Microalbuminuria and Coronary Heart Disease Risk in an Ethnically Diverse UK Population: A Prospective Cohort Study

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Microalbuminuria (MA) is a strong risk factor for subsequent chronic disease, both renal and coronary heart disease (CHD), in European origin populations, but CHD risks differ by ethnicity, and it was hypothesized that prevalence of MA and relations with CHD may also differ. Combined analyses of two population-based cohorts started in 1988 and consisted of 1460 Europeans (70% male), 946 South Asians (78% male), and 559 African Caribbeans (51% male) who resided in London and were aged 40 to 69. Baseline fasting blood, overnight urine collection, and clinical measurements were performed. Prevalent CHD was defined by clinical history or major electrocardiogram changes. Age-adjusted albumin excretion rates (AER; geometric means, μg/min) were significantly higher in African Caribbeans (men: 6.1, 95% confidence interval [CI] 5.5 to 6.7; women: 5.7, 95% CI 5.2 to 6.2) than in South Asians (men: 4.3, 95% CI 4.0 to 4.5; women 3.4, 95% CI 3.0 to 3.8) and Europeans (men: 4.5, 95% CI 4.3 to 4.8; women: 3.3, 95% CI 3.1 to 3.6). MA was associated with both prevalent CHD and CHD mortality in South Asian men (hazard ratio 2.5; 95% CI 1.3 to 4.8) and in European women (hazard ratio 13.0; 95% CI 2.6 to 64.2) but not in any other group. Greater AER in African Caribbeans and the absence of association with CHD contrast with lower AER in South Asian men and European women, both strongly associated with CHD prevalence and mortality. These differences suggest that the pathogenesis of kidney disease and its link with CHD differ by ethnicity and gender.

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Microalbuminuria (MA) is an early indicator of generalized microvascular disease and is strongly predictive of progressive kidney disease in people with diabetes (1). It is also an independent predictor of cardiovascular and all-cause mortality in people with and without diabetes (2–5). The mechanisms underlying the association between MA and kidney and cardiovascular disease are unclear but are thought to reflect widespread endothelial dysfunction and microvascular damage (6) and possibly inflammation (7).

Most of the research on the risks of MA and its associations with kidney and cardiovascular disease has been carried out in populations of European origin, and such associations may not hold true for other ethnic groups. Many non-European populations, such as South Asians and African Caribbeans, have high rates of type 2 diabetes (8,9), but rates of cardiovascular disease vary. In the United Kingdom, for example, South Asians have higher rates and African Caribbeans have lower rates of coronary heart disease (CHD) than comparable Europeans (10).

Evidence for ethnic group differences in rates of MA is scant and conflicting, and previous studies have largely been restricted to people with diabetes. We might expect that, in comparison with Europeans, MA would be more frequent in South Asians, given their elevated levels of other CHD risk factors, and likewise in African Caribbeans in association with higher BP (11–13). In the United Kingdom, MA was found to be twice as frequent in South Asians as in Europeans in a clinic population (14) and in a population-based study (15). In the United States, in people with diabetes, MA is twice as prevalent in black individuals as in white individuals (16). In contrast, the UK Prospective Diabetes Study (UKPDS) found similar prevalence of MA in Europeans, South Asians, and African Caribbeans with newly diagnosed type 2 diabetes (17). We sought to compare rates of MA in South Asians, African Caribbeans, and Europeans across the range of glucose tolerance in the largest UK population–based samples comparing ethnic minorities and to determine associations with CHD prevalence and mortality.

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Materials and Methods

Study Design

We used data from two population-based studies that were conducted to identical protocols between 1988 and 1991 in West London and since followed for deaths and causes of death. Both studies have

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previously been described in detail (8,11) and were approved by local research ethics committees.

Participants

The study group described here includes only those participants who provided timed overnight urine collections. All participants were aged between 40 and 69 yr (mean age 53 yr; SD 6.9) and comprised 1460 white Europeans (70% male), 946 South Asians (78% male), and 559 African Caribbeans (51% male). Recruitment was from ethnicity- and gender-stratified random samples from general practitioner (GP) practice lists. "South Asian" describes people of Indian, Pakistani, and Bangladeshi origins; 71% of South Asians in this study were born in India. The Southall study, the source of all South Asians in this study, preferentially sampled men to address the original study objectives. The majority (82%) of the African Caribbean study population were born in the Caribbean Islands.

Baseline Measurements

Ethnic group was assigned by the interviewer on the basis of name, appearance, and country of birth, supplemented with direct inquiry in cases of doubt. Participants attended a local hospital after an overnight fast. BP and anthropometric measurements were recorded; a resting electrocardiogram (ECG) was performed; and fasting blood samples were taken for measurement of plasma triglycerides, cholesterol, HDL cholesterol, glucose, and insulin. For participants who were not known to have diabetes, an oral glucose load was given and plasma glucose and insulin were measured 2 h later. ECG were coded, according to the Minnesota Classification (18), by two experienced coders who were blinded to all other information on each subject.

Timed overnight urine collections were carried out and urine albumin was measured, using a highly sensitive immunoturbidimetric method (19) with goat anti-human albumin antisera (Sanofi Diagnostics, Pasteur, MN) and human serum albumin standards (ORHA 20/21 grade HAS; Behring Diagnostics, Hoechst, UK). Urine was tested to identify urinary tract infection; participants with positive test results were asked to repeat the overnight urine collection after treatment.

Laboratory measurements for the two studies were made at the same hospital chemical pathology laboratory and were described in detail in earlier publications (9,20). Self-completion questionnaires included items on socioeconomic status, medical history, and lifestyle.

Follow-Up

Participants were flagged for mortality and cause of death by the Office for National Statistics.

Statistical Analyses

Microalbuminuria was defined by the World Health Organization recommended a cutoff value for albumin excretion rate (AER) of >20 μg/min (21). Diabetes, impaired fasting glucose, and impaired glucose tolerance were defined according to World Health Organization 1999 criteria (21). Participants who were receiving treatment for hypertension were ranked at the highest levels of systolic, diastolic, and mean arterial BP for the study population.

Age-standardized prevalences of microalbuminuria were described in ethnic and gender strata, using the whole study population as the standard. Linear and quartile (median) regression models were used, separately in men and women, to determine the extent to which ethnic group differences in AER were explained by measured cardiovascular disease risk factors.

Early life influences are regarded as independent risk factors for many adult diseases, including cardiovascular disease (22), and adult height is predicted by birth weight and length (23). Inverse associations have been demonstrated between adult height and cardiovascular disease (24,25) and between adult height and diabetic nephropathy (26). Rapid catch-up growth in childhood has also been associated with increased CHD mortality in adulthood (27). Although our data set does not contain information regarding early life growth, adult height and weight were measured. We have attempted to identify people whose early life circumstances had been unfavorable and were followed by a period of rapid catch-up growth by categorizing those who were below the median for height and above the median for weight ("short for weight") for each ethnic and gender group.

Prevalent CHD was defined as history of doctor-diagnosed angina or heart attack and/or the presence of major ECG changes (major Q waves, defined by Minnesota codes 1-1 or 1-2, or left bundle branch block, defined by code 7-1-1). CHD-related deaths were identified by *International Classification of Diseases, Ninth Revision*, codes 410 to 4149, and *International Classification of Diseases, Tenth Revision*, codes I200 to I259, appearing as a cause of death in any position on the death certificate.

Logistic regression models were used to describe associations between MA and prevalent CHD in each ethnic group stratified by gender. The models were adjusted for significantly associated confounders and intermediaries. Cox proportional hazards models were used to explore associations between MA and CHD mortality. Because of the small numbers of CHD-related deaths, additional covariates were restricted to bivariate analyses in European and South Asian men. Interactions between AER and ethnicity and every other measured risk factor were assessed in regression models. Statistical significance was accepted at the 5% level. Analyses were performed in STATA Version 8 (StataCorp LP, College Station, TX).

Results

Participants with and without Missing AER Data

Approximately 27% of all study participants had insufficient data to calculate AER; this was due to reluctance of participants to return with timed urine collections. South Asian women were more likely to have missing AER (30 *versus* 20% of European and African Caribbean women; $P = 0.01$). South Asian men were also more likely to have missing AER (33 *versus* 26% of European and 30% of African Caribbean men; $P = 0.001$). Prevalence of current/former smoking was higher in South Asian men and in African Caribbean women with missing AER data (respectively, 32 *versus* 22% [$P = 0.001$] and 27 *versus* 14% [$P = 0.01$]). CHD mortality was significantly greater in South Asian men with missing AER (rate ratio 1.6; $P = 0.03$). Comparison of other characteristics of those with and without AER data revealed no significant differences in any other measured risk factors or in the prevalence of CHD or diabetes within any ethnic/gender group.

Prevalence of CHD

CHD was most prevalent in European and South Asian men (11%) and least prevalent in European women (6%), South Asian women (2%), and African Caribbeans (5 and 4% in men and women, respectively; Table 1).

Risk Factors for Microalbuminuria and CHD

South Asians and African Caribbeans were more likely to be glucose intolerant and insulin resistant and to have higher BP

Table 1. Baseline characteristics of study population[a]

	European		South Asian		African-Caribbean	
	Men (n = 1015)	Women (n = 445)	Men (n = 741)	Women (n = 205)	Men (n = 284)	Women (n = 275)
Age (SD)	53.9 (7.1)	53.2 (6.6)	51.9 (7.3)	50.6 (6.7)	54.0 (5.8)	53.2 (5.8)
Age-adjusted averages (95% CI)						
systolic BP (mmHg [median])	122.9 (121.2 to 124.6)	119.3 (116.9 to 121.7)	126.8 (124.9 to 128.7)	126.6 (123.3 to 129.9)	128.2 (125.2 to 131.1)	134.3 (131.3 to 137.3)
diastolic BP (mmHg [median])	77.8 (77.0 to 78.6)	75.5 (74.3 to 76.7)	81.8 (80.9 to 82.7)	78.6 (77.0 to 80.3)	83.1 (81.6 to 84.6)	85.1 (83.7 to 86.6)
mean arterial pressure (mmHg [median])	92.3 (91.4 to 93.2)	90.5 (89.3 to 91.7)	96.3 (95.2 to 97.3)	94.4 (93.1 to 95.8)	99.7 (98.2 to 101.1)	97.8 (96.4 to 99.3)
BMI (means)	25.8 (25.6 to 26.0)	26.9 (26.6 to 27.2)	26.0 (25.7 to 26.2)	26.9 (26.6 to 27.2)	27.3 (26.9 to 27.6)	28.2 (27.9 to 28.6)
waist-to-hip ratio (mean)	0.94 (0.93 to 0.94)	0.82 (0.81 to 0.82)	0.99 (0.98 to 0.99)	0.84 (0.83 to 0.84)	0.96 (0.95 to 0.96)	0.84 (0.83 to 0.84)
height (cm [mean])	174.4 (174.1 to 174.8)	161.0 (160.6 to 161.5)	169.2 (168.8 to 169.6)	155.9 (155.4 to 156.4)	173.1 (172.6 to 173.6)	159.8 (159.3 to 160.3)
waist (cm [mean])	91.8 (91.1 to 92.5)	79.9 (78.8 to 81.0)	93.4 (92.7 to 94.2)	86.1 (84.4 to 87.7)	89.1 (87.9 to 90.3)	88.3 (87.0 to 89.7)
triglycerides (geometric mean; mmol/L)	1.46 (1.41 to 1.50)	1.29 (1.24 to 1.34)	1.72 (1.66 to 1.78)	1.52 (1.45 to 1.59)	1.15 (1.09 to 1.21)	1.01 (0.97 to 1.07)
HDL (geometric mean; mmol/L)	1.26 (1.24 to 1.28)	1.55 (1.52 to 1.59)	1.15 (1.13 to 1.17)	1.41 (1.38 to 1.45)	1.38 (1.35 to 1.41)	1.70 (1.66 to 1.74)
fasting glucose (median; mmol/L)	5.39 (5.33 to 5.44)	5.29 (5.21 to 5.36)	5.58 (5.52 to 5.65)	5.18 (5.07 to 5.28)	5.69 (5.59 to 5.79)	5.62 (5.53 to 5.72)
fasting insulin (median; pmol/L)	7.14 (6.79 to 7.49)	5.29 (4.83 to 5.75)	11.74 (11.35 to 12.14)	7.67 (7.02 to 8.32)	8.97 (8.35 to 9.59)	9.91 (9.35 to 10.49)
HOMA insulin resistance (median)	1.78 (1.64 to 1.85)	1.27 (1.12 to 1.41)	2.90 (2.78 to 3.01)	1.77 (1.56 to 1.97)	2.23 (2.05 to 2.42)	2.51 (2.33 to 2.69)
Age-standardized prevalences (95% CI)						
microalbuminuria (AER 20 to 199 μg/min)	5.9 (4.5 to 7.4)	2.7 (1.2 to 4.1)	6.0 (4.2 to 7.7)	2.7 (0.4 to 5.0)	6.8 (3.9 to 9.8)	7.3 (4.3 to 10.3)
impaired fasting glucose[b]	9.2 (7.4 to 11.0)	8.6 (6.0 to 11.2)	7.5 (2.5 to 12.6)	1.6 (0 to 3.2)	13.7 (9.6 to 17.7)	11.0 (7.2 to 14.9)
impaired glucose to lerance[c]	1.8 (0.9 to 2.6)	4.3 (2.4 to 6.2)	3.3 (2.0 to 4.6)	8.1 (4.0 to 12.2)	8.3 (5.0 to 11.7)	8.8 (5.3 to 12.3)
diabetes[d]	7.8 (6.1 to 8.7)	4.8 (2.8 to 6.8	22.6 (19.6 to 25.7)	17.5 (11.9 to 23.2)	18.0 (13.5 to 22.5)	17.2 (12.8 to 21.5)
receiving medication for hypertension	9.2 (7.5 to 10.9)	11.1 (8.2 to 13.9)	15.9 (13.2 to 18.6)	15.7 (10.3 to 21.1)	18.8 (14.4 to 23.3)	28.8 (23.5 to 34.1)
major Q waves and/or LBBB on ECG	5.1 (3.8 to 6.4)	2.0 (0.7 to 3.4)	5.0 (3.4 to 6.6)	1.5 (0 to 3.5)	2.6 (0.8 to 4.4)	1.3 (0 to 2.6)
previously diagnosed (by doctor) CHD	8.4 (6.7 to 10.0)	3.8 (2.0 to 5.5)	8.2 (6.1 to 10.2)	0.5 (0 to 1.6)	3.1 (1.1 to 5.1)	2.9 (0.8 to 4.9)
CHD, defined by major ECG changes and/or previous diagnosis	11.2 (9.3 to 13.1)	5.6 (3.5 to 7.8)	10.8 (8.5 to 13.1)	2.0 (0 to 4.3)	5.0 (2.5 to 7.5)	4.2 (1.8 to 6.6)
short height for weight[e]	16.9 (15.2 to 18.7)	18.4 (15.2 to 21.6)	16.2 (14.3 to 18.2)	21.6 (16.8 to 26.4)	15.6 (12.2 to 19.1)	18.0 (14.0 to 22.1)
current/former smoker	68.8 (66.0 to 71.7)	51.1 (46.5 to 55.8)	22.3 (19.3 to 25.3)	2.5 (0.3 to 4.7)	44.3 (38.4 to 50.1)	14.4 (10.1 to 18.8)
manual occupation	64.5 (61.5 to 67.5)	55.1 (50.4 to 59.8)	72.5 (69.2 to 75.7)	74.6 (67.7 to 81.4)	85.4 (81.1 to 89.7)	61.6 (55.8 to 67.3)
years of education (% with ≥11 yr)	38.2 (35.2 to 41.2)	41.9 (37.4 to 46.5)	70.4 (66.0 to 73.8)	45.0 (36.8 to 53.2)	54.5 (48.8 to 62.9)	52.4 (46.3 to 58.4)
CHD deaths (n; rate/1000 person yr)	59 (4.3)	9 (1.5)	47 (4.5)	1 (0.34)	4 (1.05)	1 (0.28)

[a]CI, confidence interval; BMI, body mass index; HOMA, homeostasis model assessment; AER, albumin excretion rate; LBB, left bundle branch block; ECG, electrocardiogram; CHD, coronary heart disease.

[b]Defined as fasting glucose ≥6.1 and <7.0 mmol/L (22).

[c]Defined as fasting glucose <7.0 mmol/L and 2 h glucose >7.8 and <11.1 mmol/L (22).

[d]Includes people with known diabetes and those with newly diagnosed diabetes by World Health Organization 1999 criteria (fasting glucose ≥7 mmol/L or 2 h glucose ≥11.1 mmol/L.

[e]Below median for height and above median for weight (ethnicity- and gender-specific medians).

than Europeans. In addition, South Asians had adverse and African Caribbeans had favorable lipid profiles (Table 1). No participants were receiving lipid-lowering medication. Ten percent of Europeans, 15% of South Asians, and 25% of African Caribbeans were receiving antihypertensive medication. There were no ethnic group differences in proportions of people who were receiving β blockers (9%), calcium channel blockers (3.5%), and angiotensin-converting enzyme inhibitors (<2%). African Caribbeans were more likely to be receiving diuretics (12%) than South Asians and Europeans (7 and 6%).

AER and Microalbuminuria

Prevalence of MA was greatest in African Caribbeans and equivalent in South Asians and Europeans. Similarly, age-adjusted levels of AER (geometric means) were highest in African Caribbean men (6.1 μg/min) and women (5.7 μg/min) when compared with Europeans ($P < 0.001$ for men and women). South Asian men had lower AER than European men across the glucose to lerance spectrum (fully adjusted model $P = 0.001$). Levels of AER were almost identical in South Asian and European women in all categories of glucose tolerance ($P = 0.9$; Table 2, Figure 1).

South Asians who were short for weight had significantly higher AER than those who were not (age-adjusted geometric means: men 5.58 *versus* 4.06 μg/min [$P < 0.001$]; women 4.72 *versus* 3.01 μg/min [$P = 0.017$]). European men who were short for weight had a less marked increase in AER (5.20 *versus* 4.41 μg/min; $P = 0.02$); there were no associations between stature and AER in European women and African Caribbeans.

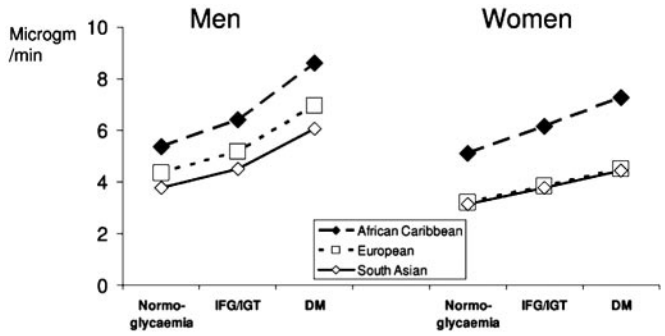

Figure 1. Age-adjusted albumin excretion rates, glucose tolerance, and ethnicity (geometric means: μg/min).

Ethnic group and gender patterns in AER remained after multivariate adjustment (Table 2). Other cardiovascular risk factors did not account for the ethnic differences in AER.

Associations between Microalbuminuria and Prevalent CHD

Unadjusted odds ratios (OR) indicated significant associations between MA and prevalent CHD in both South Asian men and European women. These associations were reduced in South Asian men by multivariate adjustment (OR 1.93; $P = 0.10$). The associations were weaker in European men and

Table 2. AER geometric means (adjusted linear regression models)[a]

	Geometric Mean	95% CI	*P*
Men			
adjusted for age			
European	4.6	4.3 to 4.8	Reference group
South Asian	4.3	4.0 to 4.6	0.11
African Caribbean	6.1	5.5 to 6.7	<0.001
adjusted for age, fasting glucose, glucose tolerance category[b], SBP[c], BMI, and manual occupation			
European	4.8	4.5 to 5.0	Reference group
South Asian	4.1	3.9 to 4.4	0.001
African Caribbean	5.7	5.2 to 6.3	0.002
Women			
adjusted for age			
European	3.3	3.1 to 3.6	Reference group
South Asian	3.4	3.0 to 3.8	0.80
African Caribbean	5.7	5.2 to 6.2	<0.001
adjusted for age, glucose tolerance category[b], SBP[c], BMI, and height			
European	3.7	3.3 to 4.1	Reference group
South Asian	3.7	3.2 to 4.4	0.94
African Caribbean	5.6	4.9 to 6.3	<0.001

[a]SBP, systolic BP.
[b]Normoglycemia, impaired fasting glucose/impaired glucose tolerance, and diabetes (World Health Organization 1999 criteria [22]).
[c]Quartiles of SBP (treated hypertension ranked in upper quartile).

absent in African Caribbean men. No South Asian or African Caribbean women with CHD had MA (Table 3).

Associations between AER, Microalbuminuria, and CHD Mortality in Europeans and South Asian Men

South Asian men who died with CHD had significantly higher baseline age-adjusted AER than survivors and those who died from other causes (age-adjusted geometric means 6.63 *versus* 4.15 μg/min; $P < 0.001$). A similar pattern was observed in European women (5.99 *versus* 3.27 μg/min; $P = 0.011$), although in European men, the difference was smaller (5.54 *versus* 4.54 μg/min; $P = 0.21$).

Twenty-eight percent of South Asian men with CHD at baseline died of CHD during the follow-up period, compared with 19 and 13% of European men and women, respectively, and 4 and 6% of African Caribbean men and women, respectively. The small number of CHD deaths meant that we were unable to conduct separate analyses for those with and without baseline CHD.

There was a significant association between baseline MA and CHD mortality in South Asian men and in European women and a weaker association in European men. Bivariate adjustments in European and South Asian men for smoking status, baseline CHD, and glucose tolerance status did not alter these associations. However, adjustment for quartiles of systolic BP (treated hypertension ranked in top quartile) and multivariate adjustment reduced the strength and significance of the association in South Asian men. Other measured risk factors, including measures of obesity, did not influence the associations in either ethnic group. Very few CHD-related deaths occurred in African Caribbeans and South Asian women, and these were not associated with baseline MA or AER (Table 3).

Discussion

In this UK population–based study, we demonstrated that African Caribbean men and women had the highest AER (age-adjusted geometric means 6.1 and 5.7 μg/min) and the highest prevalence of microalbuminuria (6.8 and 7.3%) of all three ethnic groups, regardless of glucose tolerance status. AER were significantly lower in South Asian men than in European men (fully adjusted model 4.2 *versus* 4.8 μg/min; $P = 0.001$) and were similar in South Asian and European women (3.7 μg/min). These ethnic group differences were not explained by measured risk factors. Within all three ethnic groups, people with diabetes had the highest AER. Surprisingly, microalbuminuria and AER levels were strongly associated with prevalent CHD in two groups with lower levels of AER—South Asian men and European women—whereas weak associations were seen in European men and none at all were seen in African Caribbeans. Although CHD-related deaths were infrequent, ethnic- and gender-specific associations between MA and CHD mortality mirror those observed between MA and prevalent CHD.

Comparison with Other Studies

Our findings of similar AER and prevalence of MA in UK South Asians and Europeans confirm those of UKPDS (17) in people with type 2 diabetes but do not correspond with the high rates of ESRD in South Asians (28) or the findings of Mather *et al.* (14) and Fischbacher *et al.* (15). The last two studies were smaller than ours. The by study Mather *et al.* was based on a clinic population, which may have been biased toward those with less well-controlled diabetes, particularly in the South Asian group. The South Asians who were recruited to Fischbacher's study that was set in Newcastle (15) consisted of 38% Indians, the remainder being of Pakistani or Bangladeshi origins. In contrast, 71% of South Asians in our study were Indian. Differences may also be partly explained by our use of AER rather than the albumin-creatinine ratio (ACR). We considered AER to be a more appropriate indicator of microvascular disease than the ACR, which, because of its dependence on muscle mass and dietary protein intake, is prone to marked gender and ethnic group variation and hence may be misleading (29).

However, in the United Kingdom, in those with diabetes, South Asians are known to have a 13-fold increase in risk for ESRD compared with Europeans (30), and in those without diabetes, South Asians have a 3.5-fold increase in risk (28,30,31). A large US primary care study of people with diabetes found that those of Asian origin without hypertension had two-fold prevalence of microalbuminuria (32). These observations seem to be at odds with our findings and are discussed further below.

Our findings of higher AER and prevalence of MA in UK African Caribbeans, although in conflict with the findings of UKPDS (17), were expected, given the markedly increased prevalence of ESRD seen in UK African Caribbeans compared with the white population (6.5- and 3.7-fold in people with and without diabetes) (31) and similar increased prevalence of ESRD in African Americans (33,34). The UKPDS study recruited people with newly diagnosed diabetes, whereas ours was a population-based study across the range of glucose tolerance, and in those with diabetes, more than half had been previously diagnosed.

Studies from Pakistan (35) and South East Asia (36) demonstrate wide variations by ethnic subgroup in the prevalence of dipstick proteinuria. However, these studies do not have European comparators and do not provide evidence regarding determinants of micro- or macroalbuminuria in populations representative of our study group of first-generation migrants of largely Indian origin.

Possible Explanations for Ethnicity and Gender Differences in AER

None of the measured risk factors explained the ethnic and gender group differences in the levels of AER or prevalence of MA. Adjustment for BP and glucose tolerance only partly attenuated the differences in AER between African Caribbeans and Europeans. No participants were receiving lipid-lowering medications, and ethnic group differences in use of antihypertensives existed only for diuretics, which were more likely to be prescribed for African Caribbeans; thus, it is most unlikely that medication use can explain any of the ethnic group differences in AER.

Inflammation plays a central role in initiation and progres-

Table 3. Associations between prevalent CHD, CHD mortality, and microalbuminuria

	Europeans		South Asians		African Caribbeans[a]	
	Men	Women[a]	Men	Women[a]	Men	Women
Microalbuminuria: Odds ratios for association with prevalent CHD[b]						
n[c]	1015 (119 cases)	443 (25 cases)	738 (76 cases)	205 (3 cases)	283 (15 cases)	275 (12 cases)
unadjusted	1.43 (0.71 to 2.89)	6.20 (1.57 to 24.52)	2.71 (1.29 to 5.73)	—	0.89 (0.11 to 7.08)	No CHD cases had microalbuminuria
adjusted for age	1.29 (0.63 to 2.63)	7.16 (1.75 to 29.31)	2.39 (1.11 to 5.14)	—	0.80 (0.10 to 6.45)	
adjusted for age and smoking status	1.21 (0.60 to 2.55)	6.72 (1.62 to 27.924	2.49 (1.15 to 5.39)	—	0.75 (0.09 to 6.11)	
adjusted for age and glucose tolerance category	1.12 (0.54 to 2.32)	7.11 (1.72 to 29.3)	2.20 (1.01 to 4.82)	—	0.68 (0.08 to 5.67)	
adjusted for age and SBP[d]	1.37 (0.66 to 2.83)	8.29 (1.92 to 35.76)	2.25 (1.03 to 4.91)	—	0.62 (0.07 to 5.25)	
adjusted for age, smoking status,[e] glucose tolerance category,[f] and SBP[d]	1.09 (0.52 to 2.28)	6.17 (1.43 to 26.54)	1.93 (0.87 to 4.26)	—	0.68 (0.08 to 5.60)	
Microalbuminuria: Hazard ratios for association with CHD mortality[c]						
n[c]	1017 (59 deaths)	445 (9 deaths)	743 (47 deaths)	206 (1 death)[a]	283 (4 deaths)[a]	276 (1 death)[a]
unadjusted	1.89 (0.81 to 4.39)	10.79 (2.24 to 52.0)	3.01 (1.35 to 6.72)	—	—	—
adjusted for current age	1.75 (0.75 to 4.08)	13.01 (2.63 to 64.2)	2.47 (1.10 to 5.52)	—	—	—
adjusted for current age and baseline CHD[c]	1.89 (0.81 to 4.41)	—	2.14 (0.94 to 4.89)	—	—	—
adjusted for current age and smoking status[e]	1.78 (0.77 to 4.14)	—	2.45 (1.09 to 5.48)	—	—	—
adjusted for current age and glucose tolerance category[f]	1.52 (0.65 to 3.60)		2.31 (1.03 to 5.20)	—	—	—
adjusted for current age and SBP[d]	1.56 (0.67 to 3.64)	—	2.03 (0.90 to 4.59)	—	—	—
adjusted for age, smoking status,[e] glucose tolerance category,[f] and SBP[d]	1.41 (0.60 to 3.34)		1.90 (0.94 to 4.31)			

[a]South Asian women excluded because of the small numbers of cases with prevalent CHD or deaths caused by CHD. African Caribbeans were excluded from mortality analyses because of small numbers of deaths caused by CHD. European women: mortality analyses limited to age adjustment only.

[b]Prevalent CHD defined by doctor-diagnosed angina or heart attack and/or the presence of major Q waves or LBBB on ECG. Because of the small number of CHD deaths, analyses in European women were limited to adjustment for current age.

[c]Number available for analysis (some participants did not have sufficient data to establish presence of CHD). CHD deaths defined by *International Classification of Diseases, Ninth Revision* codes 410 to 4149 or *International Classification of Diseases, Tenth Revision* codes I200 to I259

[d]Quartiles of SBP (treated hypertension ranked in upper quartile).

[e]Smoking status: current, former, never.

[f]Normoglycemia, impaired fasting glucose/impaired glucose tolerance, and diabetes (World Health Organization 1999 criteria [22]).

sion of atherosclerotic disease (37). We did not measure inflammatory markers or measures of endothelial dysfunction, which may contribute to ethnic group differences. However, C-reactive protein (CRP) levels that were measured in a UK population–based study were slightly lower in African Caribbeans (38), indicating that CRP could not account for the greater degree of MA in African Caribbeans. Variable reports of CRP levels exist for South Asians; the UK population–based study found similar levels compared with the general population (38), whereas other studies of South Asians in the United Kingdom (39) and Canada (40) have found elevated levels of CRP.

Possible Explanations for Ethnicity and Gender Differences in Associations between Microalbuminuria and Kidney Disease and CHD

It is not surprising that MA is strongly associated with CHD prevalence and mortality in South Asians, given the predisposition to coronary disease in this population, and further that this is a classically insulin-resistant group, in which strong relations among diabetes, albuminuria, and CHD are to be expected. The low risk for microalbuminuria is more remarkable, especially given the greater risks for ESRD. However, although diabetes contributes to some of the excess risk for ESRD, a greater prevalence of idiopathic interstitial nephritis is also observed (28). These patients present at late stages of disease with shrunken kidneys, as early stages are asymptomatic, and may not be associated with albuminuria to the same extent as diabetic nephropathy. The cause of this condition is unknown but may have genetic as well as environmental components. In support of the latter, South Asian infants are known to have lower birth weights than those of European origin (41), and this and other associated abnormalities of early growth are associated with inter alia, an early expression of insulin resistance, and perhaps disordered kidney growth, resulting in a susceptibility to kidney disease (42). We have no data on birth weight in our cohort but do show that South Asians who are short for weight have higher AER, which may be a late expression of low birth weight and other intrauterine growth abnormalities. Competing causes of ESRD may be one explanation for the low rates of microalbuminuria; another is that CHD occurs relatively early in South Asians, such that premature deaths may have selected out those with the toxic combination of albuminuria and diabetes. In direct contrast, we show that African Caribbeans have higher rates of microalbuminuria compared with Europeans, which is not predictive of CHD.

Unlike South Asians, African Caribbeans do not demonstrate the classical picture of insulin resistance. Thus, although diabetes is highly prevalent and clamp studies do suggest that African Caribbeans are more resistant to the glucose homeostatic effects of insulin compared with Europeans, the lipid profile remains highly favorable across the spectrum of glucose intolerance (9). Thus, despite the twin insults of diabetes and MA, the enhanced risks for CHD are mitigated by the retained favorable lipid profile. This may again be due to genetic factors, although thus far no plausible genetic explanation has been forthcoming. In addition, although the high rates of diabetes alone may account for the greater prevalence of microalbuminuria, again, like the South Asians, the enhanced risk for ESRD in African Caribbeans is probably not due simply to diabetes but may be due to other renal conditions, such as time membranous nephropathy and focal segmental nephrosclerosis (43). Although albuminuria does occur in these conditions, it is less likely to be related to the other abnormalities associated with diabetic albuminuria and therefore may explain further why microalbuminuria is less predictive of CHD in this ethnic group.

Finally, we show that although microalbuminuria has a lower prevalence in European women compared with European men, the associations with coronary disease are more marked. This again may be due to selective early mortality from diabetes-associated CHD in men.

Limitations

We acknowledge that the study has limitations. Numbers of CHD events were small. There was a high level of noncompliance in provision of timed overnight urine collections; this seemed to be "convenience" related. However, there is an excess in mortality rates for South Asian men and higher prevalence of smoking in South Asian men and African Caribbean women who did not provide timed urine collections. If we assume that those with missing data are less healthy than those with complete data, then we might expect to have underestimated levels of AER in all groups but to a greater extent in South Asians and African Caribbeans, both groups having higher proportions of missing data than Europeans. However, other baseline risk factor levels are similar within ethnic and gender groups, and the relatively small between-group differences in proportions with missing data seem unlikely to explain wholly the unexpectedly low levels of AER in South Asians and, if anything, may have caused an underestimation of the extent of elevation of AER in African Caribbeans.

It is also possible that overnight urine collection times may have been misreported, although unreported analyses of ACR, which was not time dependent and for which there were few missing data, indicated similar ethnicity and gender patterns in associations between ACR and CHD in our study population. This finding suggests that differential misreporting of collection times is unlikely and confirms that there is no reason to believe that there are systematic differences between those who did and did not provide overnight urine samples in terms of the relationship between MA and CHD prevalence and mortality.

Conclusions

In this unique UK cohort, we found greater levels of AER in African Caribbeans across the spectrum of glucose tolerance and absence of association with CHD, indicating that AER and MA may be better predictors of renal disease than cardiovascular disease in UK African Caribbeans. In contrast, lower levels of AER in South Asians and European women strongly predict CHD mortality and suggest that relatively low levels of albumin excretion may warrant investigation and early treatment in these groups. These ethnic group and gender differences were not explained by measured risk factors and suggest

that the pathogenesis of kidney disease and, therefore its link with CHD, may differ with ethnicity and gender.

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