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Research Article Complications

The increased risk of microvascular complications in South Asians with type 1 diabetes is influenced by migration: results from the UK–India multi-ethnic migration study

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What's new?

- The impact of South Asian ethnicity and migration on the natural history of type 1 diabetes is not well understood.
- South Asians in India have a greater risk of retinopathy and diabetic kidney disease and lower risk of neuropathy than white Europeans in the UK. The excess risk of diabetic kidney disease is mitigated for South Asians in the UK.
- These associations persist despite adjusting for classical risk factors for microvascular complications such as glycaemic control, blood pressure, disease duration or markers of insulin resistance.
- The results call for us to be particularly vigilant for the complications of type 1 diabetes in South Asians.

Abstract

Aim We aimed to explore the association between South Asian ethnicity and complications of type 1 diabetes, and whether this is affected by migration.

Methods In this retrospective cohort study, data on diabetes control and complications were obtained for South Asians in India (South Asians_{India}, $n = 2592$) and the UK (South Asians_{UK}, $n = 221$) and white Europeans in the UK ($n = 1431$). Multivariable logistic regression was used to identify associations between ethnicity and diabetic kidney disease, retinopathy and neuropathy adjusting for age, sex, BMI, disease duration, HbA_{1c}, blood pressure (BP) and cholesterol.

Results South Asians_{India} had significantly greater adjusted odds of diabetic kidney disease [odds ratio (OR) 5.0, 95% confidence intervals (CI) 3.6–7.1] and retinopathy (OR 1.8, 95% CI 1.2–2.5), but lower odds of neuropathy (OR 0.5, 95% CI 0.4–0.6) than white Europeans. South Asians_{India} had significantly greater adjusted odds of diabetic kidney disease (OR 3.0, 95% 1.8–5.3) than South Asians_{UK}, but there was no significant difference in the odds of other complications.

Conclusions In this hypothesis-generating study, we report that South Asian ethnicity is associated with greater risk of diabetic kidney disease and retinopathy, and lower risk of neuropathy than white European ethnicity. Part of the excess diabetic kidney disease risk is reduced in South Asians_{UK}. These associations cannot be accounted for by differences in vascular risk factors. Our findings in South Asians with type 1 diabetes mirror previous findings in type 2 diabetes and now need to be validated in a study of the effect of ethnicity on type 1 diabetes complications where healthcare is provided in the same setting.

<H1>Introduction

Type 1 diabetes is an autoimmune disease characterized by the destruction of insulin-secreting pancreatic β cells, and subsequent insulin deficiency [1]. Type 1 diabetes affects ~ 40 million adults worldwide and 8 million adults in South Asia [2]. South Asians represent a quarter of the world population [3], and 7% of the UK population [4].

It is important to understand the influence of South Asian ethnicity on type 1 diabetes control and complications. Comparative ethnic studies can provide evidence for a potential genetic contribution to the development and complications of type 1 diabetes, and improve our understanding of the underlying pathological mechanisms. Furthermore, an understanding of the effect of ethnicity on the natural history of chronic conditions can influence management. As an example, the medication algorithm for hypertension differs in Afro-Caribbean and white European ethnic groups [5].

The association and natural history of South Asian ethnicity in type 2 diabetes has been explored previously. South Asians who have migrated develop type 2 diabetes at a younger age, have poorer glycaemic control and higher rates of diabetic retinopathy, diabetic kidney disease and cardiovascular disease than white Europeans [6]. By contrast, few studies have been undertaken on South Asians with type 1 diabetes. We have previously undertaken a systematic review of available literature in this area [7]. We reported that migrant South Asians with type 1 diabetes have poorer glycaemic control than white Europeans, but experience equal rates of retinopathy, diabetic kidney disease and cardiovascular disease. However, we noted that the original studies were of poor quality and produced conflicting results, and a meta-analysis was not performed.

The aim of this study is to investigate in detail the influence of South Asian ethnicity on glycaemic control and diabetes complications in type 1 diabetes, and to determine the effect of migration on these outcomes. Similar to type 2 diabetes, we hypothesized that the natural

history of type 1 diabetes and its complications will differ between the South Asian and white ethnic groups.

<H1>Methods

This is a retrospective cohort study using data from routine clinical care in the UK and India. The data for the UK cohort were obtained from the adult diabetes clinic at University Hospitals of Leicester, UK, a tertiary centre, from 2012 to 2014. Type 1 diabetes affects over 370 000 adults in the UK, representing 10% of adults diagnosed with diabetes [8]. Leicester is an ethnically diverse city, with a population of 340 000 comprising mostly white European (45%) and South Asian (37%) (with 28% being of Indian heritage) ethnicities [9]. The diagnosis of type 1 diabetes was made clinically, and would only have been confirmed with antibody and C-peptide testing if felt appropriate as per National Institute for Health and Care Excellence (NICE) guidelines [10]. Ethnicity was classified according to self-identification in clinical records using UK census categories. All white European ($n = 1431$) and South Asian_{UK} ($n = 221$) clinic attenders with type 1 diabetes were included in the current analysis. The data for the Indian cohort were obtained from Dr Mohan's Diabetes Specialities Centre, a secondary and tertiary care clinic, in Chennai, from 1991 to 2015. The prevalence of type 1 diabetes in India is ~ 10.2 per 100 000 population, with a higher prevalence in urban than rural areas [11]. Chennai is the fourth largest city in India, with a population of 8.7 million at the 2011 census [12]. Type 1 diabetes was defined as acute onset of polyuria, polydipsia and unexplained weight loss, and/or diabetic ketoacidosis, fasting C-peptide < 0.3 pmol/ml and stimulated C-peptide < 0.6 pmol/ml, and continuous need for insulin therapy from the time of diagnosis. All clinic attenders with type 1 diabetes were eligible for this study (South Asians_{India}, $n = 2592$).

The requirement for informed consent was waived for this retrospective study using anonymized routine data.

We obtained data on age, sex, weight, height, blood pressure (BP), HbA_{1c} and lipids from the routinely held clinical records at the final clinic attendance. Outcome measures were the presence or absence of diabetic kidney disease, retinopathy and neuropathy at the final clinic attendance. Both British and Indian cohorts had at least yearly screening for diabetes complications.

The diagnostic criteria for diabetes complications were similar in India and the UK. Retinopathy was diagnosed by ophthalmic examination in India, and retinal photographic screening followed by ophthalmic examination in the UK. Grading was as per the criteria used in the Early Treatment Diabetic Retinopathy Study criteria [13]. Diabetic kidney disease

was defined by increased urinary albumin or protein excretion. This was graded as microalbuminuria [albumin to creatinine ratio (ACR) 30–299 µg/mg], macroalbuminuria (ACR > 300 µg/mg) or proteinuria (24-h urine protein excretion > 500 mg). Neuropathy was assessed using a biothesiometer to measure the vibratory perception threshold at the hallux. Peripheral neuropathy was diagnosed if mean vibratory perception threshold > 20 V over three measurements taken by a single observer.

<H2>Statistical analysis

Significant differences in baseline characteristics between ethnic groups were identified by one-way analysis of variance (ANOVA) for continuous normally distributed variables, Kruskal–Wallis *H* test for continuous non-normally distributed variables, and χ^2 test for categorical variables.

The association between ethnicity and each diabetes complication was explored using logistic regression analysis. Older age at diagnosis, longer type 1 diabetes duration, male sex, greater height, higher BMI, higher systolic blood pressure (SBP), higher HbA_{1c} and higher total cholesterol are known risk factors for microvascular and macrovascular complications of type 1 diabetes [14]. Therefore, this analysis was performed without and with adjustment for the following potentially confounding variables: age at diagnosis, type 1 diabetes duration, sex, height, BMI, SBP, HbA_{1c} and total cholesterol. Owing to overdispersion, logistic regression models for retinopathy were fitted with a quasi-binomial model. Participants with missing data on a diabetes complication at their final clinic attendance were regarded as missing from the analysis for that complication.

Because missing data affected a substantial proportion of the South Asian_{India} data set (Table 1), testing for possible selection bias was undertaken. Clinical characteristics of those with missing data were compared with those with complete data using *t*-test for continuous normally distributed variables, Mann–Witney *U*-test for continuous non-normally distributed variables and χ^2 test for categorical variables.

To ensure that the timing of the data collection (India 1991–2015, UK 2012–2014) did not influence the study results, we undertook a sensitivity analysis. South Asians_{India} participants with last clinic attendance dates before 2012 were removed to match with dates from UK data set (South Asians_{India} *n* = 1057).

Data on ischaemic heart disease was collected but was not analysed because of the small number of outcomes.

All analyses were performed using R version 3.4.3.

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<H2>Ethics statement

The requirement for informed consent or ethical approval was waived for this retrospective study using anonymized data from routine clinic letters.

<H1>Results

Baseline characteristics were significantly different between the ethnic groups. South Asians_{India} were younger (median 25.8 years vs. 37.1 and 29.1 years, $P < 0.001$), shorter (mean 1.6 m vs. 1.7 and 1.6 m, $P < 0.001$) and leaner (mean BMI 20.6 kg/m² vs. 25.5 and 24.6 kg/m², $P < 0.001$) than white Europeans and South Asians_{UK} respectively (Table 1). Diabetes control was significantly different between the three cohorts. South Asians_{India} had higher HbA_{1c} [mean 83 mmol/mol (9.8%) vs. 70 mmol/mol (8.5%) and 72 mmol/mol (8.7%), $P < 0.001$], lower SBP (mean 115 mmHg vs. 130 and 126 mmHg, $P < 0.001$), higher total to HDL cholesterol ratio (mean 3.6 vs. 3.0 and 3.4, $P < 0.001$) and higher triglycerides (mean 2.5 mmol/l vs. 1.4 and 1.5 mmol/l, $P < 0.001$) than white Europeans and South Asians_{UK} respectively (Table 1).

The prevalence of each diabetes complication was significantly different between the groups. South Asians_{India} had higher prevalence of diabetic kidney disease (19%) than white Europeans (7.4%) and South Asians_{UK} (8.1%) ($P < 0.001$). White Europeans had higher prevalence of retinopathy (45% vs. 36% and 34%, $P < 0.001$) and neuropathy (25% vs. 9.7% and 11%, $P < 0.001$) than South Asians_{India} and South Asians_{UK} respectively (Table 2).

After adjusting for age at diagnosis, type 1 diabetes duration, sex, height, BMI, SBP, HbA_{1c} and total cholesterol in a multivariable logistic regression analysis, there remained differences in the odds of each diabetes complication between the groups. South Asians_{India} had significantly greater odds of diabetic kidney disease [odds ratio (OR) 5.0, 95% confidence intervals (CI) 3.6–7.1] and retinopathy (OR 1.8, 95% CI 1.2–2.5), but lower odds of neuropathy (OR 0.5, 95% CI 0.4–0.6) compared with white Europeans. South Asians_{India} had significantly greater odds of diabetic kidney disease (OR 3.0, 95% 1.8–5.3) than South Asians_{UK}. However, there were no significant differences in the adjusted odds of retinopathy and neuropathy between South Asians_{India} and South Asians_{UK} (Table 3, Fig. 1).

Testing for selection bias showed differences between South Asians_{India} with missing data and those with complete data. Those with missing data were significantly more likely to be female and have lower BMI, shorter type 1 diabetes duration and higher HbA_{1c}. Sensitivity analysis demonstrated that matching the timing of data collection gave similar results as using the complete data set (Table S1).

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<H1>Conclusions

This is the first study to demonstrate that South Asians_{India} with type 1 diabetes have poorer glycaemic control, lower SBP, and a higher total to HDL cholesterol ratio than white Europeans and South Asians_{UK}.

Diabetic kidney disease was more prevalent in South Asians_{India} with type 1 diabetes than in white Europeans and South Asians_{UK}, and this finding held true after adjusting for several potentially confounding variables. This suggests that the South Asian population that have migrated to the UK are less prone to diabetic kidney disease. From our local knowledge of the clinic population, we estimate that the migrant population may have been in the UK for up to three generations but the differences could be explained by universal healthcare enabling better risk factor control in the UK, unmeasured confounding factors such as medication, smoking and dietary protein, and the healthy migrant phenomenon.

After adjusting for potential confounders, South Asians_{India} had greater odds of retinopathy than white Europeans, and there was no significant difference between South Asians_{India} and South Asians_{UK}. Neuropathy was more prevalent in white Europeans than in South Asians_{India} and South Asians_{UK}, and this result was maintained after adjustment for confounding variables. In particular, these associations are independent of glycaemic control. These findings suggest that South Asian ethnicity carries a predisposition to retinopathy but affords some protection from neuropathy in type 1 diabetes. We speculate that the increased retinopathy seen in South Asians_{India} may have a genetic component because the odds for adjusted retinopathy are not significantly different in South Asians in the India and UK, therefore the difference between South Asians and white Europeans is likely to have a genetic component. In support, recent studies do show that genes can play a role in different rates of retinopathy across ethnicities [15] and this is clearly an area for future research.

<H2>Comparison with other studies

As outlined previously, no study has explored the effect of South Asian ethnicity and migration on the natural history of type 1 diabetes and its complications. Our findings are consistent with a recent systematic review which showed that South Asians have poorer glycaemic control than white Europeans [7]. The underlying reasons for this require speculation. Undoubtedly, differences in healthcare systems can contribute to the detected difference. However, there is also evidence that within the same healthcare system, South Asians have poorer glycaemic control than white Europeans. The reasons for this are not clear, but these differences may not be explained by traditional factors that influence glycaemic control such as insulin resistance [16].

Previous smaller studies have reported that South Asians and white Europeans are at equal risk of diabetic kidney disease, retinopathy and IHD [7]. By contrast, we found that South Asians_{India} are at greater risk of diabetic kidney disease and retinopathy than white Europeans, despite adjusting for age at diagnosis, type 1 diabetes duration, sex, height, BMI, SBP, HbA_{1c} and total cholesterol. We found that South Asians_{UK} had lower odds of diabetic kidney disease, but not retinopathy.

Our findings are consistent with previous reports that South Asians are at lower risk of neuropathy than white Europeans [7,17]. Interestingly, we found this to hold true after adjustment for potential confounders, including height.

<H2>Strengths and limitations

This study offers an insight into diabetes control and complications in a large, multi-ethnic, multinational population with type 1 diabetes. Previous studies have assessed the association between South Asian ethnicity and complications in type 1 diabetes, however, none have compared migrant, native and host populations. The study population was large; hence we were able to apply robust statistical analyses.

This study has limitations. Differences in healthcare systems between India and the UK mean there are differences in access to healthcare, follow-up frequency, screening for complications, and type 1 diabetes diagnosis and therapy between the three cohorts. There are limitations arising from the quality of data collection because the data in this analysis were collected for the primary purpose of clinical care. Although retinopathy is more likely to be picked up by retinal screening in the UK than by fundoscopy in India, the adjusted odds of retinopathy are greater in South Asians_{India} than in white Europeans. Furthermore, the odds are not significantly different for South Asians in India and in the UK. Although there is a risk that the real rates for retinopathy will be even higher in South Asians in India than that detected with hand-held fundoscopic examination, this will likely increase the odds ratio even further than that we have described. Testing for selection bias suggests that South Asians_{India} with missing data have poorer diabetes control than those included in the analysis.

Unmeasured factors may be contributing to type 1 diabetes complications, such as smoking, physical activity, diet, socio-economic status, antihypertensive and lipid-modifying drugs. The diagnosis of type 1 diabetes was purely clinical in many cases, hence people with young-onset type 2 diabetes requiring insulin may have been included. Although the study population was large, the South Asian_{UK} cohort was small. A sample size power calculation was undertaken to determine if a sufficiently large sample was present to detect a reasonable clinical difference. This illustrated that the sample size was sufficient to be confident about

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our conclusions for all complications (data not shown). South Asians are a heterogeneous group; the populations of Chennai and Leicester may not be fully representative of other native and migrant South Asian populations across the Indian Subcontinent and in the West. Because of the healthy migrant phenomenon, it is possible that the differences identified between South Asians_{India} and South Asians_{UK} reflect differences that were present before migration.

<H2>Implications

Our data suggest for the first time in people with type 1 diabetes, that South Asian ethnicity is associated with greater risk of retinopathy and diabetic kidney disease, and lower risk of neuropathy. These associations cannot be explained by classical risk factors for microvascular complications such as glycaemic control, BP, disease duration or markers of insulin resistance. We also show for the first time that some of the risk of diabetic kidney disease in South Asians is mitigated in those who have migrated to the UK. We have recently shown that South Asians have a similar prevalence of microalbuminuria and rate of decline of renal function to white Europeans [18]. This supports our suggestion that diabetic kidney disease risk is similar across ethnicities and that environmental factors perhaps associated with better health care may contribute to the difference between the diabetic kidney disease rates seen in South Asians from UK and India.

It is notable that South Asian ethnicity transforms the risks of retinopathy, diabetic kidney disease and neuropathy in type 2 diabetes in an identical fashion. When adjusted for confounders, the risk of retinopathy and diabetic kidney disease are increased in type 2 diabetes, and the risks of neuropathy decreased [19–22]. The modifying effect of South Asian ethnicity can either be genetic or environmental. With regard to the latter, the relative contributions of diet and physical activity need further exploration.

Although we cannot be wholly confident about the consistency of data collection across the two healthcare systems, the comparison we describe is unique and may be considered hypothesis-generating. Further studies using other large cohorts are now required to confirm our findings, and to explore whether ethnic disparities in diabetes complications can be minimized through appropriate type 1 diabetes management, or whether some of the differences we describe are unique to the South Asian genetic background. This can be facilitated through following up existing cohorts as well as establishing larger cohorts of migrant South Asians with formal collection of demographic, ethnic and clinical data, and collection of biological samples for formal genetic testing.

Meanwhile, the results of this study call for us to be particularly vigilant for the vascular complications of type 1 diabetes in the South Asian ethnic group.

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Competing interests

None declared.

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FIGURE 1. Odds ratios for the risk of diabetic complications in South Asians_{India} compared with South Asians_{UK} (●) and white Europeans (○).

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<H1>Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity analysis of South Asians_{India} data set to match with date of data collection for British data set

Table 1. Characteristics of participants at the final clinic attendance

	South Asian _{India} (n = 2592)		White European (n = 1431)		South Asian _{UK} (n = 221)		P-value*
	Missing		Missing		Missing		
Age, years (median, IQR)	25.8 (14.8–37.1)	0	37.1 (20.7–52.4)	0	29.1 (18.9–32.2)	0	<0.001
Age at diagnosis, years (median, IQR)	16.0 (9.6–24.8)	0	14.4 (9.2–26.8)	17	13.7 (8.8–28.8)	2	0.772
Type 1 diabetes duration, years (median, IQR)	6.9 (1.9–14.5)	0	15.1 (5.8–29.3)	17	10.9 (5.3–20.5)	2	< 0.001
Male sex, N (%)	1452 (56.0)	0	749 (52.3)	0	115 (52.0)	0	0.060
Weight, kg	49.7 ± 17.0	21	72.5 ± 21.2	135	64.5 ± 19.2	11	< 0.001
Height, m	1.55 ± 0.19	38	1.67 ± 0.15	149	1.60 ± 0.16	11	< 0.001
BMI, kg/m ²	20.6 ± 4.5	29	25.5 ± 5.8	124	24.6 ± 5.1	8	< 0.001
SBP, mmHg	115 ± 18	140	130 ± 17	225	126 ± 17	32	< 0.001
DBP, mmHg	74 ± 9	143	75 ± 10	225	75 ± 12	32	0.320
HbA _{1c} , mmol/mol (%)	83 ± 26 (9.8)	216	70 ± 19 (8.5)	46	72 ± 19 (8.7)	3	< 0.001
Total cholesterol, mmol/l	4.30 ± 1.03	324	4.48 ± 0.96	250	4.53 ± 1.03	34	< 0.001
HDL cholesterol, mmol/l	1.25 ± 0.33	826	1.59 ± 0.53	376	1.43 ± 0.40	58	<0.001
Triglycerides, mmol/l	2.54 ± 1.83	362	1.36 ± 0.34	253	1.48 ± 1.16	34	< 0.001
Total cholesterol to HDL ratio	3.61 ± 1.14	455	3.03 ± 0.99	377	3.40 ± 1.11	58	< 0.001

Values are given as mean ± SD unless stated otherwise. Missing data are indicated.

*P-values are given for one-way analysis of variance (ANOVA) for continuous normally distributed variables, Kruskal–Wallis H test for continuous non-normally distributed variables and χ^2 test for categorical variables.

Table 2. Prevalence of type 1 diabetes complications

	South Asian _{India} (n = 2592)		White European (n = 1431)		South Asian _{UK} (n = 221)		P-value*

	Missing		Missing		Missing		
Diabetic kidney disease	365 (19)	658	106 (7.4)	0	18 (8.1)	0	0.001
Retinopathy	598 (36)	949	642 (45)	0	74 (33)	0	0.001
Neuropathy	157 (9.7)	974	354 (25)	0	24 (10.9)	0	0.001

Values are given as number (%) and missing data are indicated.

*P-values are given for χ^2 test for diabetic kidney disease, retinopathy and neuropathy.

Table 3. Unadjusted and adjusted risk of type 1 diabetes complications in South Asians_{India} compared with reference categories of White Europeans and South Asians_{UK}

Reference category	Unadjusted		Adjusted†	
	White European	South Asian _{UK}	White European	South Asian _{UK}
Diabetic kidney disease	2.9 (2.3–3.7) P < 0.001	2.63 (1.6–4.6) P < 0.001	5.0 (3.6–7.1) P < 0.001	3.0 (1.8–5.3) P < 0.001
Retinopathy	0.7 (0.6–0.8) P < 0.001	1.1 (0.9–1.5) P = 0.397	1.8 (1.2–2.5) P = 0.005	1.8 (1.0–3.5) P = 0.067
Neuropathy	0.3 (0.3–0.4) P < 0.001	0.9 (0.6–1.4) P = 0.588	0.5 (0.4–0.6) P < 0.001	0.9 (0.5–1.6) P = 0.741

Figures are odds ratio (95% confidence interval) and P-value*.

*P-values are given for logistic regression models for each diabetes complication.

†Adjusted for age at diagnosis, type 1 diabetes duration, sex, height, BMI, SBP, HbA_{1c} and total cholesterol.

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