in a multi-ethnic population.
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Supplementary Tables

Supplementary Table III: Cox Proportional Hazard Regression Analysis. Population specific IMD quintiles. Multivariate (adjusted) analyses

		Model 1				Model 2				Model 3	
		Complete Cohort		ACR Tested Cohort		Complete Cohort		ACR Tested Cohort		ACR Tested Cohort	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(0.001*)	Reference population	(<0.001*)
	South Asian	0.674 (0.596 - 0.762)	<0.001	0.753 (0.606 - 0.934)	0.01	0.68 (0.601 - 0.769)	<0.001	0.788 (0.634 -0.979)	0.031	0.7 (0.562 - 0.871)	0.001
	Black	0.598 (0.510 - 0.701)	<0.001	0.529 (0.403 - 0.694)	<0.001	0.621 (0.528 - 0.729)	<0.001	0.579 (0.44 - 0.763)	<0.001	0.538 (0.408 - 0.71)	<0.001
Age (years)	**50 and under**	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)
	51-60	1.957 (1.424 - 2.689)	<0.001	1.536 (0.918 - 2.569)	0.102	2.09 (1.519 - 2.874)	<0.001	1.569 (0.936 - 2.628)	0.087	1.516 (0.905 - 2.541)	0.114
	61-70	4.526 (3.369 - 6.082)	<0.001	3.659 (2.268 - 5.906)	<0.001	4.945 (3.671 - 6.661)	<0.001	3.728 (2.297 - 6.051)	<0.001	3.543 (2.184 - 5.747)	<0.001
	71-80	10.113 (7.596 - 13.463)	<0.001	8.166 (5.147 - 12.955)	<0.001	10.951 (8.189 - 14.646)	<0.001	7.987 (4.984 - 12.8)	<0.001	7.42 (4.633 - 11.883)	<0.001
	81-90	24.007 (17.865 - 32.260)	<0.001	16.998 (10.429 - 27.704)	<0.001	25.291 (18.692 - 34.221)	<0.001	16.211 (9.819 - 26.762)	<0.001	15.724 (9.531 - 25.943)	<0.001
	>90	68.995 (48.423 - 98.305)	<0.001	62.046 (33.832 - 113.786)	<0.001	68.684 (47.891 - 98.504)	<0.001	53.526 (28.861 - 99.272)	<0.001	52.376 (28.275 - 97.022)	<0.001
Gender	**Female as reference**	1.45 (1.302 - 1.615)	<0.001	1.809 (1.483 - 2.206)	<0.001	1.446 (1.298 - 1.611)	<0.001	1.82 (1.492 - 2.221)	<0.001	1.785 (1.462 - 2.179)	<0.001
Smoker	**Non-smoker as reference**	1.715 (1.488 - 1.975)	0.001	1.987 (1.567 - 2.519)	<0.001	1.687 (1.464 - 1.945)	<0.001	1.961 (1.546 - 2.487)	<0.001	1.889 (1.488 - 2.397)	<0.001
HoB IMD Rank	**Quintile 1 (least deprived)**	0.687 (0.578 - 0.817)	<0.001	0.705 (0.505 - 0.984)	0.04	0.698 (0.587 - 0.829)	<0.001	0.741 (0.53 - 1.036)	0.079	0.768 (0.549 - 1.074)	0.123
	Quintile 2	0.854 (0.725 - 1.005)	0.057	0.891 (0.683 - 1.162)	0.394	0.847 (0.719 - 0.996)	0.045	0.893 (0.684 - 1.164)	0.402	0.935 (0.716 - 1.22)	0.619
	Quintile 3	0.917 (0.779 - 1.079)	0.295	0.735 (0.555 - 0.974)	0.032	0.815 (0.778 - 1.078)	0.289	0.754 (0.57 - 0.999)	0.049	0.793 (0.598 - 1.051)	0.107
	Quintile 4	0.845 (0.719 - 0.992)	0.04	0.797 (0.615 - 1.034)	0.087	0.829 (0.706 - 0.974)	0.023	0.804 (0.62 - 1.043)	0.1	0.837 (0.645 - 1.086)	0.18
	Quintile 5 (most deprived)	Reference population	(0.001*)	Reference population	(0.127*)	Reference population	(0.001*)	Reference population	(0.22*)	Reference population	(0.362*)
Comorbidities	**0**	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)
	1	1.042 (0.868 - 1.251)	0.66	1.397 (0.928 - 2.103)	0.109	1.019 (0.859 - 1.21)	0.828	1.461 (0.994 - 2.148)	0.053	1.374 (0.935 - 2.021)	0.106
	2	1.256 (1.043 - 1.512)	0.016	1.829 (1.241 - 2.696)	0.002	1.201 (1.004 - 1.437)	0.045	1.69 (1.161 - 2.46)	0.006	1.48 (1.016 - 2.157)	0.041
	3	1.822 (1.493 - 2.224)	<0.001	2.544 (1.701 - 3.803)	<0.001	2.12 (1.74 - 2.582)	<0.001	2.708 (1.816 - 4.039)	<0.001	2.276 (1.521 - 3.408)	<0.001
	4	2.741 (2.172 - 3.459)	<0.001	3.911 (2.507 - 6.101)	<0.001	2.653 (2.063 - 3.411)	<0.001	3.779 (2.403 - 5.944)	<0.001	3.207 (2.037 - 5.051)	<0.001
	5	3.927 (2.976 - 5.18)	<0.001	6.363 (3.952 - 10.244)	<0.001	3.691 (2.553 - 5.336)	<0.001	6.488 (3.614 - 11.648)	<0.001	5.317 (2.962 - 9.548)	<0.001
	6	6.666 (4.287 - 10.366)	<0.001	11.583 (5.902 - 22.73)	<0.001	5.079 (1.618 - 15.946)	0.005	9.982 (2.386 - 41.769)	0.002	10.519 (2.513 - 44.026)	0.001
	7	2.993 (0.418 - 21.429)	0.275	8.507 (1.152 - 62.821)	0.036						
eGFR (ml/min)	**>120**					2.00 (1.485 - 2.693)	<0.001	1.458 (0.817 - 2.601)	0.202	1.385 (0.775 - 2.473)	0.271
	90-120					Reference population	(<0.001*)	Reference population	(<0.001*)	Reference population	(<0.001*)
	60-89					0.815 (0.694 - 0.957)	0.012	0.934 (0.702 - 1.243)	0.641	0.906 (0.681 - 1.206)	0.498
	45-59					1.096 (0.912 - 1.316)	0.33	1.397 (1.016 - 1.922)	0.04	1.288 (0.936 - 1.772)	0.12
	30-44					1.34 (1.082 - 1.659)	0.007	1.925 (1.35 - 2.744)	<0.001	1.544 (1.079 - 2.21)	0.018
	15-29					2.927 (2.266 - 3.781)	<0.001	3.281 (2.112 - 5.098)	<0.001	2.103 (1.335 - 3.314)	0.001
ACR (mg/mmol)	**Optimal (<1.1)**									Reference population	(<0.001*)
	High Normal (1.1-2.99)									1.041 (0.791 - 1.37)	0.773
	High (3.0-29.99)									1.84 (1.466 - 2.309)	<0.001
	Very High (30 - 200)									2.982 (2.15 - 4.136)	<0.001
	Nephrotic (>200)									3.584 (1.967 - 6.528)	<0.001

* P-value for overall effect

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 (Figure 1)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
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	3-5
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	4 (Figure 1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
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	4 (Figure 1)
		(b) Give reasons for non-participation at each stage	4 (Figure 1)
		(c) Consider use of a flow diagram	4 (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 (Table 1), 9 (Table 2)
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	7 (Table 1), 9 (Table 2)
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
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	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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The impact of chronic kidney disease and cardiovascular comorbidity on mortality in a multi-ethnic population: a retrospective cohort study

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The impact of chronic kidney disease and cardiovascular comorbidity on mortality in a multi-ethnic population: a retrospective cohort study

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3,690 words

Abstract

Objective: To assess the impact of chronic kidney disease (CKD) and cardiovascular comorbidity on mortality in a multi-ethnic primary care population.

Design: Retrospective, cohort study.

Setting: Inner-city primary care trust in West Midlands, United Kingdom.

Participants: Individuals aged 40 years and older, of South Asian, black or white ethnicity, registered with a general practice and with their kidney function checked within the last 12 months (n=31,254).

Outcome Measure: All-cause mortality.

Results: Reduced estimated Glomerular Filtration Rate, higher albuminuria, older age, white ethnicity (versus South-Asian or black ethnicity) and increasing cardiovascular comorbidities were independent determinants of a higher mortality risk. In the multivariate model including comorbidities and kidney function, the hazard ratio for mortality for South Asians was 0.697 (95% confidence interval (CI) 0.56 – 0.868, p=0.001) and for blacks was 0.533 (95% CI 0.403 – 0.704, p<0.001) compared to whites.

Conclusions: The hazard ratio for death is lower for South Asian and black individuals compared to white individuals. This is, in part, independent of age, gender, socio-economic status, kidney function and comorbidities. Risk of death is higher in individuals with CKD and with a higher cumulative cardiovascular comorbidity.

Article summary

- Article focus
  - Retrospective, primary care based cohort study
  - Investigating relationship between ethnicity and cardiovascular comorbidity
  - Inner city population with high deprivation
- Key messages
  - Renal function (both eGFR and ACR) conveys prognostic significance
  - Risk of death increases with a higher cumulative comorbidity score
  - Hazard ratio for death is lower for South Asian and black individuals compared to white individuals
- Strengths and limitations of this study
  - Sample size with inclusion of many practices
  - Ethnicity data self-reported and well recorded (>80%)
  - Individuals of white ethnicity relatively underrepresented

Introduction

Chronic kidney disease (CKD) is a risk factor for increased mortality,**[1]** with an increased risk of death associated with both declining excretory renal function and albuminuria.**[2-4]** CKD prevalence and the risk imparted by CKD may vary by ethnicity; for example, some studies indicate that CKD is more common in people of white ethnicity **[5 ,6]** but non-white ethnic groups have a faster progression to end-stage kidney disease.**[7 ,8]** Paradoxically, when treated with chronic dialysis treatment, people of non-white ethnicity have a lower mortality risk than people of white ethnicity.**[9 ,10]** An increased risk of death is also associated with other comorbidities, including hypertension, diabetes and cardiovascular disease (CVD). **[11-16]**

Whilst previous studies have indicated survival differences between ethnic groups,**[8 ,17-21]** there has been limited reporting in these studies on the relative impact of comorbidities including kidney function on a population basis. This paucity of data reflects a shortfall in the availability of population based primary care databases linked to estimated Glomerular Filtration Rate (eGFR) and albuminuria reporting and traceable to mortality. Furthermore there is minimal comparative data on people of South Asian ethnicity; comparative studies usually report data on Chinese-Asians.**[5]**

In the United Kingdom, there has been a systematic improvement in chronic disease recognition through a primary care pay for performance system, the Quality and Outcomes Framework (QOF). **[22 ,23]** This system utilises chronic disease registers for the identification, monitoring and management of patients with known comorbidities; a component of this monitoring involves measuring and documenting renal function. These disease registers can be combined with laboratory results and linked with demographic and mortality data to better identify determinants of outcomes.

We have therefore utilised chronic disease registers to perform a retrospective cohort study of the relationship between CKD, cardiovascular (CV) comorbidity and mortality within a deprived, inner-city multi-ethnic population. Our study hypotheses were

1. There are differences in mortality between different ethnic groups.
2. These differences in mortality are explained by known risk factors including comorbidities, renal function, demographic and socioeconomic factors.

This study incorporated all stages of kidney function except stage 5 CKD (an eGFR below 15ml/min/1.73m^2) in patients with known CV comorbidities and focused on three ethnic groups: South Asian (including individuals of Bangladeshi, Indian and Pakistani descent), black (individuals from or who have ancestors from Africa or the Caribbean) and white.

Methods

Ethics: The data was fully anonymised and was available as a component of an on-going clinical development programme. The responsible NHS R&D Consortium stated that this study did not require

ethical submission to an NHS research ethics committee as it represented an evaluation of part of an on-going primary care trust (PCT) programme. For PCT data extraction the PCT professional executive committee and GP locality leads provided approval for the programme, including evaluation and publication.

Cohort identification: The cohort was derived from Heart of Birmingham (Teaching) Primary Care Trust (HoB PCT) which had a registered population of 312,070 (September 2008). The majority of the population (62%) were non-white.**[24]** Sixty nine percent of the population were below 40 years of age. Data were collected centrally, utilising software able to identify comorbidities through their classification on chronic disease registers **[Enhanced Healthcare Services, Essex, UK].** Complete sets of anonymised data were available for 63 out of 73 general practices within HoB PCT comprising a population of 285,221 and these were extracted from electronic downloads. **Figure 1** illustrates the selection process for inclusion in the study.

The inclusion criteria comprised individuals aged 40 years and over whom had kidney function testing performed within the previous 12 months as recommended by national guidelines.**[25]** Data for the following variables were collected: age, gender, ethnicity, current smoking status, socio-economic status (SES), eGFR and\or creatinine, urinary albumin:creatinine ratio (ACR) and vascular comorbidity (atrial fibrillation, chronic kidney disease, diabetes mellitus, heart failure, hypertension, ischaemic heart disease and stroke) as defined by a relevant clinical (Read) code specified by the UK pay for performance (QOF) business rules.**[26]** Ethnicity was self-reported, considered the 'gold standard' for classification.**[27]**

A standardised Isotope Dilution Mass Spectrometry (IDMS) MDRD eGFR **[28]** was reported from one of three local biochemistry laboratories, however eGFR reporting was not universally recorded on primary care systems in 2008 and if this was not available the eGFR was calculated by utilising laboratory provided correction factors for the creatinine to generate IDMS traceable MDRD eGFR. One general practice in the catchment area was excluded as IDMS traceable creatinine was not available from a fourth laboratory that provided blood tests specifically for that catchment area.

Socio-economic status (SES) was assessed using the Index of Multiple Deprivation (IMD 2007); **[29]** this utilises the postcode from an individual's address to identify the Lower Layer Super Output Area (LSOA) where the individual resides. Each of the 32,482 LSOAs in England are assigned a score and rank for the IMD 2007, with lower ranks corresponding to the most deprived areas. The Index of Multiple Deprivation has been validated as superior to traditional deprivation indexes such as the Townsend score,**[30]** due to its use of multiple domains reflective of socioeconomic deprivation.**[31]** The IMD 2007 score incorporates seven areas of deprivation: income deprivation; employment deprivation; health deprivation and disability; education; skills and training deprivation; barriers to housing and services; living environment deprivation; and crime. For the analyses presented, deprivation was divided into national quintiles, with the most deprived quintile as the reference population (i.e. how mortality in less deprived quintiles compared to the most deprived quintile).

Mortality data was obtained from the Primary Care Mortality Database ,**[32]** a resource developed by The NHS Information Centre in partnership with the Office for National Statistics (ONS). Data obtained from ONS records is linked to the general practice where the individual was registered and therefore allows data to be extracted for specific general practices (i.e. those within HoB PCT). Individuals included in this analysis were either still registered with a HoB PCT GP at the end of the follow up period or had died whilst still registered at the practice. The follow up period was 23 months from May 2008 until February 2011. Individuals who had left the included practises during the follow up were excluded from this analysis (11.1%).

Statistical Analyses

All analyses were performed using PASW statistics 18 for Windows **[IBM, Chicago, Il, USA]**.

Measurements for kidney function were divided into categories; eGFR into six categories (15-29, 30-44, 45-59, 60-89, 90-119 and ≥120 ml/min) with the eGFR range between 90 and 119 ml/min as the

reference population. Individuals with an eGFR <15 ml/min were excluded from the analysis. ACR was divided into five categories (<1.1 mg/mmol 'optimal', 1.1-2.99 'high normal', 3-29.99 'high', 30-199.99 'very high' and ≥200 'nephrotic') in line with the KDIGO consensus conference.**[33]**

The relationship between age and mortality was not linear. Therefore, age was divided into six categories (50 years and under, 51-60, 61-70, 71-80, 81-90, greater than 90 years) with the youngest group serving as comparator.

Descriptive statistics are presented as mean with standard deviation or median with interquartile range depending on distribution. Continuous variables were compared using ANOVA (normal distribution) with post-hoc Bonferroni analysis or Kruskal-Wallis (non-parametric distribution) tests. Chi-squared tests were used to compare categorical variables.

Cox regression survival analysis was used to evaluate the association of ethnicity and mortality, both before and after adjusting for covariates. Data are presented using survival plots, hazard ratios (HRs) with 95% confidence intervals (95% CI) and p-values. Both univariate (unadjusted) and multivariate (adjusted) regression analyses are presented. The proportionality hazard assumption, assessed using log(-log(survival function))plots, was met for all covariates.

The association between comorbidity, ethnicity and mortality was assessed by univariate analyses for all risk factors and then presented as three models. Choice of model variables were determined by the availability in the dataset of demographic and clinical risk factors consistent with those utilised by other investigators in previous work in similar populations,**[34 ,35]** where the variable was available in our target population. Model 1 incorporates the number of identified vascular comorbidities (zero to seven), ethnicity, age, gender, smoking status and SES. Model 2 includes eGFR level with removal of CKD from the comorbidity score (possible scores therefore zero to six) in order to avoid the association between declining renal function and the likelihood of being on the CKD register. Model 3 added ACR to the variables in Model 2.

A complete case model was used in the analyses. All data were complete with the exception of ACR. Therefore data were analysed for all individuals identified (unadjusted, Model 1 and Model 2) and then repeated for individuals who had an ACR recorded (unadjusted and Models 1-3). An 'enter' technique was used for the regression analysis.

Results

Complete Cohort

At inception (May 2008) 31,254 individuals fulfilled inclusion criteria for analysis. People of South Asian ethnicity formed the largest ethnic group (16,724, 53.4%), followed by people of white ethnicity (9146, 29.3%) and black ethnicity (5384, 17.2%). Baseline characteristics of the study population are shown in **Table 1**. The age distribution differed between groups with South Asians significantly younger than the other two ethnic groups. There was no significant difference in gender between the three ethnic groups.

Smoking was least common in the South Asian group. The majority of all three ethnic groups resided in the most deprived quintile, with a higher proportion of people of South Asian and black ethnicity in this quintile than people of white ethnicity.

Table 1: Baseline characteristics by ethnicity. Complete Cohort.

		All	White	South Asian	Black	p-value
Number	**n (%)**	31254 (100)	9146 (29.3)	16724 (53.4)	5384 (17.2)	
Age	**median (lower, upper quartile)**	59.0 (50.0,71.0)	65.0 (55.0, 75.0)	56.0 (49.0, 68.0)	61.0 (48.0, 73.0)	<0.001
	50 and under (%)	8421 (26.9)	1515 (16.6)	5124 (30.6)	1782 (33.1)	<0.001
	51-60 (%)	8017 (25.7)	1948 (21.3)	5170 (30.9)	899 (16.7)	
	61-70 (%)	6650 (21.3)	2459 (26.9)	3206 (19.2)	985 (18.3)	
	71-80 (%)	6006 (19.2)	2109 (23.1)	2568 (15.4)	1329 (24.7)	
	81-90 (%)	1974 (6.3)	1008 (11.0)	604 (3.6)	362 (6.7)	
	>90 (%)	186 (0.6)	107 (1.2)	52 (0.3)	27 (0.5)	
Gender	**female (%)**	15248 (48.8)	4384 (47.9)	8184 (48.9)	2680 (49.8)	0.085
Smoking	**n (%)**	5150 (16.5)	2285 (25.0)	1812 (10.8)	1053 (19.6)	<0.001
IMD Rank	**Quintile 1 (least deprived) (%)**	152 (0.5)	59 (0.6)	92 (0.6)	1 (0.0)	<0.001
	Quintile 2 (%)	316 (1.0)	132 (1.4)	173 (1.0)	11 (0.2)	
	Quintile 3(%)	3348 (10.7)	1860 (20.3)	1255 (7.5)	233 (4.3)	
	Quintile 4 (%)	5144 (16.5)	2243 (24.5)	2238 (13.4)	663 (12.3)	
	Quintile 5 (most deprived) (%)	22294 (71.3)	4852 (53.1)	12966 (77.5)	4476 (83.1)	
AF	**n (%)**	807 (2.6)	515 (5.6)	212 (1.3)	80 (1.5)	<0.001
CKD	**n (%)**	3648 (11.7)	1318 (14.4)	1691 (10.1)	639 (11.9)	<0.001
Diabetes	**n (%)**	9931 (31.8)	1771 (19.4)	6415 (38.4)	1745 (32.4)	<0.001
Heart Failure	**n (%)**	822 (2.6)	308 (3.4)	385 (2.3)	129 (2.4)	<0.001
Hypertension	**n (%)**	16505 (52.8)	5181 (56.6)	8063 (48.2)	3261 (60.6)	<0.001
IHD	**n (%)**	4226 (13.5)	1417 (15.5)	2386 (14.3)	423 (7.9)	<0.001
Stroke	**n (%)**	1476 (4.7)	570 (6.2)	673 (4.0)	233 (4.4)	<0.001
Comorbidities	**median (lower, upper quartile)**	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.075
	0 (%)	9879 (31.6)	2829 (30.9)	5459 (32.6)	1591 (29.6)	<0.001
	1 (%)	10707 (34.3)	3253 (35.6)	5524 (33)	1930 (35.8)	
	2 (%)	6845 (21.9)	1898 (20.8)	3694 (22.1)	1253 (23.3)	
	3 (%)	2667 (8.5)	785 (8.6)	1451 (8.7)	431 (8)	
	4 (%)	828 (2.6)	254 (2.8)	447 (2.7)	127 (2.4)	
	5 (%)	268 (0.9)	103 (1.1)	124 (0.7)	41 (0.8)	
	6 (%)	55 (0.2)	23 (0.3)	23 (0.1)	9 (0.2)	
	7 (%)	5 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)	
Creatinine (µmol/L)	**mean (SD)**	87.0 (25.8)	88.2 (24.7)	84.6 (25.4)	92.3 (28)	<0.001
eGFR (ml/min)	**median (lower, upper quartile)**	80.2 (66.7, 94.3)	74.9 (62.3, 88.8)	81.3 (68.1, 95.3)	85.5 (72.3, 100.1)	<0.001
	>120 (%)	1473 (4.7)	264 (2.9)	802 (4.8)	407 (7.6)	<0.001
	90-120 (%)	8523 (27.3)	1842 (20.1)	4841 (28.9)	1840 (34.2)	
	60-89 (%)	16373 (52.4)	5077 (55.5)	8776 (52.5)	2520 (46.8)	
	45-59 (%)	3447 (11.0)	1389 (15.2)	1627 (9.7)	431 (8.0)	
	30-44 (%)	1134 (3.6)	466 (5.1)	517 (3.1)	151 (2.8)	
	15-29 (%)	304 (1.0)	108 (1.2)	161 (1.0)	35 (0.7)	
Died	**n (%)**	1435 (4.6)	681 (7.4)	541 (3.2)	213 (4.0)	<0.001

The number of vascular comorbidities was similar between groups, with 11-13% of each ethnic group having three or more comorbidities. Prevalence of different vascular comorbidities varied between groups: the white group had a lower reported prevalence of diabetes but a higher prevalence of CKD, atrial fibrillation, heart failure and stroke.

Median eGFR (corrected for ethnicity as appropriate) was 80.2 ml/min and was lowest in the white group (74.9 ml/min compared to 81.3 ml/min for South Asian individuals and 85.5 ml/min for those of black ethnicity; p<0.001). 21.5% of White, 13.8% of South Asian and 11.5% of Black individuals had an eGFR between 15 and 59 ml/min consistent with stage 3-4 CKD.

At the end of the study period a higher proportion of white individuals had died (7.4%) compared to the two other ethnic groups (South Asian 3.2%, Black 4.0%; p<0.001).

Albumin Creatinine Ratio Cohort

An ACR had been tested in 7022 (42.0%), 2275 (24.9%) and 1908 (20.9%) of South Asian, black and white individuals respectively. **Table 2** lists the baseline characteristics for this subgroup. The median ACR was 1.1 mg/mmol and was highest in the South Asian group (1.2 mg/mmol compared to 1.0 mg/mmol for both white and black individuals; p<0.001). There were similar trends to the whole cohort for age distribution, eGFR, smoking status, and deprivation.

Those with an ACR tested were more likely to have a greater vascular comorbid burden (18-20% having three or more comorbidities). A higher proportion of individuals of South Asian descent, male gender and with diabetes had their ACR tested.

In concordance to the whole group analyses, deaths in the ACR cohort were highest amongst white individuals (7.8%) compared to the South Asian (3.6%) and black individuals (3.7%) (p<0.001).

Univariate Analysis

The univariate (unadjusted) analysis for the complete cohort (**Table 3a**) demonstrated unadjusted HRs for death of 0.421 (95% CI 0.376 – 0.471, p<0.001) for people of South Asian ethnicity and 0.522 (95% CI 0.447 – 0.609, p<0.001) for people of black ethnicity compared to people of white ethnicity. The mortality rate increased exponentially with age and a higher HR was observed for male gender, current smokers and total number of comorbidities. No difference in mortality was found between deprivation quintiles. Using an eGFR of 90-119 ml/min as reference, a J-shaped relationship was observed with a higher risk of death seen for both higher and lower eGFR values. The HR for death increased progressively by stage of CKD with an eGFR <90 ml/min.

The univariate analysis was repeated for those individuals who had their ACR reported (**Table 3b**) with similar trends identified to the whole population analysis with the exception of no observed difference between individuals with an eGFR of ≥120 ml/min compared to 90-119 ml/min. A progressive increase in HR for death was seen with each increasing category for ACR.

Table 2: Baseline characteristics by ethnicity. ACR tested cohort.

		All	White	South Asian	Black	p-value
Number	**n (%)**	11205 (100)	1908 (17)	7022 (62.7)	2275 (20.3)	
Age (years)	**median (lower, upper quartile)**	59.0 (50.0, 71.0)	65.0 (55.0, 75.0)	57.0 (50.0, 68.0)	65.0 (49.0, 74.0)	<0.001
	50 and under (%)	1900 (25.9)	304 (15.9)	1961 (27.9)	635 (27.9)	<0.001
	51-60 (%)	3024 (27.0)	413 (21.6)	2239 (31.9)	372 (16.4)	
	61-70 (%)	2370 (21.2)	496 (26.0)	1423 (20.3)	451 (19.8)	
	71-80 (%)	2251 (20.1)	456 (23.9)	1152 (16.2)	643 (28.3)	
	81-90 (%)	611 (5.5)	222 (11.6)	226 (3.2)	163 (7.2)	
	>90 (%)	49 (0.4)	17 (0.9)	21 (0.3)	11 (0.5)	
Gender	**female (%)**	4348 (38.8)	682 (35.7)	2754 (39.2)	912 (40.1)	0.008
Smoking	**n (%)**	1869 (16.7)	518 (27.1)	872 (12.4)	479 (21.1)	<0.001
IMD Rank	**Quintile 1 (least deprived) (%)**	30 (0.3)	4 (0.2)	25 (0.4)	1 (0.0)	<0.001
	Quintile 2 (%)	84 (0.7)	19 (1.0)	60 (0.9)	5 (0.2)	
	Quintile 3(%)	712 (6.4)	233 (12.2)	540 (5.7)	78 (3.4)	
	Quintile 4 (%)	1458 (13.0)	339 (17.8)	876 (12.5)	243 (10.7)	
	Quintile 5 (most deprived) (%)	8921 (79.6)	1313 (68.8)	5660 (80.6)	1948 (85.6)	
AF	**n (%)**	233 (2.1)	113 (5.9)	91 (1.3)	29 (1.3)	<0.001
CKD	**n (%)**	1637 (14.6)	356 (18.7)	921 (13.1)	360 (15.8)	<0.001
Diabetes	**n (%)**	6828 (60.9)	990 (51.9)	4505 (62.4)	1333 (58.6)	<0.001
Heart Failure	**n (%)**	310 (2.8)	74 (3.9)	175 (2.5)	61 (2.7)	0.005
Hypertension	**n (%)**	6189 (55.2)	1092 (57.2)	3679 (52.4)	1418 (62.3)	<0.001
IHD	**n (%)**	1556 (13.9)	281 (14.7)	1071 (15.3)	201 (8.8)	<0.001
Stroke	**n (%)**	480 (4.3)	97 (5.1)	283 (4.0)	100 (4.4)	0.126
Comorbidities	**median (lower, upper quartile)**	1.0 (1.0, 2.0)	2.0 (1.0,2.0)	1.0 (1.0, 2.0)	2.0 (1.0,2.0)	0.818
	0 (%)	2510 (22.4)	472 (24.7)	1514 (21.6)	524 (23.0)	<0.001
	1 (%)	3139 (28.0)	466 (24.4)	2103 (29.9)	870 (25.1)	
	2 (%)	3438 (30.7)	574 (30.1)	2093 (29.8)	771 (33.9)	
	3 (%)	1481 (13.2)	261 (13.7)	928 (13.2)	292 (12.8)	
	4 (%)	448 (4.0)	79 (4.1)	284 (4.0)	85 (3.7)	
	5 (%)	154 (1.4)	46 (2.4)	83 (1.2)	25 (1.1)	
	6 (%)	32 (0.3)	10 (0.5)	15 (0.2)	7 (0.3)	
	7 (%)	3 (<0.1)	0 (<0.1)	2 (<0.1)	1 (<0.1)	
Creatinine (µmol/L)	**mean (SD)**	89.1 (27.6)	91.8 (26.2)	86.2 (26.8)	95.8 (29.6)	<0.001
eGFR (ml/min)	**median (lower, upper quartile)**	81.1 (66.3, 95.9)	74.3 (59.7, 89.8)	82 (67.4, 89.8)	84.2 (70.0, 98.9)	<0.001
	>120 (%)	611 (5.5)	67 (3.5)	380 (5.4)	164 (7.2)	<0.001
	90-120 (%)	3234 (28.9)	404 (21.2)	2091 (29.8)	739 (32.5)	
	60-89 (%)	5451 (48.6)	953 (49.9)	3453 (49.2)	1045 (45.9)	
	45-59 (%)	1300 (11.6)	323 (16.9)	750 (10.7)	227 (10.0)	
	30-44 (%)	487 (4.3)	131 (6.9)	274 (3.9)	82 (3.6)	
	15-29 (%)	122 (1.1)	30 (1.6)	74 (1.1)	18 (0.8)	
ACR (mg/mmol)	**median (lower, upper quartile)**	1.1 (0.4, 3.4)	1.0 (1.4, 2.8)	1.2 (0.5, 3.8)	1.0 (0.3, 2.9)	<0.001
	Optimal (<1.1) (%)	5641 (50.3)	1026 (53.8)	3400 (48.4)	1214 (53.4)	<0.001
	High Normal (1.1-2.99) (%)	2485 (22.2)	426 (22.3)	1560 (22.2)	499 (21.9)	
	High (3.0-29.99) (%)	2594 (23.2)	402 (21.1)	1717 (24.4)	475 (20.9)	
	Very High (30 - 200) (%)	413 (3.7)	49 (2.6)	287 (4.1)	77 (3.4)	
	Nephrotic (>200) (%)	73 (0.7)	5 (0.3)	58 (0.8)	10 (0.4)	
Died	**n (%)**	484 (4.3)	149 (7.8)	250 (3.6)	85 (3.7)	<0.001

Table 3: Cox Proportional Hazard Regression Analysis. Univariate (unadjusted) analyses

		Complete Cohort (3a)		ACR Tested Cohort (3b)	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	1	(<0.001*)	1	(<0.001*)
	South Asian	0.421 (0.376 - 0.471)	<0.001	0.444 (0.362 - 0.545)	<0.001
	Black	0.522 (0.447 - 0.609)	<0.001	0.467 (0.357 - 0.611)	<0.001
Age (years)	**50 and under**	1	(<0.001*)	1	(<0.001*)
	51-60	2.127 (1.553 - 2.914)	<0.001	1.757 (1.057 - 2.921)	0.03
	61-70	5.429 (4.078 - 7.228)	<0.001	4.646 (2.926 - 7.345)	<0.001
	71-80	12.971 (9.887 - 17.016)	<0.001	11.363 (7.376 - 17.505)	<0.001
	81-90	32.86 (29.952 - 43.275)	<0.001	24.725 (15.769 - 38.767)	<0.001
	>90	90.904 (65.097 - 126.943)	<0.001	82.731 (46.684 - 146.612)	<0.001
Gender	**Female as reference**	1.375 (1.238 - 1.529)	<0.001	1.401 (1.155 - 1.699)	0.001
Smoker	**Non-smoker as reference**	1.154 (1.009 - 1.317)	0.036	1.259 (1.006 - 1.574)	0.044
IMD Rank	**Quintile 1 (least deprived)**	0.860 (0.385 - 1.919)	0.713	<0.001 (<0.001 - >10^5)	0.939
	Quintile 2	0.822 (0.465 - 1.453)	0.501	<0.001 (<0.001 - >10^5)	0.897
	Quintile 3	1.002 (0.846 - 1.186)	0.983	1.151 (0.818 - 1.619)	0.419
	Quintile 4	0.925 (0.800 - 1.070)	0.297	0.774 (0.577 - 1.039)	0.088
	Quintile 5 (most deprived)	1	(0.802*)	1	(0.42*)
AF		5.588 (4.757 - 6.565)	<0.001	6.123 (4.568 - 8.207)	<0.001
CKD		3.442 (3.074 - 3.854)	<0.001	3.498 (2.904 - 4.213)	<0.001
Diabetes		1.346 (1.209 - 1.498)	<0.001	1.939 (1.577 - 2.385)	<0.001
Heart Failure		7.622 (6.595 - 8.804)	<0.001	7.279 (5.681 - 9.327)	<0.001
Hypertension		2.079 (1.857 - 2.325)	<0.001	2.05 (1.681 - 2.499)	<0.001
IHD		2.796 (2.495 - 3.132)	<0.001	3.136 (2.592 - 3.795)	<0.001
Stroke		3.654 (3.154 - 4.233)	<0.001	3.709 (2.855 - 4.817)	<0.001
Comorbidities	**0**	1	(<0.001*)	1	(<0.001*)
	1	1.775 (1.487 - 2.118)	<0.001	1.630 (1.094 - 2.430)	0.016
	2	2.930 (2.458 - 3.493)	<0.001	2.917 (2.023 - 4.205)	<0.001
	3	5.486 (4.550 - 6.615)	<0.001	5.580 (3.837 - 8.113)	<0.001
	4	9.584 (7.691 - 11.942)	<0.001	9.855 (6.511 - 14.917)	<0.001
	5	17.591 (13.490 - 22.939)	<0.001	21.091 (13.479 - 33.001)	<0.001
	6	28.391 (18.411 - 43.782)	<0.001	33.673 (17.519 - 64.722)	<0.001
	7	11.873 (1.664 - 84.728)	0.014	29.402 (4.031 - 214.462)	0.001
eGFR (ml/min)	**>120**	1.492 (1.110 - 2.007)	0.008	1.072 (0.603 - 1.903)	0.813
	90-120	1	(<0.001*)	1	(<0.001*)
	60-89	1.360 (1.162 - 1.591)	<0.001	1.504 (1.138 - 1.987)	0.04
	45-59	3.849 (3.239 - 4.573)	<0.001	4.255 (3.155 - 5.737)	<0.001
	30-44	6.590 (5.401 - 8.041)	<0.001	7.715 (5.564 - 10.699)	<0.001
	15-29	14.465 (11.341 - 18.450)	<0.001	15.054 (9.942 - 22.796)	<0.001
ACR (mg/mmol)	**Optimal (<1.1)**			1	(<0.001*)
	High Normal (1.1-2.99)			1.363 (1.038 - 1.788)	0.026
	High (3.0-29.99)			2.967 (2.381 - 3.697)	<0.001
	Very High (30 - 200)			6.253 (4.493 - 14.005)	<0.001
	Nephrotic (>200)			7.932 (4.493 - 14.005)	<0.001

* P-value for overall effect

Multivariate Analysis

Following adjustment for covariates the differences in ethnicity remained; people of South Asian and black ethnicities had a lower HR for death in all analyses.

Model 1 (complete cohort, incorporating the number of identified comorbidities, see **Supplementary Table I**) analysed the complete cohort and showed an adjusted HR for death of 0.673 (95% CI 0.595 – 0.761, p<0.001) for people of South Asian ethnicity and 0.592 (95% CI 0.504 – 0.696, p<0.001) for people of black ethnicity compared to people of white ethnicity. When the analysis was restricted to the cohort with ACR tests available the HR for death was 0.757 (95% CI 0.61 – 0.939, p=0.011) for people of South Asian ethnicity and 0.526 for people of black ethnicity (95% CI 0.4 – 0.692, p<0.001) compared to people of white ethnicity. For the complete cohort, mortality risk was lower in IMD quintiles 3 and 4 (compared to the most deprived quintile 5). No significant difference between IMD quintiles was identified in the ACR cohort. Increasing age (51 and over in complete cohort, 61 and over in ACR cohort), smoking status and male gender was significant in analyses for both cohorts. An increased HR for death was observed for two or more comorbidities, with the HR increasing as the number of comorbidities increased.

Kidney function (eGFR) was incorporated into Model 2 (with the removal of CKD from the comorbidity score, see **Supplementary Table I**) and in the complete cohort the HR for people of South-Asian ethnicity was 0.678 (95% CI 0.6 – 0.767 p<0.001) and for people of black ethnicity was 0.789 (95% CI 0.635 – 0.98, p=0.032) compared to people of white ethnicity. Similarly, when the analysis was restricted to the cohort of patients with ACR tests available people of South Asian and Black ethnicity had a lower proportion of deaths compared to people of white ethnicity with HRs of 0.614 (95% CI 0.522 – 0.722, p<0.001) and 0.575 (95% CI 0.435 – 0.759, p<0.001) respectively. In the complete cohort mortality risk was lower in the IMD quintile 4. More than two comorbidities were associated with an increasing HR and an increased HR of death compared to the reference eGFR range (90-119 ml/min) was seen with an eGFR ≥120 ml/min and ≥45 ml/min. An eGFR of 60-89 ml/min was associated with a lower HR. In the analysis of those with ACR tested, an eGFR <60 ml/min was associated with progressively higher HR by CKD stage.

In model 3 (all vascular comorbidities except CKD and the addition of eGFR and ACR, **Table 4**) the HR for death for people of South Asian ethnicity was 0.697 (95% CI 0.56 – 0.868, p=0.001) and for people of black ethnicity was 0.533 (95% CI 0.403 – 0.704, p<0.001) compared to people of white ethnicity **(Figure 2)**. Older age, male gender, being a current smoker and increasing comorbidity (two or more) were associated with an increased HR of death **(Figure 3)**. An ACR of 'high' or greater (i.e. ≥3.0 mg/mmol) and an eGFR <45 ml/min was also associated with an increased HR for death. No significant differences in HRs were observed between deprivation quintiles.

Table 4: Cox Proportional Hazard Regression Analysis. Multivariate (adjusted) analyses. Model 3.

		ACR Tested Cohort	
		Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	1	(<0.001*)
	South Asian	0.697 (0.56 - 0.868)	0.001
	Black	0.533 (0.403 - 0.704)	<0.001
Age (years)	**50 and under**	1	(<0.001*)
	51-60	1.519 (0.907 - 2.546)	0.112
	61-70	3.521 (2.17 - 5.712)	<0.001
	71-80	7.381 (4.61 - 11.818)	<0.001
	81-90	15.721 (9.534 - 25.922)	<0.001
	>90	51.641 (27.889 - 95.621)	<0.001
Gender	**Female as reference**	1.782 (1.46 - 2.176)	<0.001
Smoker	**Non-smoker as reference**	1.886 (1.488 - 2.392)	<0.001
IMD Rank	**Quintile 1 (least deprived)**	<0.001 (<0.001 - >10^5)	0.952
	Quintile 2	<0.001 (<0.001 - >10^5)	0.913
	Quintile 3	0.978 (0.68 - 1.387)	0.902
	Quintile 4	0.788 (0.585 - 1.062)	0.118
	Quintile 5 (most deprived)	1	(0.65*)
Comorbidities	**0**	1	(<0.001*)
	1	1.371 (0.932 - 2.016)	0.109
	2	1.486 (1.019 - 2.166)	0.039
	3	2.29 (1.53 - 3.428)	<0.001
	4	3.153 (2.002 - 4.964)	<0.001
	5	5.141 (2.869 - 9.212)	<0.001
	6	10.54 (2.52 - 44.084)	0.001
eGFR (ml/min)	**>120**	1.396 (0.782 - 2.492)	0.26
	90-120	1	(<0.001*)
	60-89	0.907 (0.982 - 1.207)	0.505
	45-59	1.282 (0.932 - 1.763)	0.126
	30-44	1.566 (1.095 - 2.239)	0.014
	15-29	2.073 (1.315 - 3.268)	0.002
ACR (mg/mmol)	**Optimal (<1.1)**	1	(<0.001*)
	High Normal (1.1-2.99)	1.032 (0.784 - 1.359)	0.821
	High (3.0-29.99)	1.837 (1.464 - 2.305)	<0.001
	Very High (30 - 200)	2.956 (2.132 - 4.099)	<0.001
	Nephrotic (>200)	3.838 (2.108 - 6.985)	<0.001

* P-value for overall effect

Discussion

This study utilised routinely available clinical and laboratory data, including kidney function assessed by eGFR and ACR, from a large primary care population. We included in the analysis detailed SES and, importantly, studied three ethnic groups, South-Asian, black and white. Prior to this research, there has been uncertainty about the impact of ethnicity and SES on clinical outcomes in people with significant comorbidities including CKD. The comprehensive nature of the dataset coupled with the ability to utilise the Primary Care Mortality Database has allowed us to assess the relative impact of these factors on survival.

We found that previous associations between lower eGFR and higher ACR and increased mortality applied to this population. Furthermore, these associations remained significant when adjusted for ethnicity, age, gender, cardiovascular risk factors and SES. These results add weight to the risk stratification benefit of measuring ACR has in high risk groups.

A strong cumulative impact of comorbidity on CKD and ethnicity was shown. Whereas traditional comorbidity scores such as the Charlson Comorbidity Index **[36]** are difficult to calculate accurately in a large primary care setting, our study demonstrates that a simple cumulative score provides prognostic information. Individual comorbidities were present in varying frequencies within different ethnic groups, a finding consistent with that found in other ethnically diverse populations.**[37]** Whilst individual comorbidities were associated with different mortality risks, we found the cumulative effect of comorbidities conveyed the greatest prognostic implication. A similar approach, but also including non-cardiovascular risk factors has recently been described.**[38]** Our study suggests that routinely collected clinical data concerning cumulative comorbidity may be utilised to quantify risk, however further work would be required to validate this as a tool for use in clinical care.

SES was measured by the IMD 2007 score; a cumulative deprivation index score incorporating seven areas of deprivation which has been validated as superior to other deprivation scores.**[31]** One notable finding is that we did not demonstrate any association between mortality when corrected for all other factors including comorbidity and ethnicity. This is not consistent with several other studies, which have shown that there is an independent relationship between SES and mortality across disease states and ethnic groups within the UK.**[39-42]** This relationship varies by population group studied **[43]** and there have been limited studies investigating health disparities in similar, inner-city populations. Whilst we studied a health care system that is free at the point of care, limiting possible health access issues, the majority of individuals were from the most deprived national quintile and our study may therefore underestimate the influence of the complete spectrum of SES on mortality. To attempt to correct for this, we re-ran the analyses dividing the cohort into equal quintiles. All analyses continued to indicate the effect of ethnicity and the importance of cardiovascular comorbidity and renal function. The univariate

analysis (**Supplementary Table II**) and the most comprehensive multivariate analysis (Model 3, (**Supplementary Table III**) did not show any differences between most and least deprived quintiles.

One of the seven areas included in the IMD is health deprivation, raising the possibility of an inbuilt relationship between deprivation and health even before analyses are undertaken. The possible implication of this was investigated by Adams and White **[44]** who analysed data having removed the health domain from IMD 2004 and found that its removal had little, practical, effect. This suggests the presence of the health domain is unlikely to influence our result.

We found that the risk of death was lower for people of South Asian and black ethnicity compared to people of white ethnicity, and this remained in all analyses (adjusted and unadjusted) performed. Previous studies comparing the outcomes of different ethnic groups have been limited in their generalizability. They have either looked at disease specific mortality **[8 ,18 ,20 ,21]** or have been based in populations that do not have access to free comprehensive healthcare. The finding that differences in mortality risk between ethnic groups is independent of age, gender, SES, kidney function and comorbidities require further work. Variables, such as health promotion targeted at specific groups, differences in medication usage or factors related to genetic diversity may offer potential explanations for this variation. **[45 ,46].**

A major strength in this study is the sample size, which included sixty-two practices of varying list size and number of practitioners. Ethnicity was documented in over 80% of the population studied; this is, much higher than normally found in primary care records.**[47]** Self-reporting is considered the 'gold standard' method of assessing ethnicity,**[27]** taking into account an individual's culture and self-identity. Renal function was described in terms of eGFR and ACR, the latter becoming of increased prominence in the stratification of cardiovascular risk.

Our analyses have used data from primary care coding and recording systems, which formed part of the electronic downloads. These downloads indicate who is on a specific cardiovascular risk register and therefore may not classify people correctly. There is a relative paucity of published literature regarding the correct identification of people onto the correct risk registers **[23 ,48][49 ,50]**. Surrogate measures of accuracy of the data include previous studies looking at gaming for QOF points (falsely classifying people with conditions they do not have thereby increasing revenue) or exception reporting (excluding individuals who have not had the appropriate monitoring completed) suggest that both these are rare.**[23 ,51 ,52]**

When comparing the breakdown of the population studied in these analyses to the source population, it is important to highlight two key differences. Firstly, there is a relative underrepresentation of individuals of white ethnicity, consistent with previous research.**[53]** This is most marked in those who had their ACR measured; a higher number of males and individuals with diabetes or of South Asian ethnicity had an ACR measured. Comparing the whole cohort to those who had their ACR reported showed similar trends for mortality in respect of age, eGFR, smoking status and SES, suggests a generalizability of results.

Secondly one criterion for inclusion was the recording of renal function within the previous twelve months. This is likely to have resulted in an overrepresentation of comorbidity as people with CV conditions would be more likely to have their renal function checked. A further consideration is that the accuracy and applicability of creatinine based eGFR equations, such as the formula used in this analysis, in non-white ethnic groups is a subject of ongoing research.**[54-56]** Cystatin based equations may be more accurate,**[57]** but are not routinely measured in clinical practice.

In summary, we have shown the determinants of mortality were multifactorial in a high risk population and that ethnicity should be considered as a non-traditional risk factor for mortality; the HR for death was lower for South Asian and black individuals compared to white individuals which was, in part, independent of age, gender, SES, renal function and comorbidities. Furthermore, a simple cumulative comorbidity system may have prognostic utility. Renal function (eGFR and ACR) provides additional information and gender, age and smoking status remain significant risk factors for mortality.

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Competing Interests

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Contributorship

Mark Jesky: study design, data analysis, preparation of manuscript
Amanda Lambert: study design, data acquisition and analysis, review of manuscript
AC Felix Burden: study design, data acquisition, review of manuscript
Paul Cockwell: study design, data analysis, preparation and review of manuscript

Data sharing

No other data will be available.

Figure legends

Figure 1. Flow Diagram indicating selection process for inclusion in the analyses

Figure 2. Cox Regression Survival Plot indicating cumulative survival between ethnicities in Model 3 (comorbidities, eGFR and ACR). Table below survival plot demonstrates number of individuals who remained in follow up at each time-point.

Figure 3. Hazard ratio (HR) for death by number of comorbidities. Multivariate (adjusted) analysis: Model 3

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Supplementary Tables

Supplementary Table I: Cox Proportional Hazard Regression Analysis. National IMD quintiles. Multivariate (adjusted) analyses

		Model 1				Model 2			
		Complete Cohort		ACR Tested Cohort		Complete Cohort		ACR Tested Cohort	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)
	South Asian	0.673 (0.595 - 0.761)	<0.001	0.757 (0.61 - 0.939)	0.011	0.678 (0.6 - 0.767)	<0.001	0.789 (0.635 - 0.98)	0.032
	Black	0.592 (0.504 - 0.696)	<0.001	0.526 (0.4 - 0.692)	<0.001	0.614 (0.522 - 0.722)	<0.001	0.575 (0.435 - 0.759)	<0.001
Age (years)	**50 and under**	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)
	51-60	1.958 (1.425 - 2.691)	<0.001	1.538 (0.919 - 2.573)	0.101	2.09 (1.52 - 2.874)	<0.001	1.571 (0.937 - 2.632)	0.086
	61-70	4.512 (3.358 - 6.062)	<0.001	3.634 (2.252 - 5.867)	<0.001	4.918 (3.651 - 6.625)	<0.001	3.697 (2.278 - 6.002)	<0.001
	71-80	10.075 (7.568 - 13.412)	<0.001	8.124 (5.122 - 12.887)	<0.001	10.904 (8.153 - 14.582)	<0.001	7.95 (4.962 - 12.738)	<0.001
	81-90	23.973 (17.839 - 32.217)	<0.001	17.018 (10.444 - 27.73)	<0.001	25.203 (18.626 - 34.104)	<0.001	16.155 (9.79 - 26.659)	<0.001
	>90	68.62 (48.166 - 97.759)	<0.001	61.221 (33.372 - 112.31)	<0.001	68.189 (47.554 - 97.777)	<0.001	52.695 (28.401 - 97.77)	<0.001
Gender	**Female as reference**	1.451 (1.303 - 1.616)	<0.001	1.806 (1.48 - 2.203)	<0.001	1.447 (1.298 - 1.612)	<0.001	1.819 (1.491 - 2.22)	<0.001
Smoker	**Non-smoker as reference**	1.722 (1.495 - 1.983)	<0.001	1.986 (1.567 - 2.517)	<0.001	1.692 (1.469 - 1.95)	<0.001	1.959 (1.546 - 2.483)	<0.001
IMD Rank	**Quintile 1 (least deprived)**	1.081 (0.484 - 2.416)	0.849	<0.001 (<0.001 - >10^5)	0.951	1.115 (0.499 - 2.494)	0.79	<0.001 (<0.001 - >10^5)	0.951
	Quintile 2	0.906 (0.512 - 1.603)	0.734	<0.001 (<0.001 - >10^5)	0.916	0.896 (0.506 - 1.587)	0.707	<0.001 (<0.001 - >10^5)	0.917
	Quintile 3	0.821 (0.689 - 0.979)	0.028	0.979 (0.692 - 1.387)	0.907	0.841 (0.705 - 1.003)	0.054	0.984 (0.694 - 1.395)	0.929
	Quintile 4	0.733 (0.63 - 0.852)	<0.001	0.753 (0.559 - 1.015)	0.062	0.737 (0.634 - 0.857)	<0.001	0.776 (0.576 - 1.046)	0.096
	Quintile 5 (most deprived)	1	(0.001*)	1	(0.478*)	1	(0.002*)	Reference population	(0.592*)
Comorbidities	**0**	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)
	1	1.045 (0.87 - 1.254)	0.64	1.394 (0.926 - 2.098)	0.112	1.024 (0.863 - 1.215)	0.788	1.459 (0.993 - 2.145)	0.055
	2	1.262 (1.049 - 1.52)	0.014	1.831 (1.242 - 2.701)	0.002	1.208 (1.099 - 1.445)	0.039	1.698 (1.166 - 2.471)	0.006
	3	1.824 (1.495 - 2.226)	<0.001	2.551 (1.706 - 3.814)	<0.001	2.118 (1.739 - 2.58)	<0.001	2.719 (1.823 - 4.055)	<0.001
	4	2.722 (2.157 - 3.435)	<0.001	3.866 (2.479 - 6.031)	<0.001	2.643 (2.055 - 3.399)	<0.001	3.713 (2.362 - 5.838)	<0.001
	5	3.892 (2.949 - 5.136)	<0.001	6.247 (3.880 - 10.057)	<0.001	3.641 (2.518 - 5.265)	<0.001	6.203 (3.461 - 11.118)	<0.001
	6	6.535 (4.202 - 10.162)	<0.001	10.83 (5.527 - 21.219)	<0.001	5.069 (1.615 - 15.909)	0.005	10.017 (2.395 - 41.898)	0.002
	7	3.085 (0.431 - 22.084)	0.262	8.972 (1.217 - 66.15)	0.031				
eGFR (ml/min)	**>120**					2.02 (1.5 - 2.721)	<0.001	1.466 (0.822 - 2.616)	0.195
	90-120					1	(<0.001*)	1	(<0.001*)
	60-89					0.82 (0.699 - 0.962)	0.015	0.936 (0.704 - 1.245)	0.649
	45-59					1.102 (0.917 - 1.324)	0.301	1.395 (1.014 - 1.918)	0.041
	30-44					1.342 (1.084 - 1.662)	0.007	1.947 (1.367 - 2.775)	<0.001
	15-29					2.929 (2.267 - 3.784)	<0.001	3.256 (2.095 - 5.059)	<0.001

* P-value for overall effect

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Supplementary Tables

Supplementary Table II: Cox Proportional Hazard Regression Analysis. Population specific IMD quintiles. Univariate (unadjusted) analyses

		Complete Cohort (2a)		ACR Tested Cohort (2b)	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
HoB IMD Rank	**Quintile 1 (least deprived)**	0.942 (0.798 - 1.111)	0.476	0.831 (0.6 - 1.152)	0.268
	Quintile 2	0.947 (0.806 - 1.113)	0.507	0.943 (0.725 - 1.227)	0.664
	Quintile 3	0.895 (0.761 - 1.054)	0.183	0.71 (0.537 - 0.938)	0.016
	Quintile 4	0.923 (0.786 - 1.084)	0.33	0.908 (0.701 - 1.179)	0.465
	Quintile 5 (most deprived)	1	(0.75*)	1	(0.154*)

* P-value for overall effect

Impact of CKD and comorbidity on mortality in a multi-ethnic population.
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Supplementary Tables

Supplementary Table III: Cox Proportional Hazard Regression Analysis. Population specific IMD quintiles. Multivariate (adjusted) analyses

		Model 1				Model 2				Model 3	
		Complete Cohort		ACR Tested Cohort		Complete Cohort		ACR Tested Cohort		ACR Tested Cohort	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	**White**	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(0.001*)	1	(<0.001*)
	South Asian	0.674 (0.596 - 0.762)	<0.001	0.753 (0.606 - 0.934)	0.01	0.68 (0.601 - 0.769)	<0.001	0.788 (0.634 -0.979)	0.031	0.7 (0.562 - 0.871)	0.001
	Black	0.598 (0.510 - 0.701)	<0.001	0.529 (0.403 - 0.694)	<0.001	0.621 (0.528 - 0.729)	<0.001	0.579 (0.44 - 0.763)	<0.001	0.538 (0.408 - 0.71)	<0.001
Age (years)	**50 and under**	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)
	51-60	1.957 (1.424 - 2.689)	<0.001	1.536 (0.918 - 2.569)	0.102	2.09 (1.519 - 2.874)	<0.001	1.569 (0.936 - 2.628)	0.087	1.516 (0.905 - 2.541)	0.114
	61-70	4.526 (3.369 - 6.082)	<0.001	3.659 (2.268 - 5.906)	<0.001	4.945 (3.671 - 6.661)	<0.001	3.728 (2.297 - 6.051)	<0.001	3.543 (2.184 - 5.747)	<0.001
	71-80	10.113 (7.596 - 13.463)	<0.001	8.166 (5.147 - 12.955)	<0.001	10.951 (8.189 - 14.646)	<0.001	7.987 (4.984 - 12.8)	<0.001	7.42 (4.633 - 11.883)	<0.001
	81-90	24.007 (17.865 - 32.260)	<0.001	16.998 (10.429 - 27.704)	<0.001	25.291 (18.692 - 34.221)	<0.001	16.211 (9.819 - 26.762)	<0.001	15.724 (9.531 - 25.943)	<0.001
	>90	68.995 (48.423 - 98.305)	<0.001	62.046 (33.832 - 113.786)	<0.001	68.684 (47.891 - 98.504)	<0.001	53.526 (28.861 - 99.272)	<0.001	52.376 (28.275 - 97.022)	<0.001
Gender	**Female as reference**	1.45 (1.302 - 1.615)	<0.001	1.809 (1.483 - 2.206)	<0.001	1.446 (1.298 - 1.611)	<0.001	1.82 (1.492 - 2.221)	<0.001	1.785 (1.462 - 2.179)	<0.001
Smoker	**Non-smoker as reference**	1.715 (1.488 - 1.975)	0.001	1.987 (1.567 - 2.519)	<0.001	1.687 (1.464 - 1.945)	<0.001	1.961 (1.546 - 2.487)	<0.001	1.889 (1.488 - 2.397)	<0.001
HoB IMD Rank	**Quintile 1 (least deprived)**	0.687 (0.578 - 0.817)	<0.001	0.705 (0.505 - 0.984)	0.04	0.698 (0.587 - 0.829)	<0.001	0.741 (0.53 - 1.036)	0.079	0.768 (0.549 - 1.074)	0.123
	Quintile 2	0.854 (0.725 - 1.005)	0.057	0.891 (0.683 - 1.162)	0.394	0.847 (0.719 - 0.996)	0.045	0.893 (0.684 - 1.164)	0.402	0.935 (0.716 - 1.22)	0.619
	Quintile 3	0.917 (0.779 - 1.079)	0.295	0.735 (0.555 - 0.974)	0.032	0.815 (0.778 - 1.078)	0.289	0.754 (0.57 - 0.999)	0.049	0.793 (0.598 - 1.051)	0.107
	Quintile 4	0.845 (0.719 - 0.992)	0.04	0.797 (0.615 - 1.034)	0.087	0.829 (0.706 - 0.974)	0.023	0.804 (0.62 - 1.043)	0.1	0.837 (0.645 - 1.086)	0.18
	Quintile 5 (most deprived)	1	(0.001*)	1	(0.127*)	1	(0.001*)	1	(0.22*)	1	(0.362*)
Comorbidities	**0**	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)	1	(<0.001*)
	1	1.042 (0.868 - 1.251)	0.66	1.397 (0.928 - 2.103)	0.109	1.019 (0.859 - 1.21)	0.828	1.461 (0.994 - 2.148)	0.053	1.374 (0.935 - 2.021)	0.106
	2	1.256 (1.043 - 1.512)	0.016	1.829 (1.241 - 2.696)	0.002	1.201 (1.004 - 1.437)	0.045	1.69 (1.161 - 2.46)	0.006	1.48 (1.016 - 2.157)	0.041
	3	1.822 (1.493 - 2.224)	<0.001	2.544 (1.701 - 3.803)	<0.001	2.12 (1.74 - 2.582)	<0.001	2.708 (1.816 - 4.039)	<0.001	2.276 (1.521 - 3.408)	<0.001
	4	2.741 (2.172 - 3.459)	<0.001	3.911 (2.507 - 6.101)	<0.001	2.653 (2.063 - 3.411)	<0.001	3.779 (2.403 - 5.944)	<0.001	3.207 (2.037 - 5.051)	<0.001
	5	3.927 (2.976 - 5.18)	<0.001	6.363 (3.952 - 10.244)	<0.001	3.691 (2.553 - 5.336)	<0.001	6.488 (3.614 - 11.648)	<0.001	5.317 (2.962 - 9.548)	<0.001
	6	6.666 (4.287 - 10.366)	<0.001	11.583 (5.902 - 22.73)	<0.001	5.079 (1.618 - 15.946)	0.005	9.982 (2.386 - 41.769)	0.002	10.519 (2.513 - 44.026)	0.001
	7	2.993 (0.418 - 21.429)	0.275	8.507 (1.152 - 62.821)	0.036						
eGFR (ml/min)	**>120**					2.00 (1.485 - 2.693)	<0.001	1.458 (0.817 - 2.601)	0.202	1.385 (0.775 - 2.473)	0.271
	90-120					1	(<0.001*)	1	(<0.001*)	1	(<0.001*)
	60-89					0.815 (0.694 - 0.957)	0.012	0.934 (0.702 - 1.243)	0.641	0.906 (0.681 - 1.206)	0.498
	45-59					1.096 (0.912 - 1.316)	0.33	1.397 (1.016 - 1.922)	0.04	1.288 (0.936 - 1.772)	0.12
	30-44					1.34 (1.082 - 1.659)	0.007	1.925 (1.35 - 2.744)	<0.001	1.544 (1.079 - 2.21)	0.018
	15-29					2.927 (2.266 - 3.781)	<0.001	3.281 (2.112 - 5.098)	<0.001	2.103 (1.335 - 3.314)	0.001
ACR (mg/mmol)	**Optimal (<1.1)**									1	(<0.001*)
	High Normal (1.1-2.99)									1.041 (0.791 - 1.37)	0.773
	High (3.0-29.99)									1.84 (1.466 - 2.309)	<0.001
	Very High (30 - 200)									2.982 (2.15 - 4.136)	<0.001
	Nephrotic (>200)									3.584 (1.967 - 6.528)	<0.001

* P-value for overall effect

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 (Figure 1)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
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	3-5
Bias	9	Describe any efforts to address potential sources of bias	16-18
Study size	10	Explain how the study size was arrived at	4 (Figure 1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	4 (Figure 1)
		(*e*) Describe any sensitivity analyses	n/a
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	4 (Figure 1)
		(b) Give reasons for non-participation at each stage	4 (Figure 1)
		(c) Consider use of a flow diagram	4 (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 (Table 1), 10 (Table 2)
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	8 (Table 1), 10 (Table 2)
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	11
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, 16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
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	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

The impact of chronic kidney disease and cardiovascular comorbidity on mortality in a multi-ethnic population: a retrospective cohort study

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Key Words

Chronic Kidney Disease, Comorbidity, Epidemiology, Ethnicity

Word Count (excluding title page, abstract, references, figures and tables)

3,690 words

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Abstract

Objective: To assess the impact of chronic kidney disease (CKD) and cardiovascular comorbidity on mortality in a multi-ethnic primary care population.

Design: Retrospective, ~~observational~~ cohort study.

Setting: Inner-city primary care trust in West Midlands, United Kingdom.

Participants: Individuals aged 40 years and older, of South Asian, black or white ethnicity, registered with a general practice and with their kidney function checked within the last 12 months (n=31,254).

Outcome Measure: All-cause mortality.

Results: Reduced estimated Glomerular Filtration Rate, higher albuminuria, older age, white ethnicity (versus South-Asian or black ethnicity) and increasing cardiovascular comorbidities were independent determinants of a higher mortality risk. In the multivariate model including comorbidities and kidney function, the hazard ratio for mortality for South Asians was 0.697 (95% confidence interval (CI) 0.56 – 0.868, p=0.001) and for blacks was 0.533 (95% CI 0.403 – 0.704, p<0.001) compared to whites.

Conclusions: The hazard ratio for death is lower for South Asian and black individuals compared to white individuals. This is, in part, independent of age, gender, socio-economic status, kidney function and comorbidities. Risk of death is higher in individuals with CKD and with a higher cumulative cardiovascular comorbidity.

Article summary

- Article focus
  - Retrospective, primary care based cohort study
  - Investigating relationship between ethnicity and cardiovascular comorbidity
  - Inner city population with high deprivation
- Key messages
  - Renal function (both eGFR and ACR) conveys prognostic significance
  - Risk of death increases with a higher ~~C~~cumulative comorbidity score ~~can be used to risk stratify~~
  - Hazard ratio for death is lower for South Asian and black individuals compared to white individuals
- Strengths and limitations of this study
  - Sample size with inclusion of many practices
  - Ethnicity data self-reported and well recorded (>80%)
  - ~~Primary care based, looking at multiple cardiovascular comorbidities~~
  - Individuals of white ethnicity relatively underrepresented

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

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Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Introduction

Chronic kidney disease (CKD) is a risk factor for increased mortality ~~[1]~~[1] with an increased risk of death associated with both declining excretory renal function and albuminuria ~~[2-4]~~[2-4] CKD prevalence and the risk imparted by CKD may vary by ethnicity; for example, some studies indicate that CKD is more common in people of white ethnicity **[5 ,6]** but non-white ethnic groups have a faster progression to end-stage kidney disease ~~[7 8]~~**[7 ,8]** Paradoxically, when treated with chronic dialysis treatment, people of non-white ethnicity have a lower mortality risk than people of white ethnicity ~~[9 10]~~**[9 ,10]** An increased risk of death is also associated with other comorbidities, including hypertension, diabetes and cardiovascular disease (CVD) ~~[11-16]~~[11-16]

Whilst previous studies have indicated survival differences between ethnic groups ~~[8 17-21]~~**[8 ,17-21]** there has been limited reporting in these studies on the relative impact of comorbidities including kidney function on a population basis. This paucity of data reflects a shortfall in the availability of population based primary care databases linked to estimated Glomerular Filtration Rate (eGFR) and albuminuria reporting and traceable to mortality. Furthermore there is minimal comparative data on people of South Asian ethnicity; comparative studies usually report data on Chinese-Asians ~~[5]~~[5]

In the United Kingdom, there has been a systematic improvement in chronic disease recognition through a primary care pay for performance system, the Quality and Outcomes Framework (QOF) ~~[22 23]~~ **[22 ,23]** This system utilises chronic disease registers for the identification, monitoring and management of patients with known comorbidities; a component of this monitoring involves measuring and documenting renal function. ~~t~~These disease registers can be combined with laboratory results and linked with demographic and mortality data to better identify determinants of outcomes.

We have therefore utilised chronic disease registers to perform a retrospective cohort study of the relationship between CKD, cardiovascular (CV) comorbidity and mortality within a deprived, inner-city multi-ethnic population. Our study hypotheses were

1. There are differences in mortality between different ethnic groups.
2. These differences in mortality are explained by known risk factors including comorbidities, renal function, demographic and socioeconomic factors.

This study incorporated all stages of kidney function except stage 5 CKD (~~except those with~~ an eGFR below 15ml/min/1.73m^2 ~~or receiving renal replacement therapy~~) in patients with known CV comorbidities and focused on three ethnic groups: South Asian (including individuals of Bangladeshi, Indian and Pakistani descent), black (individuals from or who have ancestors from Africa or the Caribbean) and white.

Methods

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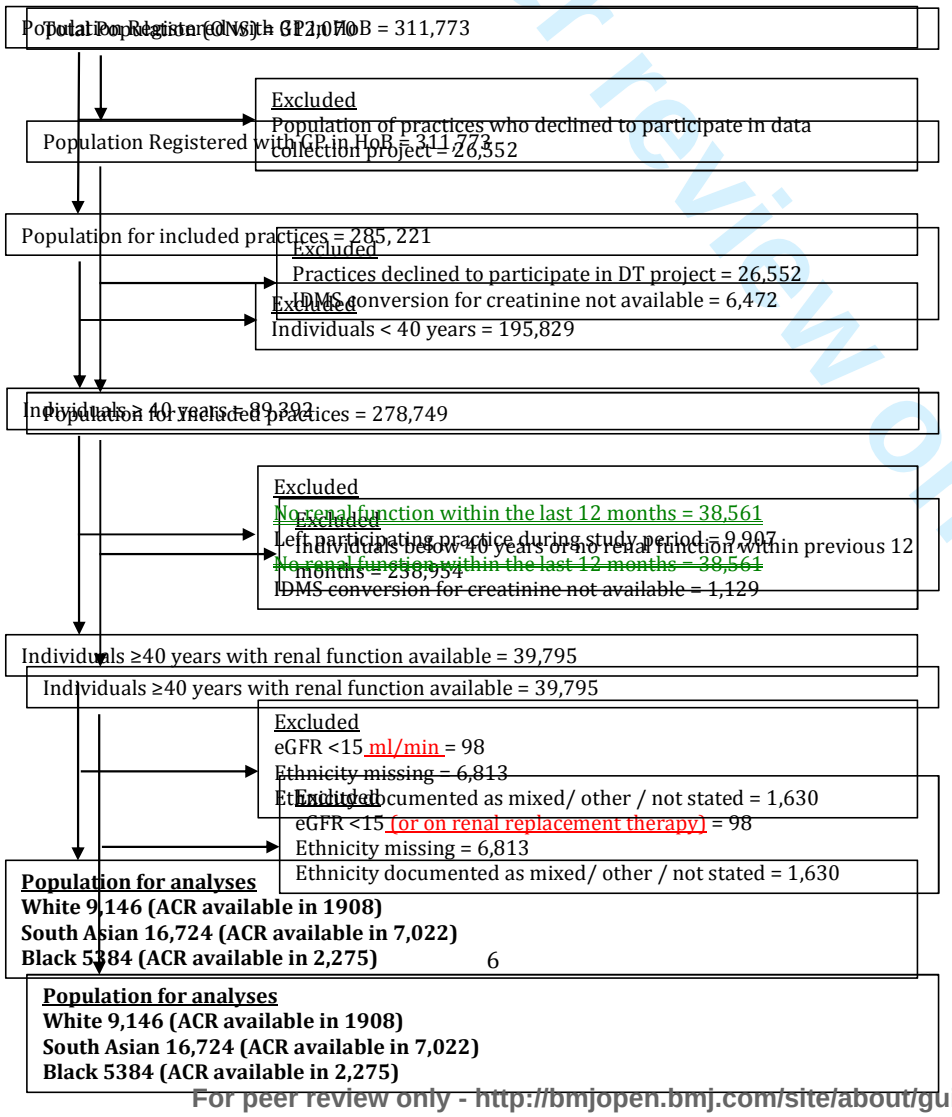
Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Ethics: The data was fully anonymised and was available as a component of an on-going clinical development programme. The responsible NHS R&D Consortium stated that this study did not require ethical submission to an NHS research ethics committee as it represented an evaluation of part of an on-going primary care trust (PCT) programme. For PCT data extraction the PCT professional executive committee and GP locality leads provided approval for the programme, including evaluation and publication.

Cohort identification: The cohort was derived from Heart of Birmingham (Teaching) Primary Care Trust (HoB PCT) which had a registered population of 312,070 (September 2008). The majority of the population (62%) were non-white **[24].[24]** Sixty nine percent of the population were below 40 years of age. Data were collected centrally, utilising software able to identify comorbidities through their classification on chronic disease registers **[Enhanced Healthcare Services, Essex, UK].** Complete sets of anonymised data were available for 63 out of 73 general practices within HoB PCT comprising a population of 285,221 and these were extracted from electronic downloads. **Figure 1** illustrates the selection process for inclusion in the study.

Figure 1. Flow Diagram indicating selection process for inclusion in the analyses



Impact of CKD and comorbidity on mortality in a multi-ethnic population.

The inclusion criteria comprised individuals aged 40 years and over whom had kidney function testing performed within the previous 12 months as recommended by national guidelines~~[25]~~.[25] Data for the following variables were collected: age, gender, ethnicity ~~(self-reported)~~, current smoking status, socio-economic status (SES), eGFR and\or creatinine, urinary albumin:creatinine ratio (ACR) and vascular comorbidity (atrial fibrillation, chronic kidney disease, diabetes mellitus, heart failure, hypertension, ischaemic heart disease and stroke) as defined by a relevant clinical (Read) code specified by the UK pay for performance (QOF) business rules ~~[26]~~.[26] Ethnicity was self-reported, considered the 'gold standard' for classification~~[27]~~.[27]

A standardised Isotope Dilution Mass Spectrometry (IDMS) MDRD eGFR **[28]** was reported from one of three local biochemistry laboratories, however eGFR reporting was not universally recorded on primary care systems in 2008 and if this was not available the eGFR was calculated by utilising laboratory provided correction factors for the creatinine to generate IDMS traceable MDRD eGFR. One general practice in the catchment area was excluded as IDMS traceable creatinine was not available from a fourth laboratory that provided blood tests specifically for that catchment area.

Socio-economic status (SES) was assessed using the Index of Multiple Deprivation (IMD 2007) ~~[29]~~; [29] this utilises the postcode from an individual's address to identify the Lower Layer Super Output Area (LSOA) where the individual resides. Each of the 32,482 LSOAs in England are assigned a score and rank for the IMD 2007, with lower ranks corresponding to the most deprived areas. The Index of Multiple Deprivation has been validated as superior to traditional deprivation indexes such as the Townsend score ~~[30]~~,[30] due to its use of multiple domains reflective of socioeconomic deprivation ~~[31]~~.[31] The IMD 2007 score incorporates seven areas of deprivation: income deprivation; employment deprivation; health deprivation and disability; education; skills and training deprivation; barriers to housing and services; living environment deprivation; and crime. For the analyses presented, deprivation was divided into national quintiles, with the most deprived quintile as the reference population (i.e. how mortality in less deprived quintiles compared to the most deprived quintile).

Mortality data was obtained from the Primary Care Mortality Database ~~[32]~~ ,[32] a resource developed by The NHS Information Centre in partnership with the Office for National Statistics (ONS). Data obtained from ONS records is linked to the general practice where the individual was registered and therefore allows data to be extracted for specific general practices (i.e. those within HoB PCT). Individuals included in this analysis were either still registered with a HoB PCT GP at the end of the follow up period or had died whilst still registered at the practice. The follow up period was 23 months from May 2008 until February 2011. Individuals who had left the included practises during the follow up were excluded from this analysis (11.1%).

Statistical Analyses

All analyses were performed using PASW statistics 18 for Windows **[IBM, Chicago, Il, USA]**.

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Measurements for kidney function were divided into categories; eGFR into six categories (15-29, 30-44, 45-59, 60-89, 90-119 and ≥~~>~~120 ml/min) with the eGFR range between 90 and 119 ml/min as the reference population. Individuals with an eGFR <15 ml/min were excluded from the analysis. ACR was divided into five categories (<1.1 mg/mmol 'optimal', 1.1-2.99 'high normal', 3-29.99 'high', 30-199.99 'very high' and ≥200 'nephrotic') in line with the KDIGO consensus conference ~~[33]~~.[33]

The relationship between age and mortality was not linear. Therefore, age was divided into six categories (50 years and under, 51-60, 61-70, 71-80, 81-90, greater than 90 years) with the youngest group serving as comparator.

Descriptive statistics are presented as mean with standard deviation or median with interquartile range depending on distribution. Continuous variables were compared using ANOVA (normal distribution) with post-hoc Bonferroni analysis or Kruskal-Wallis (non-parametric distribution) tests. Chi-squared tests were used to compare categorical variables.

Cox regression survival analysis was used to evaluate the association of ethnicity and mortality, both before and after adjusting for covariates. Data are presented using survival plots, hazard ratios (HRs) with 95% confidence intervals (95% CI) and p-values. Both univariate (unadjusted) and multivariate (adjusted) regression analyses are presented. The proportionality hazard assumption, assessed using log(-log(survival function))plots, was met for all covariates.

The association between comorbidity, ethnicity and mortality was assessed by univariate analyses for all risk factors and then presented as three models. Choice of model variables were determined by the availability in the dataset of ~~inclusion~~ demographic and clinical ~~of 'classical'~~ risk factors ~~combined with those~~ consistent with those ~~derived from~~utilised by other investigators in previous work in similar populations~~[34 35]~~.[34 ,35] where the variable was available in our target population. Model 1 incorporates the number of identified vascular comorbidities (zero to seven), ethnicity, age, gender, smoking status and SES. Model 2 includes eGFR level with removal of CKD from the comorbidity score (possible scores therefore zero to six) in order to avoid the association between declining renal function and the likelihood of being on the CKD register. Model 3 added ACR to the variables in Model 2.

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A complete case model was used in the analyses. All data were complete with the exception of ACR. Therefore data were analysed for all individuals identified (unadjusted, Model 1 and Model 2) and then repeated for individuals who had an ACR recorded (unadjusted and Models 1-3). An 'enter' technique was used for the regression analysis.

Results

Complete Cohort

At inception (May 2008) 31,254 individuals fulfilled inclusion criteria for analysis. People of South Asian~~s~~ ethnicity formed the largest ethnic group (16,724, 53.4%), followed by people of white ethnicity (9146, 29.3%) and black ethnicity (5384, 17.2%). Baseline characteristics of the study population are shown in

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Table 1. The age distribution differed between groups with South Asians significantly younger than the other two ethnic groups. There was no significant difference in gender between the three ethnic groups. Smoking was least common in the South Asian group. The majority of all three ethnic groups resided in the most deprived quintile, with a higher proportion of people of South Asian and black ethnicity in this quintile than people of white ethnicity.

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Table 1: Baseline characteristics by ethnicity. Complete Cohort.

		All	White	South Asian	Black	p-value
Number	**n (%)**	31254 (100)	9146 (29.3)	16724 (53.4)	5384 (17.2)	
Age	**median (lower, upper quartile)**	59.0 (50.0,71.0)	65.0 (55.0, 75.0)	56.0 (49.0, 68.0)	61.0 (48.0, 73.0)	<0.001
	50 and under (%)	8421 (26.9)	1515 (16.6)	5124 (30.6)	1782 (33.1)	<0.001
	51-60 (%)	8017 (25.7)	1948 (21.3)	5170 (30.9)	899 (16.7)	
	61-70 (%)	6650 (21.3)	2459 (26.9)	3206 (19.2)	985 (18.3)	
	71-80 (%)	6006 (19.2)	2109 (23.1)	2568 (15.4)	1329 (24.7)	
	81-90 (%)	1974 (6.3)	1008 (11.0)	604 (3.6)	362 (6.7)	
	>90 (%)	186 (0.6)	107 (1.2)	52 (0.3)	27 (0.5)	
Gender	**female (%)**	15248 (48.8)	4384 (47.9)	8184 (48.9)	2680 (49.8)	0.085
Smoking	**n (%)**	5150 (16.5)	2285 (25.0)	1812 (10.8)	1053 (19.6)	<0.001
IMD Rank	**Quintile 1 (least deprived) (%)**	152 (0.5)	59 (0.6)	92 (0.6)	1 (0.0)	<0.001
	Quintile 2 (%)	316 (1.0)	132 (1.4)	173 (1.0)	11 (0.2)	
	Quintile 3(%)	3348 (10.7)	1860 (20.3)	1255 (7.5)	233 (4.3)	
	Quintile 4 (%)	5144 (16.5)	2243 (24.5)	2238 (13.4)	663 (12.3)	
	Quintile 5 (most deprived) (%)	22294 (71.3)	4852 (53.1)	12966 (77.5)	4476 (83.1)	
AF	**n (%)**	807 (2.6)	515 (5.6)	212 (1.3)	80 (1.5)	<0.001
CKD	**n (%)**	3648 (11.7)	1318 (14.4)	1691 (10.1)	639 (11.9)	<0.001
Diabetes	**n (%)**	9931 (31.8)	1771 (19.4)	6415 (38.4)	1745 (32.4)	<0.001
Heart Failure	**n (%)**	822 (2.6)	308 (3.4)	385 (2.3)	129 (2.4)	<0.001
Hypertension	**n (%)**	16505 (52.8)	5181 (56.6)	8063 (48.2)	3261 (60.6)	<0.001
IHD	**n (%)**	4226 (13.5)	1417 (15.5)	2386 (14.3)	423 (7.9)	<0.001
Stroke	**n (%)**	1476 (4.7)	570 (6.2)	673 (4.0)	233 (4.4)	<0.001
Comorbidities	**median (lower, upper quartile)**	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.075
	0 (%)	9879 (31.6)	2829 (30.9)	5459 (32.6)	1591 (29.6)	<0.001
	1 (%)	10707 (34.3)	3253 (35.6)	5524 (33)	1930 (35.8)	
	2 (%)	6845 (21.9)	1898 (20.8)	3694 (22.1)	1253 (23.3)	
	3 (%)	2667 (8.5)	785 (8.6)	1451 (8.7)	431 (8)	
	4 (%)	828 (2.6)	254 (2.8)	447 (2.7)	127 (2.4)	
	5 (%)	268 (0.9)	103 (1.1)	124 (0.7)	41 (0.8)	
	6 (%)	55 (0.2)	23 (0.3)	23 (0.1)	9 (0.2)	
	7 (%)	5 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)	
Creatinine (µmol/L)	**mean (SD)**	87.0 (25.8)	88.2 (24.7)	84.6 (25.4)	92.3 (28)	<0.001
eGFR (ml/min)	**median (lower, upper quartile)**	80.2 (66.7, 94.3)	74.9 (62.3, 88.8)	81.3 (68.1, 95.3)	85.5 (72.3, 100.1)	<0.001
	>120 (%)	1473 (4.7)	264 (2.9)	802 (4.8)	407 (7.6)	<0.001
	90-120 (%)	8523 (27.3)	1842 (20.1)	4841 (28.9)	1840 (34.2)	
	60-89 (%)	16373 (52.4)	5077 (55.5)	8776 (52.5)	2520 (46.8)	
	45-59 (%)	3447 (11.0)	1389 (15.2)	1627 (9.7)	431 (8.0)	
	30-44 (%)	1134 (3.6)	466 (5.1)	517 (3.1)	151 (2.8)	
	15-29 (%)	304 (1.0)	108 (1.2)	161 (1.0)	35 (0.7)	
Died	**n (%)**	1435 (4.6)	681 (7.4)	541 (3.2)	213 (4.0)	<0.001

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The number of vascular comorbidities was similar between groups, with 11-13% of each ethnic group having three or more comorbidities. ~~The p~~Prevalence of different vascular comorbidities varied between groups: the white group had a lower reported prevalence of diabetes but a higher prevalence of CKD, atrial fibrillation, heart failure and stroke.

Median eGFR (corrected for ethnicity as appropriate) was 80.2 ml/min and was lowest in the white group (74.9 ml/min compared to 81.3 ml/min for South Asian individuals and 85.5 ml/min for those of black ethnicity; p<0.001). 21.5% of White, 13.8% of South Asian and 11.5% of Black individuals had an eGFR between 15 and 59 ml/min consistent with stage 3-4 CKD.

At the end of the study period a higher proportion of white individuals had died (7.4%) compared to the two other ethnic groups (South Asian 3.2%, Black 4.0%; p<0.001).

Albumin Creatinine Ratio Cohort

An ACR had been tested in 7022 (42.0%), 2275 (24.9%) and 1908 (20.9%) of South Asian, black and white individuals respectively. **Table 2** lists the baseline characteristics for this subgroup. The median ACR was 1.1 mg/mmol and was highest in the South Asian group (1.2 mg/mmol compared to 1.0 mg/mmol for both white and black individuals; p<0.001). There were similar trends to the whole cohort for age distribution, eGFR, smoking status, and deprivation.

Those with an ACR tested were more likely to have a greater vascular comorbid burden (18-20% having three or more comorbidities). A higher proportion of individuals of South Asian descent, male gender and with diabetes had their ACR tested.

In concordance to the whole group analyses, deaths in the ACR cohort were highest amongst white individuals (7.8%) compared to the South Asian (3.6%) and black individuals (3.7%) (p<0.001).

Univariate Analysis

The univariate (unadjusted) analysis for the complete cohort (**Table 3a**) demonstrated unadjusted HRs for death of 0.421 (95% CI 0.376 – 0.471, p<0.001) for people of South Asian ethnicity and 0.522 (95% CI 0.447 – 0.609, p<0.001) for people of black ethnicity compared to people of white ethnicity. The mortality rate increased exponentially with age and a higher HR was observed for male gender, current smokers and total number of comorbidities. No difference in mortality was found between deprivation quintiles. Using an eGFR of 90-119 ml/min as reference, a J-shaped relationship was observed with a higher risk of death seen for both higher and lower eGFR values. The HR for death increased progressively by stage of CKD with an eGFR <90 ml/min.

The univariate analysis was repeated for those individuals who had their ACR reported (**Table 3b**) with similar trends identified to the whole population analysis with the exception of no observed difference between individuals with an eGFR of ≥120 ml/min compared to 90-119 ml/min. A progressive increase in HR for death was seen with each increasing category for ACR.

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Table 2: Baseline characteristics by ethnicity. ACR tested cohort.

		All	White	South Asian	Black	p-value
Number	**n (%)**	11205 (100)	1908 (17)	7022 (62.7)	2275 (20.3)	
Age (years)	**median (lower, upper quartile)**	59.0 (50.0, 71.0)	65.0 (55.0, 75.0)	57.0 (50.0, 68.0)	65.0 (49.0, 74.0)	<0.001
	50 and under (%)	1900 (25.9)	304 (15.9)	1961 (27.9)	635 (27.9)	<0.001
	51-60 (%)	3024 (27.0)	413 (21.6)	2239 (31.9)	372 (16.4)	
	61-70 (%)	2370 (21.2)	496 (26.0)	1423 (20.3)	451 (19.8)	
	71-80 (%)	2251 (20.1)	456 (23.9)	1152 (16.2)	643 (28.3)	
	81-90 (%)	611 (5.5)	222 (11.6)	226 (3.2)	163 (7.2)	
	>90 (%)	49 (0.4)	17 (0.9)	21 (0.3)	11 (0.5)	
Gender	**female (%)**	4348 (38.8)	682 (35.7)	2754 (39.2)	912 (40.1)	0.008
Smoking	**n (%)**	1869 (16.7)	518 (27.1)	872 (12.4)	479 (21.1)	<0.001
IMD Rank	**Quintile 1 (least deprived) (%)**	30 (0.3)	4 (0.2)	25 (0.4)	1 (0.0)	<0.001
	Quintile 2 (%)	84 (0.7)	19 (1.0)	60 (0.9)	5 (0.2)	
	Quintile 3(%)	712 (6.4)	233 (12.2)	540 (5.7)	78 (3.4)	
	Quintile 4 (%)	1458 (13.0)	339 (17.8)	876 (12.5)	243 (10.7)	
	Quintile 5 (most deprived) (%)	8921 (79.6)	1313 (68.8)	5660 (80.6)	1948 (85.6)	
AF	**n (%)**	233 (2.1)	113 (5.9)	91 (1.3)	29 (1.3)	<0.001
CKD	**n (%)**	1637 (14.6)	356 (18.7)	921 (13.1)	360 (15.8)	<0.001
Diabetes	**n (%)**	6828 (60.9)	990 (51.9)	4505 (62.4)	1333 (58.6)	<0.001
Heart Failure	**n (%)**	310 (2.8)	74 (3.9)	175 (2.5)	61 (2.7)	0.005
Hypertension	**n (%)**	6189 (55.2)	1092 (57.2)	3679 (52.4)	1418 (62.3)	<0.001
IHD	**n (%)**	1556 (13.9)	281 (14.7)	1071 (15.3)	201 (8.8)	<0.001
Stroke	**n (%)**	480 (4.3)	97 (5.1)	283 (4.0)	100 (4.4)	0.126
Comorbidities	**median (lower, upper quartile)**	1.0 (1.0, 2.0)	2.0 (1.0,2.0)	1.0 (1.0, 2.0)	2.0 (1.0,2.0)	0.818
	0 (%)	2510 (22.4)	472 (24.7)	1514 (21.6)	524 (23.0)	<0.001
	1 (%)	3139 (28.0)	466 (24.4)	2103 (29.9)	870 (25.1)	
	2 (%)	3438 (30.7)	574 (30.1)	2093 (29.8)	771 (33.9)	
	3 (%)	1481 (13.2)	261 (13.7)	928 (13.2)	292 (12.8)	
	4 (%)	448 (4.0)	79 (4.1)	284 (4.0)	85 (3.7)	
	5 (%)	154 (1.4)	46 (2.4)	83 (1.2)	25 (1.1)	
	6 (%)	32 (0.3)	10 (0.5)	15 (0.2)	7 (0.3)	
	7 (%)	3 (<0.1)	0 (<0.1)	2 (<0.1)	1 (<0.1)	
Creatinine (μmol/L)	**mean (SD)**	89.1 (27.6)	91.8 (26.2)	86.2 (26.8)	95.8 (29.6)	
eGFR (ml/min)	**median (lower, upper quartile)**	81.1 (66.3, 95.9)	74.3 (59.7, 89.8)	82 (67.4, 89.8)	84.2 (70.0, 98.9)	
	>120 (%)	611 (5.5)	67 (3.5)	380 (5.4)	164 (7.2)	<0.001
	90-120 (%)	3234 (28.9)	404 (21.2)	2091 (29.8)	739 (32.5)	
	60-89 (%)	5451 (48.6)	953 (49.9)	3453 (49.2)	1045 (45.9)	
	45-59 (%)	1300 (11.6)	323 (16.9)	750 (10.7)	227 (10.0)	
	30-44 (%)	487 (4.3)	131 (6.9)	274 (3.9)	82 (3.6)	
	15-29 (%)	122 (1.1)	30 (1.6)	74 (1.1)	18 (0.8)	
ACR (mg/mmol)	**median (lower, upper quartile)**	1.1 (0.4, 3.4)	1.0 (1.4, 2.8)	1.2 (0.5, 3.8)	1.0 (0.3, 2.9)	<0.001
	Optimal (<1.1) (%)	5641 (50.3)	1026 (53.8)	3400 (48.4)	1214 (53.4)	<0.001
	High Normal (1.1-2.99) (%)	2485 (22.2)	426 (22.3)	1560 (22.2)	499 (21.9)	
	High (3.0-29.99) (%)	2594 (23.2)	402 (21.1)	1717 (24.4)	475 (20.9)	
	Very High (30 - 200) (%)	413 (3.7)	49 (2.6)	287 (4.1)	77 (3.4)	
	Nephrotic (>200) (%)	73 (0.7)	5 (0.3)	58 (0.8)	10 (0.4)	
Died	**n (%)**	484 (4.3)	149 (7.8)	250 (3.6)	85 (3.7)	<0.001

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Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Table 3: Cox Proportional Hazard Regression Analysis. Univariate (unadjusted) analyses

		Complete Cohort (3a)		ACR Tested Cohort (3b)	
		Hazard Ratio (95% Confidence Interval)	P value	Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	White	~~Reference population~~1	(<0.001*)	~~Reference Population~~1	(<0.001*)
	South Asian	0.421 (0.376 - 0.471)	<0.001	0.444 (0.362 - 0.545)	<0.001
	Black	0.522 (0.447 - 0.609)	<0.001	0.467 (0.357 - 0.611)	<0.001
Age (years)	50 and under	~~Reference population~~1	(<0.001*)	~~Reference Population~~1	(<0.001*)
	51-60	2.127 (1.553 - 2.914)	<0.001	1.757 (1.057 - 2.921)	0.03
	61-70	5.429 (4.078 - 7.228)	<0.001	4.646 (2.926 - 7.345)	<0.001
	71-80	12.971 (9.887 - 17.016)	<0.001	11.363 (7.376 - 17.505)	<0.001
	81-90	32.86 (29.952 - 43.275)	<0.001	24.725 (15.769 - 38.767)	<0.001
	>90	90.904 (65.097 - 126.943)	<0.001	82.731 (46.684 - 146.612)	<0.001
Gender	Female as reference	1.375 (1.238 - 1.529)	<0.001	1.401 (1.155 - 1.699)	0.001
Smoker	Non-smoker as reference	1.154 (1.009 - 1.317)	0.036	1.259 (1.006 - 1.574)	0.044
IMD Rank	Quintile 1 (least deprived)	0.860 (0.385 - 1.919)	0.713	<0.001 (<0.001 - >10^5)	0.939
	Quintile 2	0.822 (0.465 - 1.453)	0.501	<0.001 (<0.001 - >10^5)	0.897
	Quintile 3	1.002 (0.846 - 1.186)	0.983	1.151 (0.818 - 1.619)	0.419
	Quintile 4	0.925 (0.800 - 1.070)	0.297	0.774 (0.577 - 1.039)	0.088
	Quintile 5 (most deprived)	~~Reference population~~1	(0.802*)	~~Reference Population~~1	(0.42*)
AF		5.588 (4.757 - 6.565)	<0.001	6.123 (4.568 - 8.207)	<0.001
CKD		3.442 (3.074 - 3.854)	<0.001	3.498 (2.904 - 4.213)	<0.001
Diabetes		1.346 (1.209 - 1.498)	<0.001	1.939 (1.577 - 2.385)	<0.001
Heart Failure		7.622 (6.595 - 8.804)	<0.001	7.279 (5.681 - 9.327)	<0.001
Hypertension		2.079 (1.857 - 2.325)	<0.001	2.05 (1.681 - 2.499)	<0.001
IHD		2.796 (2.495 - 3.132)	<0.001	3.136 (2.592 - 3.795)	<0.001
Stroke		3.654 (3.154 - 4.233)	<0.001	3.709 (2.855 - 4.817)	<0.001
Comorbidities	0	~~Reference population~~1	(<0.001*)	~~Reference population~~1	(<0.001*)
	1	1.775 (1.487 - 2.118)	<0.001	1.630 (1.094 - 2.430)	0.016
	2	2.930 (2.458 - 3.493)	<0.001	2.917 (2.023 - 4.205)	<0.001
	3	5.486 (4.550 - 6.615)	<0.001	5.580 (3.837 - 8.113)	<0.001
	4	9.584 (7.691 - 11.942)	<0.001	9.855 (6.511 - 14.917)	<0.001
	5	17.591 (13.490 - 22.939)	<0.001	21.091 (13.479 - 33.001)	<0.001
	6	28.391 (18.411 - 43.782)	<0.001	33.673 (17.519 - 64.722)	<0.001
	7	11.873 (1.664 - 84.728)	0.014	29.402 (4.031 - 214.462)	0.001
eGFR (ml/min)	>120	1.492 (1.110 - 2.007)	0.008	1.072 (0.603 - 1.903)	0.813
	90-120	~~Reference population~~1	(<0.001*)	~~Reference Population~~1	(<0.001*)
	60-89	1.360 (1.162 - 1.591)	<0.001	1.504 (1.138 - 1.987)	0.04
	45-59	3.849 (3.239 - 4.573)	<0.001	4.255 (3.155 - 5.737)	<0.001
	30-44	6.590 (5.401 - 8.041)	<0.001	7.715 (5.564 - 10.699)	<0.001
	15-29	14.465 (11.341 - 18.450)	<0.001	15.054 (9.942 - 22.796)	<0.001
ACR (mg/mmol)	Optimal (<1.1)			~~Reference Population~~1	(<0.001*)
	High Normal (1.1-2.99)			1.363 (1.038 - 1.788)	0.026
	High (3.0-29.99)			2.967 (2.381 - 3.697)	<0.001
	Very High (30 - 200)			6.253 (4.493 - 14.005)	<0.001
	Nephrotic (>200)			7.932 (4.493 - 14.005)	<0.001

* P-value for overall effect

Multivariate Analysis

Following adjustment for covariates the differences in ethnicity remained; people of South Asian and black ethnicities had a lower HR for death in all analyses.

Model 1 (complete cohort, incorporating the number of identified comorbidities, see **Supplementary Table I**) analysed the complete cohort and showed an adjusted HR for death of 0.673 (95% CI 0.595 – 0.761, p<0.001) for people of South Asian ethnicity and 0.592 (95% CI 0.504 – 0.696, p<0.001) for people of black ethnicity compared to people of white ethnicity. When the analysis was restricted to the cohort with ACR tests available the HR for death was 0.757 (95% CI 0.61 – 0.939, p=0.011) for people of South Asian ethnicity and 0.526 for people of black ethnicity (95% CI 0.4 – 0.692, p<0.001) compared to people of white ethnicity. For the complete cohort, mortality risk was lower in IMD quintiles 3 and 4 (compared to the most deprived quintile 5). No significant difference between IMD quintiles was identified in the ACR cohort. Increasing age (51 and over in complete cohort, 61 and over in ACR cohort), smoking status and male gender was significant in analyses for both cohorts. An increased HR for death was observed for two or more comorbidities, with the HR increasing as the number of comorbidities increased.

Kidney function (eGFR) was incorporated into Model 2 (with the removal of CKD from the comorbidity score, see **Supplementary Table I**) and in the complete cohort the HR for people of South-Asian ethnicity was 0.678 (95% CI 0.6 – 0.767 p<0.001) and for people of black ethnicity was 0.789 (95% CI 0.635 – 0.98, p=0.032) compared to people of white ethnicity. Similarly, when the analysis was restricted to the cohort of patients with ACR tests available people of South Asian and Black ethnicity had a lower proportion of deaths compared to people of white ethnicity with HRs of 0.614 (95% CI 0.522 – 0.722, p<0.001) and 0.575 (95% CI 0.435 – 0.759, p<0.001) respectively. In the complete cohort mortality risk was lower in the IMD quintile 4. More than two comorbidities were associated with an increasing HR and an increased HR of death compared to the reference eGFR range (90-119 ml/min) was seen with an eGFR ≥120 ml/min and ≥45 ml/min. An eGFR of 60-89 ml/min was associated with a lower HR. In the analysis of those with ACR tested, an eGFR <60 ml/min was associated with progressively higher HR by CKD stage.

In model 3 (all vascular comorbidities except CKD and the addition of eGFR and ACR, **Table 4**) the HR for death for people of South Asian ethnicity was 0.697 (95% CI 0.56 – 0.868, p=0.001) and for people of black ethnicity was 0.533 (95% CI 0.403 – 0.704, p<0.001) compared to people of white ethnicity **(Figure 2)**. Older age, male gender, being a current smoker and increasing comorbidity (two or more) were associated with an increased HR of death **(Figure 3)**. An ACR of 'high' or greater (i.e. ≥3.0 mg/mmol) and an eGFR <45 ml/min was also associated with an increased HR for death. No significant differences in HRs were observed between deprivation quintiles.

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

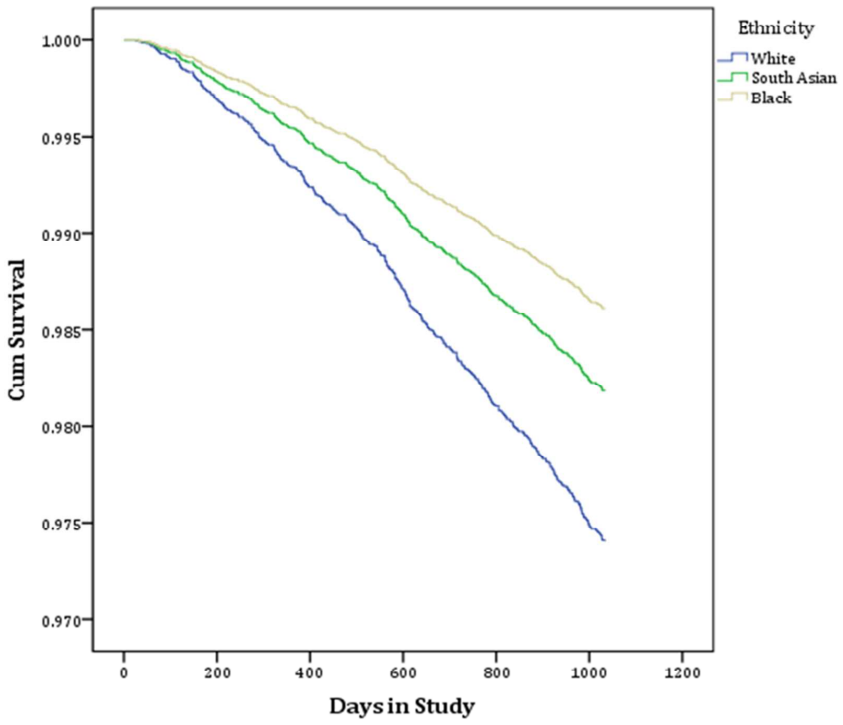
Table 4: Cox Proportional Hazard Regression Analysis. Multivariate (adjusted) analyses. Model 3.

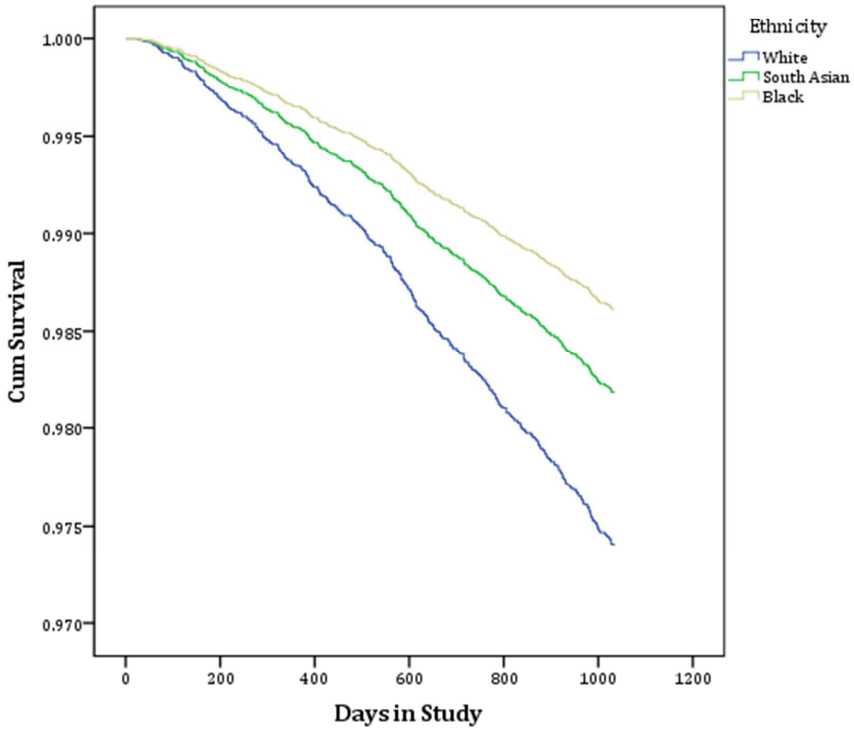
		ACR Tested Cohort	
		Hazard Ratio (95% Confidence Interval)	P value
Ethnicity	White	~~Reference Population~~1	(<0.001*)
	South Asian	0.697 (0.56 - 0.868)	0.001
	Black	0.533 (0.403 - 0.704)	<0.001
Age (years)	50 and under	~~Reference Population~~1	(<0.001*)
	51-60	1.519 (0.907 - 2.546)	0.112
	61-70	3.521 (2.17 - 5.712)	<0.001
	71-80	7.381 (4.61 - 11.818)	<0.001
	81-90	15.721 (9.534 - 25.922)	<0.001
	>90	51.641 (27.889 - 95.621)	<0.001
Gender	Female as reference	1.782 (1.46 - 2.176)	<0.001
Smoker	Non-smoker as reference	1.886 (1.488 - 2.392)	<0.001
IMD Rank	Quintile 1 (least deprived)	<0.001 (<0.001 - >10^5)	0.952
	Quintile 2	<0.001 (<0.001 - >10^5)	0.913
	Quintile 3	0.978 (0.68 - 1.387)	0.902
	Quintile 4	0.788 (0.585 - 1.062)	0.118
	Quintile 5 (most deprived)	~~Reference Population~~1	(0.65*)
Comorbidities	0	~~Reference population~~1	(<0.001*)
	1	1.371 (0.932 - 2.016)	0.109
	2	1.486 (1.019 - 2.166)	0.039
	3	2.29 (1.53 - 3.428)	<0.001
	4	3.153 (2.002 - 4.964)	<0.001
	5	5.141 (2.869 - 9.212)	<0.001
	6	10.54 (2.52 - 44.084)	0.001
eGFR (ml/min)	>120	1.396 (0.782 - 2.492)	0.26
	90-120	~~Reference Population~~1	(<0.001*)
	60-89	0.907 (0.982 - 1.207)	0.505
	45-59	1.282 (0.932 - 1.763)	0.126
	30-44	1.566 (1.095 - 2.239)	0.014
	15-29	2.073 (1.315 - 3.268)	0.002
ACR (mg/mmol)	Optimal (<1.1)	~~Reference Population~~1	(<0.001*)
	High Normal (1.1-2.99)	1.032 (0.784 - 1.359)	0.821
	High (3.0-29.99)	1.837 (1.464 - 2.305)	<0.001
	Very High (30 - 200)	2.956 (2.132 - 4.099)	<0.001
	Nephrotic (>200)	3.838 (2.108 - 6.985)	<0.001

* P-value for overall effect

Impact of CKD and comorbidity on mortality in a multi-ethnic population.

Figure 2. Cox Regression Survival Plot indicating cumulative survival. ~~Differences~~ between ethnicities in Model 3 (comorbidities, eGFR and ACR). Table below survival plot demonstrates number of individuals who remained in follow up at each time-point.





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Impact of CKD and comorbidity on mortality in a multi-ethnic population.

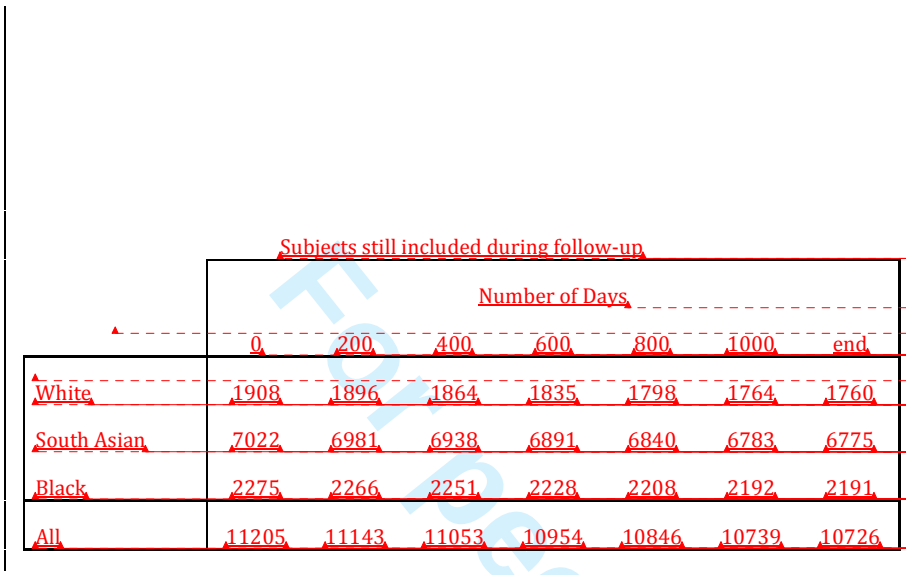

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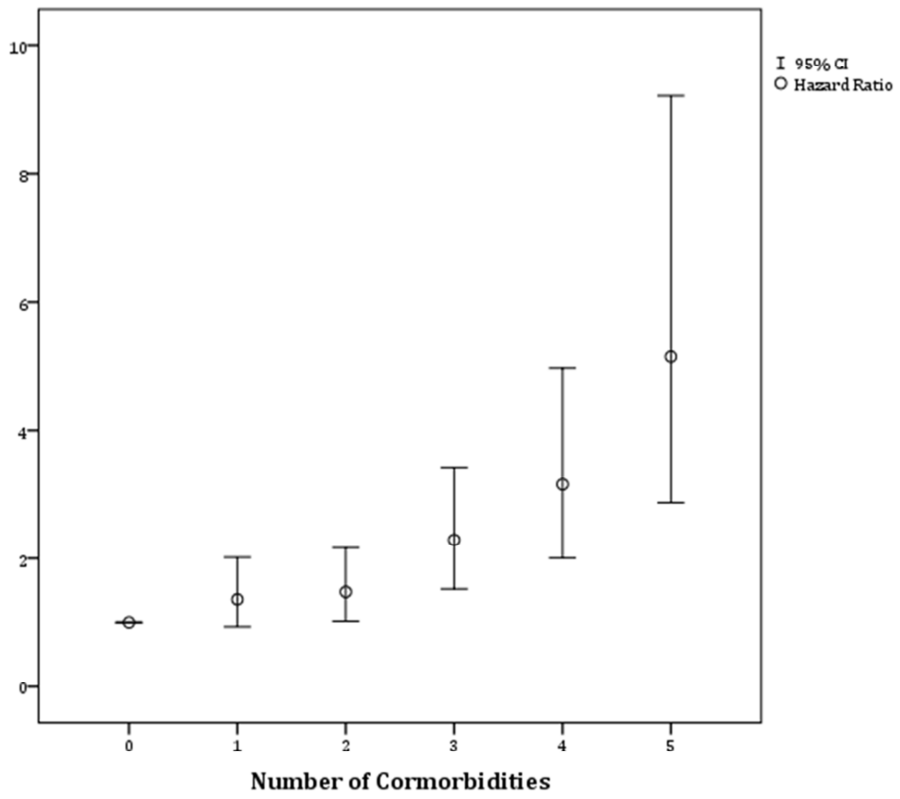
Figure 3. Hazard ratio (HR) for death by number of comorbidities. Multivariate (adjusted) analysis: Model 3



HR not illustrated for 6 comorbidities; HR 10.54 (95% CI 2.52 - 44.084)

Discussion

This study utilised routinely available clinical and laboratory data, including kidney function assessed by eGFR and ACR, from a large primary care population. We included in the analysis detailed ~~socio-economic status (~~SES~~)~~ and, importantly, studied three ethnic groups, South-Asian, black and white. Prior to this research, there has been uncertainty about the impact of ethnicity and SES on clinical outcomes in people with significant comorbidities including CKD. The comprehensive nature of the dataset coupled with the ability to utilise the Primary Care Mortality Database has allowed us to assess the relative impact of these factors on survival.

We found that previous associations between lower eGFR and higher ACR and increased mortality applied to this population. Furthermore, these associations remained significant when adjusted for ethnicity, age, gender, cardiovascular risk factors and SES. These results add weight to the risk stratification benefit of measuring ACR has in high risk groups.

A strong cumulative impact of comorbidity on CKD and ethnicity was shown. Whereas traditional comorbidity scores such as the Charlson Comorbidity Index **[36]** are difficult to calculate accurately in a large primary care setting, our study demonstrates that a simple cumulative score ~~can be used to risk stratify~~provides prognostic information. Individual comorbidities were present in varying frequencies within different ethnic groups, a finding ~~echoed in other~~consistent with that found in other ethnically diverse populations~~**[37]**~~.**[37]** Whilst ~~they were~~individual comorbidities were associated with different mortality risks, we found the cumulative effect of comorbidities conveyed the greatest prognostic implication. A similar approach, but also including non-cardiovascular risk factors has recently been described ~~**[38]**~~.**[38]** Our study ~~demonstrates~~ suggests that routinely collected clinical data concerning cumulative comorbidity ~~can~~ may be utilised to quantify risk, however ~~and~~ further work ~~to~~would be required to validate this as a ~~develop such a risk stratification tool is underway~~tool for use in clinical care. ~~Potential implications for this include identifying (and targeting) those at the highest risk.~~

SES was measured by the IMD 2007 score; a cumulative deprivation index score incorporating seven areas of deprivation which has been validated as superior to other deprivation scores ~~**[31]**~~.**[31]** One notable finding is that we did not demonstrate any association between mortality when corrected for all other factors including comorbidity and ethnicity. ~~This~~ This is not consistent with ~~with a number of~~several other studies, which have shown that there is an independent relationship between SES and mortality ~~and this applies~~ across disease states and ethnic groups within the UK ~~**[39-42]**~~.**[39-42]** This relationship varies by population group studied **[43]** and there have been limited studies investigating health disparities in similar, inner-city populations. Whilst we studied a health care system that is free at the point of care, limiting possible health access issues, the majority of individuals were from the most deprived national quintile and our study may therefore underestimate the influence of the complete spectrum of SES on mortality. To attempt to correct for this, ~~. Whilst we studied a health care system that is free at the point of care, limiting possible health access issues, the majority of individuals were from the most deprived national quintile. W~~we ~~therefore~~ re-ran the analyses dividing the cohort into equal

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quintiles. All analyses continued to indicate the effect of ethnicity and the importance of cardiovascular comorbidity and renal function. The univariate analysis (**Supplementary Table II**) and the most comprehensive multivariate analysis (Model 3, (**Supplementary Table III**) did not show any differences between most and least deprived quintiles.

One of the seven areas included in the IMD is health deprivation, raising the possibility of an inbuilt relationship between ~~and~~ deprivation and health even before analyses are undertaken. The possible implication of this was investigated by Adams and White **[44]** who analysed data having removed the health domain from IMD 2004 and found that its removal had little, practical, effect. This suggests the presence of the health domain is unlikely to influence our result.

We found that the risk of death was lower for people of South Asian and black ethnicity compared to people of white ethnicity, and this remained in all analyses (adjusted and unadjusted) performed. Previous studies comparing the outcomes of different ethnic groups have been limited in their generalizability. They have either looked at disease specific mortality **[8 ,18 ,20 ,21]** or have been based in populations that do not have access to free comprehensive healthcare. The finding that differences in mortality risk between ethnic groups is independent of age, gender, SES, kidney function and comorbidities require~~s~~ further work. ~~There may be o~~Vther ~~external factors~~ariables ~~,~~ such as health promotion targeted at specific groups, differences in medication usage or ~~which can explain this risk or~~ factors related to genetic diversity ~~which may require genome wide studies to elucidate~~may offer potential explanations for this variation. **[45 ,46]**.

A major strength in this study is the sample size, which included sixty-two practices of varying list size and number of practitioners. Ethnicity was documented in over 80% of the population studied; this is, much higher than normally found in primary care records ~~**[47]**~~.**[47]** Self-reporting is considered the 'gold standard' method of assessing ethnicity~~**[27]**~~.**[27]** taking into account an individual's culture and self-identity. Renal function was described in terms of eGFR and ACR, the latter becoming of increased prominence in the stratification of cardiovascular risk.

Our analyses have used data from primary care coding and recording systems, which formed part of the electronic downloads. These downloads indicate who is on a specific cardiovascular risk register and therefore may not classify people correctly. There is a relative paucity of published literature regarding the correct identification of people onto the correct risk registers **[23 ,48]** ~~-~~**[49 ,50]**. Surrogate measures of accuracy of the data include previous studies looking at gaming for QOF points (falsely classifying people with conditions they do not have thereby increasing revenue) or exception reporting (excluding individuals who have not had the appropriate monitoring completed) suggest that both these are rare ~~**[23 51 52]**~~.**[23 ,51 ,52]**

When comparing the breakdown of the population studied in these analyses to the source population, it is important to highlight two key differences. Firstly, t~~T~~here is a relative underrepresentation of individuals of white ethnicity, consistent with previous research~~**[53]**~~.**[53]** This is most marked in those who had their

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ACR measured; ~~d as~~ a higher number of males and individuals with diabetes or of South Asian ~~descent~~ethnicity had an ACR ~~performed~~measured. Comparing the whole cohort to those who had their ACR reported showed similar trends for mortality ~~were observed for~~in respect of age ~~distribution~~, eGFR, smoking status and ~~deprivation~~SES, suggests a generalizability of results. ~~Additionally,~~Secondly one criterion for inclusion was the recording of renal function within the previous twelve months. This is likely to have resulted in an overrepresentation of comorbidity as people with CV conditions would be more likely to have their renal function checked. A further consideration is that the accuracy and applicability of creatinine based eGFR equations, such as the formula used in this analysis, in non-white ethnic groups is a subject of ongoing research ~~[54-56]~~[54-56] Cystatin based equations may be more accurate ~~[57]~~[57] but are not routinely measured in clinical practice.

~~Not all individuals had their ACR measured and the percentage varied between ethnic groups, one of the limitations of retrospective, population based analyses. A higher number of males and individuals with diabetes or of South Asian descent had an ACR performed[53]. However, similar trends for mortality were observed for age distribution, eGFR, smoking status and deprivation, suggesting generalizability of results.~~

~~The accuracy and applicability of creatinine based estimated GFR equations, such as the formula used in this analysis, in non-white ethnic groups is a subject of ongoing research.[54-56] Cystatin based equations may be more accurate,[57] but are not available for use with routinely recorded data.~~

In summary, we have shown the determinants of mortality were multifactorial in a high risk population and that ethnicity should be considered as a non-traditional risk factor for mortality; the HR for death was lower for South Asian and black individuals compared to white individuals which was, in part, independent of age, gender, SES, renal function and comorbidities. Furthermore, a simple cumulative comorbidity system may have prognostic utility. Renal function (eGFR and ACR) provides additional information and gender, age and smoking status remain significant risk factors for mortality.

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none

Competing Interests

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