Associations Between Prediabetes, by Three Different Diagnostic Criteria, and Incident CVD Differ in South Asians and Europeans

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OBJECTIVE

We examined longitudinal associations between prediabetes and cardiovascular disease (CVD) (coronary heart disease [CHD] and stroke) in Europeans and South Asians.

RESEARCH DESIGN AND METHODS

This was a U.K. cohort study of 1,336 Europeans and 1,139 South Asians, aged 40–69 years at baseline (1988–1991). Assessment included blood pressure, blood tests, anthropometry, and questionnaires. Prediabetes was determined by OGTT or HbA_{1c}, using either International Expert Committee (IEC) (HbA_{1c} 6.0–6.5% [42–48 mmol/mol]) or American Diabetes Association (ADA) (HbA_{1c} 5.7–6.5% [39–48 mmol/mol]) cut points. Incident CHD and stroke were established at 20 years from death certification, hospital admission, primary care record review, and participant report.

RESULTS

Compared with normoglycemic individuals, IEC-defined prediabetes was related to both CHD and CVD risk in Europeans but not South Asians (subhazard ratio for CHD 1.68 [95% CI 1.19, 2.38] vs. 1.00 [0.75, 1.33], ethnicity interaction $P = 0.008$, and for CVD 1.49 [1.08, 2.07] vs. 1.03 [0.78, 1.36], ethnicity interaction $P = 0.04$). Conversely, IEC-defined prediabetes was associated with stroke risk in South Asians but not Europeans (1.73 [1.03, 2.90] vs. 0.85 [0.44, 1.64], ethnicity interaction $P = 0.11$). Risks were adjusted for age, sex, smoking, total-to-HDL cholesterol ratio, waist-to-hip ratio, systolic blood pressure, and antihypertensive use. Associations were weaker for OGTT or ADA-defined prediabetes. Conversion from prediabetes to diabetes was greater in South Asians, but accounting for time to conversion did not account for these ethnic differences.

CONCLUSIONS

Associations between prediabetes and CVD differed by prediabetes diagnostic criterion, type of CVD, and ethnicity, with associations being present for overall CVD in Europeans but not South Asians. Substantiation of these findings and investigation of potential explanations are required.

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In parallel with the global diabetes epidemic, population surveys indicate an escalating prevalence of nondiabetic hyperglycemia (12–29%, depending on definition) (1), herein referred to as "prediabetes." Historically, prediabetic states have been defined by either fasting (impaired fasting glycemia [IFG]) or postchallenge (impaired glucose tolerance [IGT]) glycemia (2), though recently HbA_{1c}-based definitions of prediabetes have been advocated (3,4). Controversy exists regarding the role of prediabetes in cardiovascular disease (CVD) risk, particularly concerning whether proactive identification and management are warranted (5).

Large prospective studies indicate that glycemia (by glucose or HbA_{1c}) below the diabetic threshold is weakly related to CVD risk (6–8), and a recent Mendelian randomization study hinted at a limited causal role for dysglycemia in coronary heart disease (CHD) (9). However, studies examining the CVD consequences of prediabetes by specific diagnostic criteria are limited to European origin populations or focus on risk factors or mortality rather than clinical disease (10–14). Host and migrant South Asian populations have a markedly greater prevalence of overt diabetes (15) and higher CVD rates than populations of European descent (16); yet, associations between prediabetes and CVD have not been compared in these ethnic groups. Relatively more prediabetes is identified by HbA_{1c} than IFG/IGT criteria in people of South Asian origin, whereas prevalence is similar by either criterion in European origin populations (17). Therefore, it has been suggested that the HbA_{1c} definition of prediabetes may be a less discerning indicator of CVD risk in South Asians (18). However, our previous work suggests that diabetes is more strongly related to CVD risk in South Asians than Europeans (16,19); whether similar ethnic differences exist for prediabetes remains unstudied.

With use of data from a community-based cohort study, our objectives were as follows: *1*) to examine longitudinal associations between prediabetes and CVD in U.K. Europeans and South Asians, *2*) to describe ethnic differences in these associations, and *3*) to explore potential reasons for any ethnic differences.

RESEARCH DESIGN AND METHODS

Study Participants and Design

The Southall And Brent REvisited (SABRE) study is a community-based multiethnic cohort study of cardiometabolic disease; details have previously been published (20). Participants aged 40–69 years at baseline (1988–1991; n = 4,857, 2,346 European, 1,710 South Asian, and 801 African Caribbean) were randomly selected from primary care physician lists and workplaces in northwest London. South Asian participants were first-generation migrants originating from the Indian subcontinent, approximately half of whom (52%) were of Punjabi Sikh origin. A male preponderance in the data exists, as the baseline study was initially designed to examine cardiometabolic disease in men. Participants were followed for death, hospitalization, and primary care consultations from baseline to 2011. All participants gave written informed consent. Approval for the baseline study was obtained from Ealing, Hounslow and Spelthorne, Parkside, and University College London research ethics committees and at follow-up from St Mary's Hospital Local Research Ethics Committee (reference no. 07/HO712/109).

Baseline Measurements

Participants underwent blood tests and blood pressure and anthropometric measurement and provided data on smoking, physical activity, and occupation using previously validated questionnaires (21). Fasting lipids, glucose, and HbA_{1c} were measured as previously described (20,22). HbA_{1c} was measured (at baseline and follow-up) using an immunoassay on a clinically automated analyzer (c311; Roche, Burgess Hill, U.K.); the high and low quality-control coefficients of variation were 2.9 and 3.3%, respectively. Those whose diabetes status was unknown underwent oral glucose tolerance testing (OGTT). We used three classification systems to define glycemic status for participants without existing diabetes. Firstly, World Health Organization 1999 criteria were used to define prediabetes (either IFG [fasting glucose $\geq$6.1 mmol/L and $<$7.0 mmol/L] or IGT [2-h OGTT plasma glucose $\geq$7.8 mmol/L and $<$11.1 mmol/L]) and new diabetes (fasting glucose $\geq$7.0 mmol/L or 2-h OGTT plasma glucose $\geq$11.1 mmol/L) (2). Secondly, glycemic categories according to the International Expert Committee (IEC) 2009 criteria (3) were based on the following HbA_{1c} cut points: prediabetes, HbA_{1c} $\geq$6.0% (42 mmol/mol) but $<$6.5% (48 mmol/mol), and new diabetes, HbA_{1c} $\geq$6.5% (48 mmol/mol). We also studied glycemia according to the American Diabetes Association (ADA) 2014 recommendations (4), which advocate HbA_{1c} cut points of $\geq$5.7% (39 mmol/mol) but $<$6.5% for prediabetes and $\geq$6.5% (as for IEC criteria) for new diabetes.

Smoking status was dichotomized as ever/never smoked. Weekly frequency of fruit and vegetable consumption was assessed by food-frequency questionnaire. Questions on physical activity provided a summary estimate of weekly energy expenditure in daily activities, walking, and sport (23). Height was measured barefoot with a stadiometer, weight with calibrated weighing scales, waist circumference halfway between the costal margin and the iliac crest, and hip circumference at the greater trochanter. Seated resting brachial blood pressure was measured using a random zero sphygmomanometer (Hawksley, London, U.K.); the mean of two measurements was used in analyses.

Follow-up Measurements

Between 2008 and 2011, survivors were invited for examination at St Mary's Hospital, London. Incident CHD was defined firstly from primary care record review adjudicated by two clinicians: diagnosis was based on symptoms, cardiac enzymes, electrocardiography findings, exercise test findings, and coronary revascularization procedures as per Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) criteria (24). Secondly, CHD was identified from Hospital Episode Statistics (HES) (ICD-9 410–415 and ICD-10 I200-I259) and data from the Office of Populations and Surveys classification of interventions and procedures (pertaining to coronary revascularization interventions or rehabilitation for ischemic heart disease, codes K401–469, K491–504, K751–759, and U541). For stroke, primary care data were reviewed in a similar manner to CHD, with diagnoses made again according to ASCOT criteria, based on symptoms, duration of symptoms, and MRI/computer tomographic imaging (24). Stroke

was also ascertained from participant report of physician-diagnosed stroke with duration of symptoms ≥24 h and from HES (ICD-9 430–439 and ICD-10 I600–698). New cases of diabetes since baseline were identified from record review, questionnaire, and clinic blood results—using *1*) fasting and post–OGTT load glucose results according to World Health Organization 1999 criteria or *2*) HbA_{1c} ≥6.5%—or death certificate data (ICD-9 2500–2509 and ICD-10 E100–149).

Statistical Analysis

Baseline characteristics were compared by follow-up status and ethnicity. Logistic and linear regression methods determined age- and sex-adjusted differences. Using age- and sex-adjusted Cox models, we compared rates of incident CHD, stroke, and CVD (CHD plus stroke) by ethnicity and studied numbers of events by glycemic categories and ethnicity. Age- and sex-adjusted associations between prediabetes (defined in three ways, as above) or new/known diabetes and CHD, stroke, and CVD were examined in each ethnic group (model 1). We then further adjusted these models for potential a priori–specified confounders, comprising CVD risk factors (smoking, total-to-HDL cholesterol ratio, waist-to-hip ratio, systolic blood pressure, and antihypertensive treatment) (model 2) and sociodemographic and lifestyle risk factors (smoking, manual occupation, physical activity, and fruit and vegetable intake) (model 3). Interactions between prediabetes or diabetes and ethnicity were sought in all models. Informative censoring may have occurred owing to death from non-CVD causes; we addressed this by using competing risks regression (competing risk = death from non-CVD cause), based on Fine and Gray (25) proportional subhazards methods. Additionally, we examined Nelson-Aalen cumulative hazard plots of CVD by glycemic categories to check for violations of the proportional hazards assumption; none were found.

Findings were further explored by comparing prevalence of CVD risk factors, medication use, and resultant risk factor control by glycemic status for each ethnic group at baseline and at follow-up to establish whether disparities in these factors may have contributed to ethnic differences in prediabetes/CVD associations. Since these comparisons suggested ethnic differences in lipid and blood pressure control by glycemic status, we sought interactions between lipids and prediabetes in models of CHD and blood pressure and prediabetes in models of stroke. We compared rates of conversion from prediabetes to overt diabetes by prediabetes criterion and ethnicity and sought to test whether greater conversion, and thus exposure to the hyperglycemia of diabetes, could account for ethnic differences observed in the association between prediabetes and CVD outcomes.

Sensitivity analyses were conducted by *1*) adjusting models for subsequent diabetes development as a time-varying covariate (26), *2*) excluding events within the first 5 years of follow-up and *3*) including people with baseline CVD (adjusting for baseline CVD).

RESULTS

We report findings from a subset of 1,336 Europeans and 1,139 South Asians without prevalent CHD or stroke at baseline either with a full set of baseline HbA_{1c} plus fasting and postload glucose measurements or with known diabetes, and who had follow-up data for CHD and stroke (Fig. 1). African Caribbeans were excluded due to small numbers. There were no consistent differences between participants for whom we did and did not have the full set of blood samples.

Overt diabetes was more prevalent and cardiometabolic risk factors were generally more adverse in South Asians than Europeans (Table 1). South Asians had a higher prevalence of HbA_{1c}-defined prediabetes than Europeans, though prevalence was similar when IFG/IGT criteria were used. For both ethnic groups, the prevalence of prediabetes was over twofold higher when defined by ADA HbA_{1c} thresholds as opposed to IEC HbA_{1c} thresholds or IFG/IGT.

Prediabetes was associated with an increased risk of CHD in Europeans but not South Asians (Table 2). Associations were strongest for IEC HbA_{1c}-defined prediabetes. This association persisted after adjustment for CVD risk factors and for sociodemographic and lifestyle factors (Table 3). Conversely, in South Asians, no measure of prediabetes was associated with CHD risk. This ethnic difference in association between

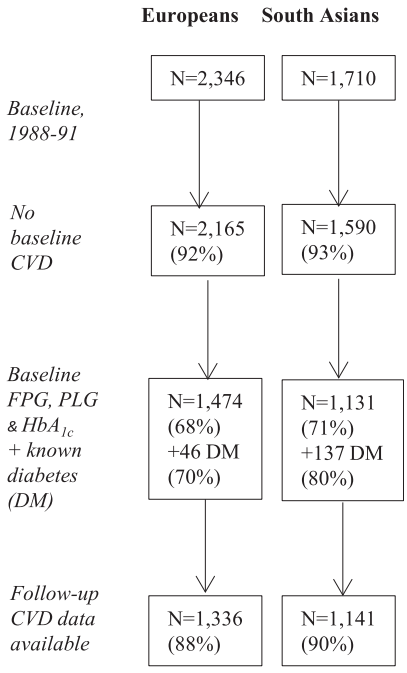

Figure 1—Follow-up of the SABRE cohort: 1988–2011. FPG, fasting plasma glucose; PLG, postload glucose.

prediabetes and CHD was significant as an interaction (P = 0.008 in the cardiovascular risk factor–adjusted model). Of note, diabetes was similarly related to CHD in each ethnic group regardless of diagnostic criteria.

In contrast, no prediabetes measure was associated with stroke risk in Europeans, whereas for South Asians, all three measures were associated in age- and sex-adjusted models (Table 3). After adjustment for CVD risk factors, only the IEC HbA_{1c}-defined prediabetes association retained significance, though associations for the other prediabetes measures remained of large magnitude. There was some evidence that this measure was more associated with stroke risk in South Asians than Europeans (ethnicity interaction P = 0.11 in the cardiovascular risk factor–adjusted model). Corresponding with ethnic differences in prediabetes associations, overt diabetes also appeared to be more strongly associated with stroke risk in South Asians than Europeans, though again this was not significant as an interaction (P = 0.18).

Findings for CVD reflected those for CHD, with strong associations for prediabetes observed in Europeans but not South Asians, particularly for the IEC HbA_{1c} criterion (P = 0.04 for ethnicity by prediabetes interaction).

Table 1—Baseline characteristics of participants in the SABRE study by ethnicity

	Europeans	South Asians	*P**
N	1,336	1,139	—
Age, years	53 (47–59)	50 (45–56)	<0.001
Women	186 (14)	214 (19)	0.001
Ever smoked	930 (70)	277 (25)	<0.001
Manual occupation	809 (61)	822 (74)	<0.001
Fruit/vegetables most days	933 (70)	782 (69)	0.9
Physical activity, megajoules/week	10 (7–15)	9 (4–12)	<0.001
BMI, kg/m^2	26.1 ± 4.0	26.1 ± 3.6	0.7
Waist-to-hip ratio			
Men	0.94 ± 0.07	0.99 ± 0.06	<0.001
Women	0.79 ± 0.09	0.87 ± 0.09	<0.001
Total cholesterol, mmol/L	6.1 ± 1.14	5.9 ± 1.05	<0.001
HDL cholesterol, mmol/L	1.3 (1.1–1.5)	1.2 (1.0–1.4)	<0.001
Total-to-HDL cholesterol ratio	4.7 (3.8–5.8)	4.9 (4.1–6.0)	<0.001
LDL cholesterol, mmol/L	4.0 ± 1.0	3.8 ± 0.91	<0.001
Triglycerides, mmol/L	1.4 (1.0–2.1)	1.7 (1.2–2.5)	<0.001
Systolic blood pressure, mmHg	123 ± 17	125 ± 18	<0.001
Diastolic blood pressure, mmHg	77 ± 11	80 ± 11	<0.001
Antihypertensive medication	113 (8)	133 (12)	<0.001
Glycemic status: IFG/IGT			
Normoglycemia	1,125 (84)	758 (67)	<0.001
Prediabetes	128 (10)	135 (12)	0.07
Diabetes†	83 (6)	246 (22)	<0.001
Glycemic status: HbA_{1c} (IEC prediabetes criteria, i.e., 6.0–6.5% [42–48 mmol/mol])			
Normoglycemia	1,170 (88)	691 (61)	<0.001
Prediabetes	92 (7)	174 (15)	<0.001
Diabetes†	74 (6)	274 (24)	<0.001
Glycemic status: HbA_{1c} (ADA prediabetes criteria, i.e., 5.7–6.5% [39–48 mmol/mol])			
Normoglycemia	903 (68)	434 (38)	<0.001
Prediabetes	359 (27)	431 (38)	<0.001
Diabetes†	74 (6)	274 (24)	<0.001

Data are median (interquartile range), *n* (%), or mean ± SD. *Age- and sex-adjusted *P* for ethnic difference. †Includes preexisting and newly diagnosed diabetes by relevant criteria.

An important potential explanation for the ethnic differences observed in the association between prediabetes and CVD outcomes is control of key CVD risk factors. At follow-up, a lower percentage of Europeans than South Asians with baseline prediabetes on lipid-lowering medication had a total cholesterol <5.0 mmol/L (55% vs. 92%, $P = 0.004$ for IEC-defined prediabetes) or an LDL cholesterol of <3.0 mmol/L (66% vs. 91%, $P = 0.03$). Rates of lipid-lowering medication use were generally higher in South Asians than Europeans with baseline prediabetes (75% vs. 58%, 68% vs. 73%, and 69% vs. 57% for IFG/IGT, IEC-defined prediabetes, and ADA-defined prediabetes, respectively) (Table 2 and Supplementary Data). Adjusting for baseline lipids alone did not explain ethnic differences, and there were no interactions between prediabetes and lipid measures on these outcomes.

Baseline diastolic, but not systolic, pressure was higher in South Asians than Europeans. But in addition, blood pressure control (defined as <140/90 mmHg for those on antihypertensives) was generally worse in South Asians than Europeans with prediabetes, both at baseline and at follow-up (Tables 1 and 2 and Supplementary Data). Further, both mean diastolic and mean systolic pressures were higher in South Asians than Europeans in those on treatment. No other baseline CVD risk factor appeared to be consistently worse in the prediabetic state in one ethnicity than the other (Table 1 and Supplementary Data). Ethnic differences in associations between prediabetes and stroke remained when adjusted for baseline blood pressure and use of antihypertensive medication, and again there were no statistically significant prediabetes × blood pressure (systolic or diastolic) interactions in either ethnic group.

For participants with prediabetes at baseline, rates of conversion to overt diabetes were higher in South Asians than Europeans: 68% vs. 40%, $P < 0.001$, for IFG/IGT; 52% vs. 30%, $P = 0.006$, for IEC-defined prediabetes; and 44% vs. 23%, $P < 0.001$, for ADA-defined prediabetes.

Sensitivity analyses adjusting for diabetes development as a time-varying covariate, excluding events within the first 5 years of follow-up and including people with baseline CVD (and adjusting for

Table 2—Distribution of incident CVD by glycemic status and ethnicity in the SABRE study

	Europeans			South Asians				
Glycemia measure	Normoglycemia	Prediabetes	New or known diabetes	Normoglycemia	Prediabetes	*P**	New or known diabetes	*P*†
CHD								
IFG/IGT	276/1,125 (25)	39/128 (30)	37/83 (45)	253/758 (33)	47/135 (35)	0.50	137/246 (56)	0.83
HbA_{1c} (IEC)	275/1,170 (24)	42/92 (46)	35/74 (47)	230/691 (33)	60/174 (34)	0.004	147/274 (54)	0.33
HbA_{1c} (ADA)	207/903 (23)	110/359 (31)	35/74 (47)	137/434 (32)	153/431 (35)	0.26	147/274(54)	0.38
Stroke								
IFG/IGT	85/1,125 (8)	12/128 (9)	11/83 (13)	53/758 (7)	17/135 (13)	0.15	46/246 (19)	0.12
HbA_{1c} (IEC)	90/1,170 (8)	8/92 (9)	10/74 (14)	47/691 (7)	20/174 (11)	0.13	49/274 (18)	0.22
HbA_{1c} (ADA)	68/903 (8)	30/359 (8)	10/74 (14)	25/434 (6)	42/431 (10)	0.10	49/274 (18)	0.13
CVD								
IFG/IGT	334/1,125 (30)	47/128 (37)	42/83 (51)	275/758 (36)	55/135 (41)	0.84	148/246 (60)	0.98
HbA_{1c} (IEC)	339/1,170 (29)	47/92 (51)	39/74 (53)	252/691 (36)	69/174 (40)	0.02	161/274 (59)	0.58
HbA_{1c} (ADA)	253/903 (28)	133/359 (37)	39/74 (53)	146/434 (34)	175/431 (41)	0.65	161/274 (59)	0.76

Data are number of events/number of participants (%). **P* for age- and sex-adjusted ethnic difference in prediabetes vs. normoglycemia. †*P* for age- and sex-adjusted ethnic difference in diabetes vs. normoglycemia.

it), did not alter the main results (data not shown).

CONCLUSIONS

We show marked ethnic differences in associations between prediabetes and CVD. Prediabetes was related to both CHD and CVD risk in Europeans but not South Asians. Strongest associations were observed for IEC rather than for ADA and OGTT criteria. In contrast, only South Asians demonstrated an association between prediabetes and stroke. Associations persisted on multivariate adjustment and on accounting for differential rates of incident diabetes diagnosis. Ethnic differences in baseline and follow-up CVD risk factor control may account for our findings (lipids for CHD in Europeans and blood pressure for stroke in South Asians).

The greater prevalence of prediabetes when defined by HbA_{1c} as opposed to glucose-based criteria in South Asians, not observed in Europeans, corresponds with previous findings (17). However, we do not corroborate suggestions that classifying a higher number of South Asians as having prediabetes when HbA_{1c} criteria are used results in a less discriminative indicator of CVD risk (18), since for CHD, prediabetes by any criterion appeared unrelated in South Asians, and for stroke, prediabetes by all criteria was associated.

For Europeans, modest associations between prediabetes and CHD correspond with previous findings (6,7). Associations between prediabetes by IEC HbA_{1c} criteria and CHD were stronger than those for glucose, reflecting either greater reproducibility of HbA_{1c} (27), or better capture of fed-state glycemic status, which may more closely associate with CHD (10). There are no comparable prospective data for South Asians. The INTERHEART case-control study reported a greater risk of myocardial infarction in the highest versus lowest quintile of HbA_{1c} in Western Europeans but not South Asians (28), the latter corroborated by cross-sectional data (29).

Elevated lipids are key determinants of CHD risk (30). Total and LDL cholesterol in those on lipid-lowering medication at follow-up were higher in Europeans than South Asians with prediabetes in SABRE, reflecting findings in people with diabetes (31). Poor lipid control in Europeans with prediabetes may have contributed to excess CHD risks compared with normoglycemic individuals (and conversely, better control in South Asians may account for the lack of excess CHD in prediabetes). Conversion rates from prediabetes to overt diabetes were higher in South Asians than Europeans, occurring at an earlier age (26). This may have resulted in more aggressive and long-standing lipid management. Another possibility is that South Asians respond better to lipid lowering (32), though this appears unlikely (33).

No associations were found between prediabetes and stroke for Europeans, whereas strong associations were seen in South Asians for all three criteria. Previous studies of Europeans report weak associations between fasting glucose, postload glucose, HbA_{1c}, and stroke (6,7). Stroke numbers were modest in SABRE and may reflect better blood pressure control than historical cohorts.

However, blood pressure control in those with prediabetes on antihypertensives was worse in South Asians than Europeans at both baseline and follow-up, suggesting suboptimal management of this key stroke risk factor (34). This may account for the positive association between prediabetes and stroke in South Asians, again related to higher diabetes conversion rates, since blood pressure appears harder to control in South Asians than Europeans with diabetes (35,36).

In addition to its use indicating likely progression to overt diabetes, prediabetes incorporation into CVD risk scoring systems (14), or its use as a treatment target per se, has been proposed (3,4). However, the amalgamation of CHD and stroke risk may result in undertreatment of stroke risk in South Asians. Furthermore, our findings indicate that prediabetes is linked to overall CVD risk in Europeans only and only for HbA_{1c}-defined prediabetes, which suggests questioning the adoption of prediabetes as a trigger for population-level primary prevention.

Mechanistically, these findings suggest that glycemia may be more related to microvascular (stroke) than macrovascular (CHD) disease in South Asians than Europeans. We have described greater levels of retinal rarefaction (37), poorer microvascular responses to ischemia (38), and more adverse

Table 3—Competing risks regression models of incident CVD by glycemic status and ethnicity: the SABRE study

	Europeans			South Asians				
Glycemia measure	Normoglycemia	Prediabetes	New or known diabetes	Normoglycemia	Prediabetes	*P*§	New or known diabetes	*P*‖
CHD								
IFG/IGT								
Model 1	1	1.19 (0.85, 1.69)	1.82 (1.28, 2.59)†	1	1.06 (0.77, 1.44)	0.50	1.86 (1.50, 2.30)‡	0.83
Model 2	1	1.03 (0.72, 1.47)	1.21 (0.81, 1.82)	1	0.97 (0.72, 1.32)	0.69	1.60 (1.26, 2.04)‡	0.66
Model 3	1	1.22 (0.87, 1.72)	1.80 (1.26, 2.57)†	1	1.06 (0.77, 1.45)	0.50	1.94 (1.56, 2.41)‡	0.84
HbA_{1c} (IEC)								
Model 1	1	1.82 (1.30, 2.53)‡	2.01 (1.39, 2.90)‡	1	0.99 (0.75, 1.32)	0.004	1.73 (1.40, 2.14)‡	0.33
Model 2	1	1.68 (1.19, 2.38)†	1.35 (0.89, 2.03)	1	1.00 (0.75, 1.33)	0.008	1.44 (1.13, 1.83)†	0.67
Model 3	1	1.80 (1.29, 2.52)†	2.00 (1.38, 2.88)‡	1	0.99 (0.74, 1.32)	0.004	1.82 (1.46, 2.26)‡	0.38
HbA_{1c} (ADA)								
Model 1	1	1.22 (0.97, 1.54)	2.02 (1.39, 2.93)‡	1	1.07 (0.85, 1.34)	0.26	1.80 (1.41, 2.28)‡	0.38
Model 2	1	1.12 (0.88, 1.42)	1.31 (0.86, 1.99)	1	0.98 (0.78, 1.24)	0.25	1.42 (1.09, 1.87)†	0.66
Model 3	1	1.22 (0.96, 1.54)	1.98 (1.36, 2.89)‡	1	1.03 (0.81, 1.30)	0.21	1.84 (1.44, 2.34)‡	0.39
Stroke								
IFG/ IGT								
Model 1	1	0.92 (0.51, 1.68)	1.44 (0.80, 2.56)	1	1.75 (1.03, 2.98)*	0.15	2.65 (1.84, 3.93)‡	0.12
Model 2	1	0.83 (0.45, 1.56)	1.15 (0.59, 2.27)	1	1.51 (0.86, 2.64)	0.21	2.22 (1.45, 3.40)‡	0.09
Model 3	1	0.97 (0.53, 1.77)	1.57 (0.88, 2.82)	1	1.60 (0.91, 2.83)	0.27	2.64 (1.79, 3.89‡	0.17
HbA_{1c} (IEC)								
Model 1	1	0.91 (0.47, 1.75)	1.55 (0.87, 2.78)	1	1.80 (1.09, 2.97)*	0.13	2.59 (1.69, 3.72)‡	0.22
Model 2	1	0.85 (0.44, 1.64)	1.30 (0.67, 2.54)	1	1.73 (1.03, 2.90)*	0.11	2.19 (1.37, 3.25)‡	0.18
Model 3	1	0.92 (0.48, 1.76)	1.67 (0.94, 3.00)	1	1.66 (1.00, 2.79)*	0.20	2.50 (1.67, 3.73)‡	0.33
HbA_{1c} (ADA)								
Model 1	1	0.97 (0.65, 1.45)	1.56 (0.86, 2.84)	1	1.69 (1.05, 2.72)*	0.10	2.93 (1.83, 4.69)‡	0.13
Model 2	1	0.95 (0.63, 1.43)	1.31 (0.66, 2.59)	1	1.60 (0.98, 2.62)	0.12	2.51 (1.52, 4.14)‡	0.12
Model 3	1	0.95 (0.64, 1.42)	1.66 (0.92, 3.02)	1	1.64 (0.99, 2.70)	0.13	2.93 (1.81, 4.72)‡	0.20
CVD								
IFG/IGT								
Model 1	1	1.17 (0.86, 1.60)	1.73 (1.24, 2.41)†	1	1.16 (0.87, 1.54)	0.84	1.83 (1.49, 2.25)‡	0.98
Model 2	1	1.03 (0.74, 1.42)	1.22 (0.83, 1.79)	1	1.05 (0.79, 1.40)	0.99	1.58 (1.25, 1.98)‡	0.51
Model 3	1	1.20 (0.88, 1.64)	1.75 (1.25, 2.45)†	1	1.12 (0.83, 1.51)	0.68	1.91 (1.54, 2.36)‡	0.94
HbA_{1c} (IEC)								
Model 1	1	1.61 (1.18, 2.20)†	1.85 (1.30, 2.63)†	1	1.06 (0.81, 1.38)	0.02	1.77 (1.44, 2.17)‡	0.58
Model 2	1	1.49 (1.08, 2.07)*	1.31 (0.88, 1.95)	1	1.03 (0.78, 1.36)	0.04	1.45 (1.15, 1.83)†	0.97
Model 3	1	1.61 (1.17, 2.21)†	1.88 (1.32, 2.67)‡	1	1.03 (0.78, 1.36)	0.02	1.82 (1.48, 2.25)‡	0.59
HbA_{1c} (ADA)								
Model 1	1	1.21 (0.98, 1.49)	1.88 (1.31, 2.68)†	1	1.19 (0.96, 1.48)	0.65	1.90 (1.51, 2.40)‡	0.76
Model 2	1	1.12 (0.90, 1.39)	1.30 (0.87, 1.94)	1	1.08 (0.87, 1.36)	0.63	1.51 (1.17, 1.96)†	0.87
Model 3	1	1.20 (0.97, 1.49)	1.89 (1.32, 2.70)‡	1	1.12 (0.90, 1.41)	0.48	1.93 (1.52, 2.44)‡	0.69

Data are subhazard ratios (95% CI). Model 1: age, sex. Model 2: age, sex, smoking, total-to-HDL cholesterol ratio, waist-to-hip ratio, systolic blood pressure, antihypertensive treatment. Model 3: age, sex, smoking, manual occupation, physical activity, and fruit and vegetable intake. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$. *P* for ethnic difference: §prediabetes vs. normoglycemia, ‖diabetes vs. normoglycemia.

cerebral circulatory autoregulation (39), and others report greater cerebral microvascular disease (40) in South Asians than Europeans, with evidence that the latter two findings were mediated by hyperglycemia. Furthermore, we have shown that the South Asian excess of stroke is largely explained by diabetes, commensurate with the current study's results regarding prediabetes (16). However, it is unclear why nondiabetic glycemia is not so obviously related to CHD in South Asians (28,29).

This study is novel in comparing associations between prediabetes and CVD in South Asians and Europeans. Strengths include the use of three different diagnostic criteria for prediabetes. HbA_{1c} was not available on all participants at baseline and, as with any cohort study, loss to follow-up may have introduced bias. However, 88% of Europeans and 90% of South Asians were followed up, and analyses comparing *1*) those with and without a full set of baseline bloods and *2*) responders and nonresponders did not detect bias. Bias may have arisen from exposure misclassification, especially given the high variability of glucose measurements (27), though this is less likely for HbA_{1c}. While the study was well powered for CHD and CVD analyses, the relatively small number of strokes made interpretation of associations more difficult, though internal validity was demonstrated, since associations between all prediabetes measures and stroke were similar. Confounders such as use of and response to antihypertensive and lipid-lowering medication will have varied over time. We attempted to address this by examination of follow-up clinic data. Finally, the South Asians in our study were of Indian origin and may not necessarily apply to other South Asian subgroups.

In summary, we show relations between prediabetes and CVD outcomes

varied by prediabetes diagnostic criterion, type of CVD, and ethnicity. Despite calls for prediabetes to be proactively identified and treated (3,4), we found that only prediabetes by IEC criteria (HbA_{1c} 6.0–6.5% [42–48 mmol/mol]) in Europeans was linked with overall CVD risk. For South Asians, who experience greater prediabetes, greater rates of conversion to diabetes, and greater risks of CVD than Europeans, prediabetes was only clearly associated with stroke. These results need substantiating, with further exploration of contributory mechanisms and evaluation of screening and interventions in prediabetes, especially in South Asian groups.

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