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Comorbidities, complications and mortality in people of South Asian ethnicity with type 1 diabetes compared with other ethnic groups: a systematic review

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ABSTRACT

Objective The aim of this systematic review is to explore the association of South Asian (SA) ethnicity on comorbidities, microvascular and macrovascular complications and mortality compared with other ethnic groups in people with type 1 diabetes mellitus (T1DM).

Design Systematic review.

Method A systematic literature search strategy was designed and carried out using Medline and Embase for full-text and abstract studies published in English from 1946 to February 2016. The initial search identified 4722 papers. We assessed 305 full-text articles in detail for potential inclusion. Ten papers met the inclusion criteria for review and an additional one paper was included from our secondary search strategy using the bibliography of included studies. In total, 11 studies were included.

Eligibility criteria for selecting studies Studies were included if they were published in English, involved SA participants with T1DM and compared them with non-SA participants and assessed one of the outcomes of comorbidities, microvascular complications, macrovascular complications and mortality.

Results SA with T1DM have higher mortality compared with white Europeans (WE), mainly contributed to by excess cardiovascular disease. SA have significantly higher glycated haemoglobin (HbA1c), lower high-density lipoprotein (HDL) and lower rates of nephropathy compared with WE. There were no differences in rates of retinopathy and nephropathy. Compared with Africans, SA had lower levels of microalbuminuria, HbA1c and systolic blood pressure and higher HDL levels. There were no significant differences in the remaining outcomes: cardiovascular disease, retinopathy, neuropathy and body mass index. Furthermore, SA have higher HbA1c levels than Malay and Chinese and higher waist: hip ratio and lower HDL levels compared with Chinese only.

Conclusion Our analysis highlights ethnic disparity in macrovascular outcomes that is so evident for type 2 diabetes mellitus may also be present for SA patients with T1DM. We highlight the need for a large, prospective, cohort study exploring the effect of ethnicity in a uniform healthcare setting.

Strengths and limitations of this study

► The strengths of this analysis are its comprehensive search strategy with clearly defined population and outcomes.

► Our search strategy incorporated both full-length papers as well as abstracts and had a secondary search strategy to ensure we did not miss any relevant papers.

► We compared the South Asian (SA) group, the largest ethnic group globally with all other indigenous ethnic groups.

► The quality of the studies were poor with the majority of studies being retrospective observational or cross-sectional.

► Furthermore, the methodology of how outcomes were assessed was not consistently reported, and the numbers of SA in each study were small.

BACKGROUND

The epidemiology of type 1 diabetes mellitus (T1DM) in South Asians (SA) is poorly understood. Its effects on metabolic control, diabetic complication rate or indeed the underlying pathogenesis has yet to be explored. SA are at higher risk than white Europeans (WE) for the development of obesity and obesity-related diseases including insulin resistance, the metabolic syndrome, type 2 diabetes mellitus (T2DM) and coronary heart disease. T2DM is two to three times more common in SA than in the WE population in the UK2 and up to three times more common among people of African origin.3 Furthermore, SA with T2DM develop the condition 5–10 years earlier than WE, have increased prevalence of diabetic complications at presentation, worse outcomes and die at a younger age.6 4 These differences have not been explored in people with T1DM.
Willi et al suggested that there were ethnic disparities in the outcomes of children with T1DM with black participants having higher mean HbA1c levels, more diabetic ketoacidosis and severe hypoglycaemic events compared with white or Hispanic participants. A recent systematic review identified 16 studies in the current literature that showed racial/ethnic minority youth with T1DM having higher haemoglobin A1c (HbA1c) compared with Caucasian youth. As the majority of these studies are conducted in the USA, their primary focus was on the black and Hispanic ethnic groups and youth with T1DM.

SA comprise 20% of the global population and 7% of the UK population. Furthermore, the incidence of T1DM appears to be similar in SA as in the background population. Therefore, there is a need to understand the effect of ethnicity on the progression of the disease. The aim of this systematic review is to explore the association of SA ethnicity on comorbidities, microvascular and macrovascular complications and mortality compared with other ethnic groups in people with T1DM.

METHODS
Terms indicative of T1DM and SA were searched for in MEDLINE (Ovid) and EMBASE using keywords and free text. The search terms included ‘Type 1 Diabetes’, ‘Insulin Dependent Diabetes’ and ‘South Asian’ as well as terms pertaining to ethnicity such as ‘ethnic or racial group’, ‘race’, ‘ethnic or racial aspects’ and ‘ethnic differences’. We also included search terms pertaining to the individual countries from South Asia as listed below. Further information on the search strategy can be found in online supplementary appendix 1. Full-length papers and abstracts published in English were included in the search from 1946 to February 2016. The search was not limited to a particular study design or outcome and the papers did not have to be peer reviewed. A secondary search strategy involved reading bibliographies of the included studies and contacting authors of the included studies and committee members of the South Asian Health Foundation (http://www.sahf.org.uk) enquiring about additional studies or ongoing research.

The inclusion criteria were based on the Population, Intervention, Comparator and Outcome (PICO) framework. The population was SA with T1DM including both children and adults. A clinical diagnosis was accepted for the definition of T1DM. We defined SA ethnicity as persons originating from the following countries: India, Pakistan, Sri Lanka, Bangladesh, Nepal, Bhutan and the Maldives, and compared their comorbidities, complications and mortality with persons of any other ethnicity not classified as SA. We investigated comorbidities (body mass index, systolic and diastolic blood pressure, HbA1c and lipid profile), microvascular complications (retinopathy, neuropathy and nephropathy), macrovascular complications (ischaemic heart disease and cerebrovascular disease) and cause-specific and all-cause mortality.

Identified titles and abstracts were reviewed independently by two researchers (KS and PC). All studies that were deemed suitable for potential inclusion were then further examined in detail by the two researchers independently to create the final list of included studies. Where there were discrepancies between the two researchers (KS and PC) this was resolved by discussion. Quality assessment and data extraction was performed by KS and then checked by PC to identify any missing information (see online supplementary appendix 2). The Newcastle–Ottawa Quality Assessment Scale for observational studies was used for quality assessment.

We were not able to perform a meta-analysis because the studies were not comparable by outcomes measured, were of poor quality and heterogeneous in the way SA ethnicity was defined. The results have been analysed as a narrative and presented as tabulations with textual description by each comorbidity and complication.

RESULTS
The initial search identified 4722 papers. After removing duplicates (1194), the remaining 3528 titles and abstracts were screened. After excluding 3225 papers in this initial screening process, 305 full-text articles were assessed in detail for potential inclusion into the analysis. Ten papers met the inclusion criteria for review. A secondary search using the bibliographies of included studies yielded an additional one paper (figure 1). A total of 11 studies were therefore included: 6 studies were from the UK, 4 from South Africa and 1 from Malaysia. Nine of the papers were full-length papers and two were abstracts. Of the included articles, one was a prospective cohort study, two were retrospective analysis of observational data and eight studies were cross-sectional analyses. The results are summarised in tables 1 and 2.

RESULTS
Comorbidities
Body mass index
Six studies explored body mass index (BMI) and general weight measurements as an outcome: three comparing SA with WE only, one comparing with WE and Africans, one comparing with Africans only and one comparing to Malay and Chinese. The three papers comparing SA to only WE demonstrated no statistically significant difference in BMI. Mehta et al in the UK showed a mean BMI of 27.5 kg/m² in SA (n=163) compared with 27.4 in WE (n=1169) (p=0.835). Similarities in BMI (kg/m²) between SA and WE have previously been reported in two different centres (median BMI 25.6 kg/m² vs 25.7 kg/m², respectively, and 30.9 kg/m² vs 25 kg/m², respectively). The results were not significant due to the small number of participants. Shenoy et al also in the UK showed no statistically significant differences in the rates
of overweight or obesity between WE (n=112) and SA (n=38) children with T1DM at any age grouping.

Brabarupan et al\textsuperscript{12} in the UK showed no statistically significant difference in BMI in SA (n=39) compared with WE (n=565) and Africans (n=38) (median 25.3 kg/m\textsuperscript{2} vs 25.0 kg/m\textsuperscript{2} vs 25.7 kg/m\textsuperscript{2}, respectively). Omar et al\textsuperscript{13} in South Africa also showed no difference between SA (n=40) and Africans (n=86) in mean % ideal body weight (91 kg/m\textsuperscript{2} vs 106 kg/m\textsuperscript{2}, respectively).

Lastly, a study by Ismail et al\textsuperscript{14} in Malaysia showed that there was no difference in BMI when comparing SA to Malay and Chinese (mean 22.0 kg/m\textsuperscript{2} vs 22.3 kg/m\textsuperscript{2} vs 22.0 kg/m\textsuperscript{2}, respectively). However, there were significant differences in waist–hip ratio between the ethnic group males with SA having significantly higher waist–hip ratio compared with Chinese (mean 0.88 vs 0.84, respectively, p=0.007).

In summary, there are no demonstrable differences in BMI between SA, WE and African ethnic groups with T1DM. However, SA males compared with Chinese males with T1DM had a higher waist–hip ratio.

Glycaemic control

Seven studies explored glycaemic control as an outcome: three comparing SA with WE only, two comparing with WE and Africans, one comparing to Africans only and one comparing with Malay and Chinese. Mehta et al\textsuperscript{11} in the UK, demonstrated higher HbA1c levels in SA (n=163) (mean 9.1\%) compared with WE (n=1169) (mean 8.5\%) (p<0.001). This is similar to the results from Brabarupan et al\textsuperscript{12} in the UK who demonstrate SA (n=39) having higher HbA1c levels (median 8.3\%) compared with WE (n=565) (median 8.0) but lower than African (n=38) (median 9.1) (p<0.05). Another UK study analysed SA and WE at two different hospitals\textsuperscript{9} and demonstrated similar HbA1c (median 9.0\% vs 9.1\%, respectively, and 8.2\% vs 8.6\%, respectively, at the two different hospitals).

Shenoy et al\textsuperscript{10} in the UK found no significant difference
## Table 1  Data extraction of studies included in systematic review

<table>
<thead>
<tr>
<th>Study &amp; year published</th>
<th>Country</th>
<th>Design</th>
<th>Method and Description</th>
<th>Number of participants &amp; Ethnic Group</th>
<th>Age description</th>
<th>Duration of Study</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brabarupan et al 2013</td>
<td>UK</td>
<td>Cross-sectional study</td>
<td>Diagnosis of T1DM and diagnosed &lt;35 years of age</td>
<td>642 individuals in total</td>
<td>WE: 564, SA: 39, African: 39</td>
<td>N/A</td>
<td>Parameters median (QR)</td>
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<td>Median age at diagnosis (years)</td>
<td>WE: 16.7, SA: 19.4, African: 19.1</td>
<td>N/A</td>
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<td>Systolic BP (mm Hg)</td>
<td>WE: 80 (72–88), SA: 73, African: 67–79</td>
<td>N/A</td>
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<td>HbA1c (%)</td>
<td>WE: 1.2 (0.5–3.0), SA: 1.2 (1.0–2.0), African: 1.2 (0.5–3.0)</td>
<td>N/A</td>
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<td>Total cholesterol (mmol/L)</td>
<td>WE: 1.49 (1.21–1.77), SA: 1.25 (0.95–1.56), African: 1.09 (0.74–1.32)</td>
<td>N/A</td>
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<td>HDL (mmol/L)</td>
<td>WE: 4.50 (3.90–5.10), SA: 4.40 (3.90–4.90), African: 4.00 (3.2–4.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sarwar et al 2019</td>
<td>UK</td>
<td>Cross-sectional study</td>
<td>Coding of T1DM from the clinical database of two centres—no diagnostic criteria included</td>
<td>WE: 278, SA: 139</td>
<td>Median age (years)</td>
<td>N/A</td>
<td>Characteristic (no of patients)</td>
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<td></td>
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<td></td>
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<td></td>
<td>Demographic data</td>
<td>No statistically significant difference in the two subgroups in relation to age, duration of diagnosis, daily insulin requirement and metabolic control (median HbA1c 8.4% vs 8.8%, respectively, for white Caucasian/SA)</td>
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<td>Obesity in children</td>
<td>No statistically significant differences noted in the rates of overweight or obesity between white Caucasian and SA children at any age group.</td>
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<tr>
<td>Shenoy et al 2004</td>
<td>UK</td>
<td>Retrospective observational study</td>
<td>Children coded as T1DM in a centre in Leicestershire—no diagnostic criteria included</td>
<td>WE: 112, SA: 38</td>
<td>Age group (n)</td>
<td>2–4 years (3), 5–9 years (33), 10–15 years (90), 16–18 years (24)</td>
<td>N/A</td>
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</tbody>
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### Study & year published
<table>
<thead>
<tr>
<th>Country</th>
<th>Design</th>
<th>Method and Description</th>
<th>Number of participants &amp; Ethnic Group</th>
<th>Duration of Study</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asmal et al.</strong> (1981) South Africa</td>
<td>Cross-sectional analysis</td>
<td>Ethnicity Two groups: Indians and Black African T1DM Clinic patients who fulfilled the following criteria: age of diagnosis of diabetes &lt;35 years, development of symptoms with/without ketosis in the absence of insulin therapy and duration of diabetes of at least 12 months</td>
<td>Black African: 52 Indians: 38</td>
<td>Mean age at onset (years)</td>
<td><strong>Basic biochemical data</strong></td>
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<td>4 weeks</td>
<td>Glucose (mmol/L)</td>
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<td>Growth hormone (ng/mL)</td>
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<td>Cortisol (µg/dL)</td>
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<td>Cholesterol (mmol/L)</td>
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<td>Triglyceride (mmol/L)</td>
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<td>Creatinine (µg/dL)</td>
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<td>Complications</td>
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<td>Chronic complications associated with microangiopathy were detected in 12 Indians (33%) and 2 blacks (4%). The most common complication was neuropathy found in 19% of Indians with diabetes and 4% of blacks with diabetes. Two Indians had evidence of diabetic ketoacidosis.</td>
</tr>
<tr>
<td><strong>Ismail et al.</strong> (2001) Malaysia</td>
<td>Cross-sectional study</td>
<td>Ethnicity Three groups: Indians, Malay and Chinese Each ethnic group identified by appearance, language and religion T1DM T1DM defined as acute symptoms associated with heavy ketonuria (&gt;3+) or ketoacidosis at diagnosis, or continuous treatment with insulin within 1 year of diagnosis Method Patients recruited from seven centres throughout Peninsular Malaysia Blood taken for lipid levels, clinical history and physical examination performed</td>
<td>Indians: 154 Malay: 297 Chinese: 128</td>
<td>Mean age (years)</td>
<td><strong>Demographic features</strong></td>
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<td>All: 28.8</td>
<td>BMI (kg/m²)</td>
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<td>Indians: 29.1</td>
<td>Waist-to-hip ratio</td>
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<td>Chinese: 27.7</td>
<td>HbA1c (%)</td>
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<td>Female: 0.85 ± 0.07</td>
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<td>Lipid profiles (mmol/L ± SEM)</td>
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<td>Total cholesterol: Indians (5.74 ± 1.25), Malay (5.64 ± 1.42), Chinese (5.55 ± 1.28)</td>
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<td>LDL cholesterol: Indians (3.89 ± 1.20), Chinese (3.55 ± 1.22), Malay (2.98 ± 1.20)</td>
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<td>HDL cholesterol (mean (95% CI)): Indians (1.28, 1.19 to 1.38), Chinese (1.57, 1.48 to 1.67), Malay (1.37, 1.28 to 1.46)</td>
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<td>Triglycerides (mean (95% CI)): Indians (1.02, 0.99 to 1.03), Chinese (0.85, 0.74 to 0.91), Malay (1.11, 1.09 to 1.23)</td>
</tr>
<tr>
<td><strong>Omar et al.</strong> (1984) South Africa</td>
<td>Cross-sectional analysis</td>
<td>Ethnicity Indians and Africans T1DM Classification of diabetes based on criteria by National Diabetes Data Group and WHO Expert Committee Patients with T1DM had always depended on insulin for control of symptoms and prevention of basal ketosis. All patients diagnosed &lt;35 years of age</td>
<td>African T1DM: 86 Indian T1DM: 40</td>
<td>Mean age of onset (range)</td>
<td><strong>Clinical characteristics of patients with T1DM</strong></td>
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<td>Mean % ideal body weight</td>
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<td>Mean duration of disease (years)</td>
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<td>Mean age of onset</td>
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**Table 1 Continued**

Papers assessing T1DM complications
<table>
<thead>
<tr>
<th>Study &amp; year published</th>
<th>Country</th>
<th>Design</th>
<th>Ethnicity</th>
<th>Mean age (years)</th>
<th>Duration of Study</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swerdlow et al (2004)</td>
<td>UK</td>
<td>Prospective cohort study</td>
<td>Grouped into SA and non-SA using software (SANGRA) followed by a clinical check</td>
<td>23</td>
<td>1972-1999</td>
<td>Mortality: The SMRs for SA patients diagnosed &lt;30 years were 3.9 (95% CI 2.0 to 6.9) in men and 10.1 (95% CI 5.6 to 16.6) in women and in the corresponding non-SA were 2.7 (95% CI 2.6 to 2.9) in men and 4.0 (95% CI 3.6 to 4.3) in women.</td>
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<tr>
<td>Mehta et al (2011)</td>
<td>UK</td>
<td>Cross-sectional study</td>
<td>Ethnicity was categorised as SA or WE based on patient record documentation or by analysis of the name using a validated name recognition software (Nam Pechan) supplemented by a visual inspection of surnames and forenames</td>
<td>45.3</td>
<td>2003-2005</td>
<td>No comorbidities: WE (N=1169): 878 (75.1), 193 (17.0); SA (N=163): 134 (82.6), 25 (15.3); p Value: 0.790.</td>
</tr>
<tr>
<td>Sivaprasad et al (2012)</td>
<td>UK</td>
<td>Cross-sectional study</td>
<td>Self-reported ethnicity based on UK census standard (Census 2001) categorised as “White European”, “African”, “South Asian”, “Mixed”, “other ethnic group” and “not known”</td>
<td>39.4</td>
<td>2008-2009</td>
<td>Prevalence: WE (N=2628): 1446 (55.0), 154 (4.4), 64 (3.3), 371 (14.1), 47 (1.7), 42.8 (37.3 to 48.3); South Asian: 47 (1.7), 171 (6.5), 54.0 (44.8 to 63.2); African: 35 (1.0), 16.6 (10.0 to 23.3); SA: 35 (1.0), 12 (0.6), 6.5 (6.6 to 7.4); CSMO: (M1P1): 318 (12.1), 10.0 (6.7 to 13.3); STDR: (R2 or R3 or M1P1): 53 (15.4), 11.2 (5.4 to 16.9); p Value: 0.025.</td>
</tr>
<tr>
<td>Study &amp; year published</td>
<td>Country</td>
<td>Design Method and Description</td>
<td>Ethnicity</td>
<td>Number of participants &amp; Ethnic Group</td>
<td>Age description</td>
<td>Duration of Study</td>
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|                        |             |                               |                                      | Black African: 52 (58%), Indians: 22 (54%), Total: 75 (58%) | Neuropathy peripheral autonomic: 20 (22%), Retinopathy: 13 (14%), Nephropathy: 3 (3%), Triopathy: 1 (1%) | Ischaemic heart disease: 4 (4%), Hypertension: 5 (5%), Cataracts: 6 (7%), Tuberculosis: 1 (2%) | |

bp, blood pressure; BMI, body mass index; CSMO, clinically significant macular oedema; CVD, cardiovascular disease; DR, diabetic retinopathy; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; IDDM, insulin-dependent diabetes mellitus; LDL, low-density lipoprotein; M1, maculopathy; NCH, New Cross Hospital; QEH, Queen Elizabeth Hospital; R1, mild to moderate non-proliferative diabetic retinopathy; R2, proliferative diabetic retinopathy; R3, proliferative diabetic retinopathy; SA, South Asian; SANGRA, South Asian Names and Group Recognition Algorithm; SMR, standardised mortality ratio; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes mellitus; TIA, transient ischaemic attack; WE, white European. *p Value <0.05.
in metabolic control between WE (n=112) and SA (n=38) children (median HbA1c 8.4% vs 8.8%, respectively). Thomas et al\textsuperscript{14} in South Africa also found no statistically significant differences between SA (n=118), WE (n=1247) and Africans (n=117) in HbA1c levels (8.7% vs 8.2% vs 9.5%, respectively). A study by Asmal et al\textsuperscript{16} in South Africa showed that SA (n=38) had similar mean glucose concentrations to Africans (n=52) (15.80 mmol/L vs 14.20 mmol/L, respectively).

Ismail et al\textsuperscript{14} in Malaysia showed that SA (n=76) have significantly higher HbA1c levels compared with Chinese (n=91) and Malay (n=102) (mean 9.3% vs 7.8% vs 9.0%, respectively, p<0.001).

In summary, studies suggest SA have higher HbA1c levels compared with WE, Malay and Chinese but lower than Africans.

### Blood pressure

Four studies determined blood pressure/hypertension as an outcome: two comparing SA with WE only, one comparing with WE and Africans and one comparing to Africans only. The three papers with a WE group all showed that SA have lower blood pressure than the comparator groups. Mehta et al\textsuperscript{11} in the UK showed a significantly lower systolic blood pressure in SA (n=163) compared with WE (n=1169) (mean value 136.4 mm Hg vs 141.6 mm Hg, respectively, p<0.004). However, there was no difference in diastolic blood pressure between SA (mean 75.4 mm Hg vs 75.4 mm Hg, respectively, p=0.41). Brabarupan et al\textsuperscript{2} in the UK also showed that SA (n=39) compared with WE (n=565) and Africans (n=38) had a lower systolic blood pressure (median 120 mm Hg vs 130 mm Hg vs 135 mm Hg, respectively, p<0.05) and a lower diastolic blood pressure (median 73 mm Hg vs 75 mm Hg vs 80 mm Hg, respectively, p<0.05). We have previously noted that there was no significant difference in systolic blood pressure between SA and WE (median 121 mm Hg vs 125 mm Hg, respectively, and 130 mm Hg vs 131.5 mm Hg, respectively, in two different centres) in a UK population.\textsuperscript{5} However, we reported that SA (n=59) had a higher diastolic blood pressure than WE (n=118) (median 86 mm Hg vs 82 mm Hg, respectively, p<0.05).\textsuperscript{9}

Lastly, Omar et al\textsuperscript{17} in South Africa showed absence of difference between SA (n=41) and Africans (n=92) in the prevalence of hypertension (5% vs 4%, respectively). The analyses in these studies were not adjusted.

In summary, studies suggest SA have lower systolic blood pressure compared with WE and Africans, but there is no difference in the diastolic blood pressure across these three ethnic groups.

### Lipid profile

Five studies examined differences in lipid profiles: two comparing SA to WE only, one comparing to WE and Africans, one comparing to Africans only and one comparing to Malay and Chinese. A UK study has previously shown that SA (n=80) have lower levels of HDL (median 1.3 mmol/L vs 1.4 mmol/L, respectively, p<0.05) and higher cholesterol/HDL ratio (median 3.6 vs 3.2, respectively, p<0.05) than WE (n=160).\textsuperscript{9} There were no statistically significant differences in the levels of total cholesterol in SA compared with WE (median 4.7 mmol/L vs 4.6 mmol/L, respectively, and 4.45 mmol/L vs 4.11 mmol/L, respectively). Another UK study\textsuperscript{12} also showed that SA (n=39) had lower levels of HDL compared with WE (n=565) but higher levels than Africans (n=38) (median 1.30 mmol/L vs 1.49 mmol/L vs 1.25 mmol/L, respectively, p<0.05). They also demonstrate absence of difference in total cholesterol levels between SA, WE and Africans (median 4.00 mmol/L vs 4.30 mmol/L vs 4.40 mmol/L, respectively) and triglyceride levels (median 1.07 mmol/L vs 0.93 mmol/L vs 0.99 mmol/L, respectively). Mehta et al\textsuperscript{11} in the UK also show similar levels of total cholesterol in SA (n=163) (mean value 4.6 mmol/L) compared with WE (n=1169) (mean value 4.8 mmol/L) (p=0.132).

Ismail et al\textsuperscript{4} in Malaysia demonstrate that SA (n=76) compared with Malay (n=102) and Chinese (91) had no statistically significant differences in total cholesterol levels (mean 5.74 mmol/L vs 5.58 mmol/L vs 5.64 mmol/L, respectively) and LDL cholesterol levels (mean 3.89 mmol/L vs 3.48 mmol/L vs 3.52 mmol/L, respectively). SA had significantly lower HDL cholesterol compared with Chinese (mean 1.28 mmol/L vs 1.57 mmol/L, respectively, p<0.01) and significantly higher triglyceride levels (mean 1.02 mmol/L vs 0.82 mmol/L, respectively, p<0.03). Lastly, Asmal et al\textsuperscript{16} in South Africa found that SA (n=38) compared with Africans (n=52) had no statistically significant differences in cholesterol levels (mean 5.17 mmol/L vs 4.78 mmol/L, respectively) and
triglyceride levels (2.81 mmol/L vs 2.27 mmol/L, respectively).

In summary, SA have lower HDL levels compared with WE and Chinese but higher than Africans. SA have higher triglyceride levels compared with Chinese. There are no differences in total cholesterol between SA and WE, African, Malay or Chinese ethnic groups.

Microvascular disease

Retinopathy

Four studies examined retinopathy; one comparing SA with WE only, two comparing to WE and Africans and one comparing to Africans only. The most relevant study by Sivaprasad et al. investigated retinopathy in T1DM in the UK cohort consisting of 2626 WE, 344 Africans and 120 SA. The mean age in this study was 39.4±16.3 years. The study found no statistically significant differences between SA, WE and Africans with T1DM in the age-standardised prevalence of maculopathy (95% CI) (16.6% (10% to 23.2%) vs 14.1% (12.8% to 15.4%) vs 13.1% (9.4% to 16.8%), respectively), clinically significant macular oedema (11.2% (5.4% to 16.9%) vs 6.5% (5.6% to 7.4%) vs 10.0% (6.7% to 13.5%), respectively), sight threatening diabetic retinopathy (17.5% (10.6% to 24.3%) vs 12.1% (10.9% to 13.3%) vs 15.9% (11.8% to 20.0%), respectively) and any diabetic retinopathy (54.0% (44.8% to 63.2%) vs 55.0% (53.2% to 56.9%) vs 42.8% (37.3% to 48.3%), respectively).

Thomas et al. in South Africa, reported that SA (n=118) were at increased risk of any diabetic retinopathy (OR 2.02, 95% CI 1.23 to 3.29) when compared with WE (n=1247), after adjustment for age at diagnosis, sex, duration of diabetes, HbA1c, hypertension and smoking status. Mehta et al. in the UK showed that SA (n=163) compared with WE (n=1169) had decreased prevalence of retinopathy (38.7% vs 48.0%, respectively, p=0.025). Lastly, Omar et al. 17 in a South African study, compared SA (n=41) to Africans (n=92) and were unable to demonstrate a statistically significant difference in the prevalence of retinopathy (22% vs 14%, respectively).

In summary, there is no difference in the prevalence of retinopathy between SA, WE and African ethnic groups.

Nephropathy

Five studies explored nephropathy and renal function as an outcome in SA with T1DM: two papers comparing to WE only, one comparing to WE and Africans and two papers comparing to Africans only. The largest study, by Mehta et al. in the UK did not show any differences between SA (n=163) and WE (n=1169) in the prevalence of nephropathy (13.5% vs 10.1%, respectively, p=0.184).

In another UK study, no statistically significant differences were found between SA (n=80) and WE (n=160) in creatinine levels (median 76 µmol/L vs 78 µmol/L, respectively), albumin/creatinine ratio (median 2.4 mg/mmol vs 2.5 mg/mmol, respectively) and eGFR (median 97.3 mL/min/1.73m² vs 91.2 mL/min/1.73m², respectively). Brabarupan et al. in the UK showed no difference in the prevalence of microalbuminuria between SA (n=39) and WE (n=565) (median 1.2 mg/mmol vs 1.2 mg/mmol, respectively); however, Africans (n=38) had significantly higher levels (median 3.7 mg/mmol) (p<0.05). There were two studies in South Africa comparing SA to Africans. The first by Omar et al. showed in their cohort of SA (n=41) and Africans (n=92), there was absence of difference in the prevalence of nephropathy (7% vs 3%, respectively). Asmal et al. also showed no statistically relevant difference between SA (n=38) and Africans (n=52) in creatinine levels (mean 68.90 µmol/L vs 79.40 µmol/L, respectively).

In summary, there is no difference in the prevalence of nephropathy or difference in renal function between SA and WE. However, in one study, SA had lower levels of microalbuminuria compared with Africans.

Neuropathy

Three studies included neuropathy as an outcome in SA: one comparing to WE only and two comparing to Africans only. The most relevant study, Mehta et al. in the UK, showed that SA (n=163) compared with WE (n=1169) have a lower prevalence of neuropathy (14.7% vs 27.8%, respectively, p<0.001). Omar et al. compared SA (n=41) to Africans (n=92) in South Africa demonstrating no statistically significant differences in the prevalence of peripheral neuropathy (32% vs 22%, respectively) and autonomic neuropathy (5% vs 4%, respectively). Asmal et al. in South Africa showed increased prevalence of neuropathy in SA (n=38) compared with Africans (n=52) (19% vs 4%, respectively); however, no statistical tests were performed.

In summary, SA have lower prevalence of neuropathy that WE. There is no difference noted in the prevalence of neuropathy between SA and Africans.

Macrovascular disease

Two studies reported cardiovascular outcomes: one comparing to WE only and the other comparing to Africans only. The largest of these studies, by Mehta et al. in the UK, did not show evidence of difference between SA (n=163) and WE (n=1169) with T1DM in prevalence of cardiovascular disease (15.3% vs 11.3%, respectively, p=0.133). Subanalysis also did not reveal a difference between SA and WE in ischaemic heart disease (12.3% vs 8.3%, respectively, p=0.093), peripheral vascular disease (1.8% vs 2.7%, respectively, p=0.79) and cerebrovascular disease (3.7% vs 1.8%, respectively, p=0.13). It is important to note that the mean age in the T1DM group was lower (mean age of SA 41.9 years and WE 45.3 years) compared with T2DM (mean age 59.2 years SA and 66.2 years WE) which may have led to an under-representation of cardiovascular outcomes in the T1DM group.

A second study compared peripheral arterial disease between SA and Africans in South Africa. Omar et al. showed that none of their participants in either the SA (n=41) or African group (n=92) had peripheral vascular disease.
disease or ischaemic heart disease. This may also be due to their younger cohort of patients and small sample size.

In summary, the prevalence of cardiovascular disease between the SA, WE and African populations do not differ.

**Mortality**

Only one study examined the association of SA ethnicity on mortality in people with T1DM. Swerdlow et al. in a UK study investigated mortality of SA patients compared with the non-SA population, approximately 97% of which were Caucasian. The patients were followed for up to 28 years. In their cohort of 424 SA patients there were 27 deaths (6.4%) and in 23326 non-SA there were 1293 deaths (5.5%). Mortality in SA and non-SA with T1DM was calculated independently by comparing with the general population mortality using standardised mortality ratios (SMRs). Compared with the reference population, the SMR for SA patients were 3.9 (95% CI 2.0 to 6.9) in men and 10.1 (6.6 to 16.6) in women. The SMR for the corresponding non-SA were 2.7 (2.6 to 2.9) in men and 4.0 (3.6 to 4.3) in women. No details are provided as to the age of death in these patients. The most common causes of death in SA patients were cardiovascular disease (29.6%) and renal disease (14.8%). The ‘other’ causes of death accounted for eight deaths (29.6%) and included sepsis, systemic lupus erythematosus, bronchopneumonia, unspecified urinary tract infection and congenital malformation. The most common causes of death in non-SA were cardiovascular disease (n=474, 36.7%) and diabetes and hypoglycaemia (n=239, 18.5%). There was 1 death due to neoplasm in SA (3.7%) and 89 in non-SA (6.9%).

In summary, mortality is higher in SA with T1DM than non-SA when compared with the reference population in the UK. SA females were in particular affected, with an SMR that was over twice that of the non-SA female T1DM population. The most common cause of death was cardiovascular disease.

**DISCUSSION**

This is the first systematic review to examine the differences in comorbidities, microvascular complications, macrovascular complications and mortality between SA and other ethnic groups with T1DM. In summary (see table 2), mortality is higher in SA with T1DM when compared with a largely WE reference population. Female SA were in particular affected, with a SMR that was over twice that of the non-SA female T1DM population. The most common cause of death was cardiovascular disease.

Overall, the studies suggest that cardiovascular disease itself is no more common in SA T1DM compared with WE. The study by Mehta et al. that examined cardiovascular disease most clearly, studied a population with a mean age in their early 40s, and is likely to be too young for cardiovascular disease to manifest clinically. While they observed a 50% higher risk of ischaemic heart disease (12.3% vs 8.3%) and twice the risk of cerebrovascular disease (1.8% vs 3.7%) in SA compared with WE, the study had less than 30% power to detect a statistically significant difference. Some risk factors for cardiovascular disease appear greater in SA, with lower HDL than WE and the Chinese and higher HbA1c. However, the most powerful risk factor for cardiovascular disease of systolic BP is lower than in WE.

Most studies also suggest SA have higher HbA1c levels than WE, Malay and Chinese but lower than African ethnic groups. Despite this, rates of retinal and nephropathic microvascular disease were the same as the WE population and some (neuropathy) even lower. There is an issue around competing risk however, as SA with T1DM may die at a younger age before developing retinopathy.

Compared with Africans, SA had lower levels of microalbuminuria, lower HbA1c, lower systolic blood pressure and higher HDL levels. There were no statistically significant differences between these two ethnic groups in the remaining complications: cardiovascular disease, retinopathy and neuropathy. There was also no difference in BMI.

**Weaknesses**

There are several weaknesses with the analysis. The quality of the studies was poor with most studies being retrospective observational or cross-sectional. It was not possible to undertake a meta-analysis of the combined studies because the results were heterogeneous in nature.

The studies included in the analysis are derived from a large range of years (1981 until 2015), a time period during which diabetes treatment and prevention of complications has changed dramatically. Ideally, the analysis should specifically consider studies which compared the different ethnic groups during the same period of observation with similar standards of therapy to eliminate bias.

Furthermore, we accepted a clinical diagnosis for T1DM in the included studies. Some studies simply relied on coding of T1DM in their clinical systems as inclusion criteria with other studies accepting a younger age of diagnosis (<30/35 years of age) and insulin dependency as their inclusion criteria. As we did not have a standardised criterion for the diagnosis of T1DM for the included studies, it may well be that some patients with juvenile-onset T2DM requiring insulin treatment may have been wrongly coded as having T1DM.

Moreover, the papers in our review did not include data on medication use which makes it unclear whether differences in blood pressure, HbA1c and lipid profiles were primarily due to ethnicity or because of differences in medication use.

Lastly, data from patients with SA ethnicity living in the UK and abroad were pooled. Prevalence of T2DM is higher in migrant SA compared with native SA thought to be secondary to urbanisation and lifestyle. It is likely that prevalence and complication rates of T1DM would also be different in migrant and native SA and
therefore grouping them together may cause inaccuracy of reporting of the results.

Strengths
The strengths of this analysis are its comprehensive search strategy with clearly defined population and outcomes. Our search strategy incorporated both full-length papers as well as abstracts, included all languages and had a secondary search strategy to ensure we did not miss any relevant papers. We compared the SA group, the largest ethnic group globally with all other indigenous ethnic groups.

Implications
Our analysis highlights two areas. First, the ethnic disparity in mortality that has previously been described in T2DM is also present for SA patients with T1DM. This disparity is most likely due to cardiovascular disease but this association remains to be proven. Given the close association between glycaemic control with cardiovascular disease and excess mortality in T1D, and the higher HbA1c in the SA population, the findings of this systematic review call for more aggressive glycaemic control in the SA T1D population. Previous literature has demonstrated how SA have increased adiposity in comparison with WE and have advocated lower cut-offs for BMI in SA; BMI >23 kg/m$^2$ as overweight and BMI >25 kg/m$^2$ as obese. These culturally tailored programmes that have been attempted for T2DM may also be required for T1DM.

In addition, we may require more stringent control of other comorbidities such as hyperlipidaemia and hypertension, though this needs to be formally addressed. Second, we highlight a need for a large, ideally prospective, multinational study exploring the effect of ethnicity in a uniform healthcare setting. This will enable consistent methodology, and standardised reporting of comorbidities and complications such as those mentioned previously, but also complications such as peripheral vascular disease, depression and bone fractures that have not previously been addressed.

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Contributors
KNS: involvement in the design of the work, data collection, data analysis, writing the paper, drafting and revision of the paper. PC: involvement in the design of the work, data collection, data analysis, helped with drafting and revision of the paper. PS: involvement in the design of the work, reviewed all drafts of the paper, helped with revision of the paper. PN: responsible for the conception and design of the work, reviewed all drafts of the paper, helped with revision of the paper.

Competing interests
KK (co-chair), PS and PN are the members of the South Asian Health Foundation Working group on diabetes.

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Comorbidities, complications and mortality in people of South Asian ethnicity with type 1 diabetes compared with other ethnic groups: a systematic review

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