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Ethnic differences in risk factors, complications and mortality in people of South Asian ethnicity with type 1 diabetes: a systematic review

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Complete List of Authors:	Sarwar, Komil; University of Birmingham, Cliff, Phoebe; University of Birmingham Saravanan, Ponnusamy; University of Warwick Warwick Medical School, ; George Eliot Hospital, Khunti, Kamlesh; University of Leicester, Department of Health Sciences Nirantharakumar, Krishnarajah; University of Birmingham Narendran, P; University of Birmingham,
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Title Page

Title of Paper: Ethnic differences in risk factors, complications and mortality in people of South Asian ethnicity with type 1 diabetes: a systematic review

Authors: Komil N Sarwar (Foundation Doctor)[1], Phoebe Cliff (Foundation Doctor)[1], Ponnusamy Saravanan (Associate Clinical Professor)[2], Kamlesh Khunti (Professor of Primary Care Diabetes and Vascular Medicine)[3], Krishnarajah Nirantharakumar (Senior Clinical Lecturer)[1], Parth Narendran (Reader in Diabetes Medicine)[1]

Institution(s) of origin: University of Birmingham, Edgbaston, Birmingham, B152TT[1]
University of Warwick, Coventry, CV4 7AL[2]
University of Leicester, University Road, Leicester LE1 7RH[3]

Corresponding author: Dr Krishnarajah Nirantharakumar

Public Health, Epidemiology and Biostatistics, University of Birmingham, Edgbaston Birmingham, B15 2TT, UK

Telephone: 44 (0)121 414 8344

Fax: +44 (0)121 414 6217

Email: k.nirantharan@bham.ac.uk

Conflicts of Interest: KK (Co-Chair) PS and PN are members of the South Asian Health Foundation Working group on Diabetes.

What is already known in this subject

- In contrast to type 2 diabetes, very little is known of the effect of South Asian ethnicity on the natural history of type 1 diabetes
- The majority of studies looking at ethnic disparities in type 1 diabetes have been conducted in the United States of America and thus their primary focus was on the black and Hispanic ethnic groups.
- South Asians comprise 20% of the global population and 7% of the UK population and there is a great need to understand the effect of South Asian ethnicity on the natural history of type 1 diabetes

What this study adds

- Our review demonstrates South Asians with type 1 diabetes have a higher mortality than white Europeans
- South Asians have poorer HbA1c control than white Europeans but better than people of African and African-Caribbean (AC) origin
- South Asians have similar rates of retinopathy and nephropathy to white Europeans but lower rate of nephropathy than people of AC origin

Ethnic differences in risk factors, complications and mortality in people of South Asian ethnicity with type 1 diabetes: a systematic review

Komil N Sarwar, Phoebe Cliff, Ponnusamy Saravanan, Kamlesh Khunti, Krishnarajah Nirantharakumar, Parth Narendran

Abstract

Objective. The epidemiology of Type 1 Diabetes (T1DM) in South Asians (SA) is poorly understood. In contrast, we know that Type 2 diabetes (T2DM) is 2-3 times more common in SAs than in the White European (WE) population. Furthermore, SA with T2DM develop the condition 5-10 years earlier than WE, have worse outcomes and die at a younger age. We aimed to conduct a systematic review to determining differences in risk factors, microvascular and macrovascular complications, and mortality in SA compared to other ethnic groups in patients with T1DM.

Design. Systematic Review

Data Sources. T1DM was searched for in SA ethnic groups in Medline and Embase.11 studies were included.

Results. Our review demonstrates SAs (and particularly female SAs) with T1DM have higher mortality compared to WE and suggests this increased mortality is contributed to by excess cardiovascular disease. SAs also have significantly higher HbA1c than WE. Despite this higher HbA1c, rates of microvascular disease appeared similar to the WE population and some (neuropathy) even lower. SAs have lower levels of HDL cholesterol, and smoking rates were half that of WE. Compared to AC, 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 outcomes: cardiovascular disease, retinopathy, neuropathy and BMI. We also demonstrate that SA have higher HbA1c levels than both Malay and Chinese and higher waist-hip ratio and lower HDL levels compared to Chinese only.

Conclusion. Our analysis highlights ethnic disparity in macrovascular outcomes that is so evident for T2DM may also be present for SA patients with T1DM. Secondly, we highlight a need for a large, ideally prospective, cohort study exploring the effect of ethnicity in a uniform healthcare setting.

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.

Weaknesses

- The quality of the studies were poor with the majority of studies being retrospective observational or cross-sectional.
- It was also not possible to undertake a meta-analysis of the combined studies because the results were heterogeneous in nature.
- 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 (T1DM) in South Asians (SA) is poorly understood. It's effects on metabolic control, diabetic complication rate, or indeed the underlying pathogenesis has yet to be explored. In contrast, we know that Type 2 Diabetes (T2DM) is 2-3 times more common in SAs than in the White European (WE) population in the United Kingdom[1], and up to three times more common among people of African and African-Caribbean (AC) origin[2]. 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[1,3]. These differences have not been explored in people with T1DM.

A study by Willi et al[4] 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 to white or Hispanic participants. A recent systematic review[5] identified 16 studies in the current literature that showed racial/ethnic minority youth with T1DM having higher HbA1c compared to Caucasian youth. As the majority of these studies are conducted in the United States of America, their primary focus was on the black and Hispanic ethnic groups and youth with T1DM.

SAs comprise 20% of the global population[1] and 7% of the UK population[7]. Furthermore, the incidence of T1DM appears to be similar in SA as in the background population[7]. Therefore, there is a need to understand the effect of ethnicity on the natural history of T1DM. The aim of this systematic review is to explore the association of SA ethnicity on risk factors, microvascular and macrovascular complications, and mortality compared to 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. Full length papers and abstracts were included in the search from 1946 to February 2016. The search was not limited to a particular language, 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 on-going research. Further information pertaining to the search strategy can be found in Appendix 1.

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 risk factors, complications and mortality to persons of any other ethnicity not classified as SA. The outcomes investigated were body mass index, systolic and diastolic blood pressure, HbA1c, lipid profile and smoking status (risk factors); retinopathy, neuropathy and nephropathy (microvascular complications); ischaemic heart disease and cerebrovascular disease (macrovascular complications); 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 (Appendix 2). The Newcastle-Ottawa Quality Assessment Scale for observational studies was used for quality assessment[8].

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 South Asian ethnicity was defined. The results have been analysed as a narrative and presented as tabulations with textual description by each risk factor and outcome.

Patient Involvement: Patients were not involved.

Results

The initial search identified 4,722 papers. After removing duplicates (1,194), the remaining 3,528 titles and abstracts were screened. After excluding 3,223 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 1 paper (Figure 1). A total of 11 studies were therefore included: 6 studies were from the United Kingdom, 4 from South Africa and 1 from Malaysia. Nine of the papers were full length papers and 2 were abstracts. Of the included articles, 1 was a prospective cohort study[9], 3 were retrospective analysis of observational data[11, 14-15]. The remaining 7 studies were cross-sectional analyses[10, 12-13, 16-19]. The results are summarised in Table 1 and Table 2.

Figure 1: Flowchart demonstrating Study Selection

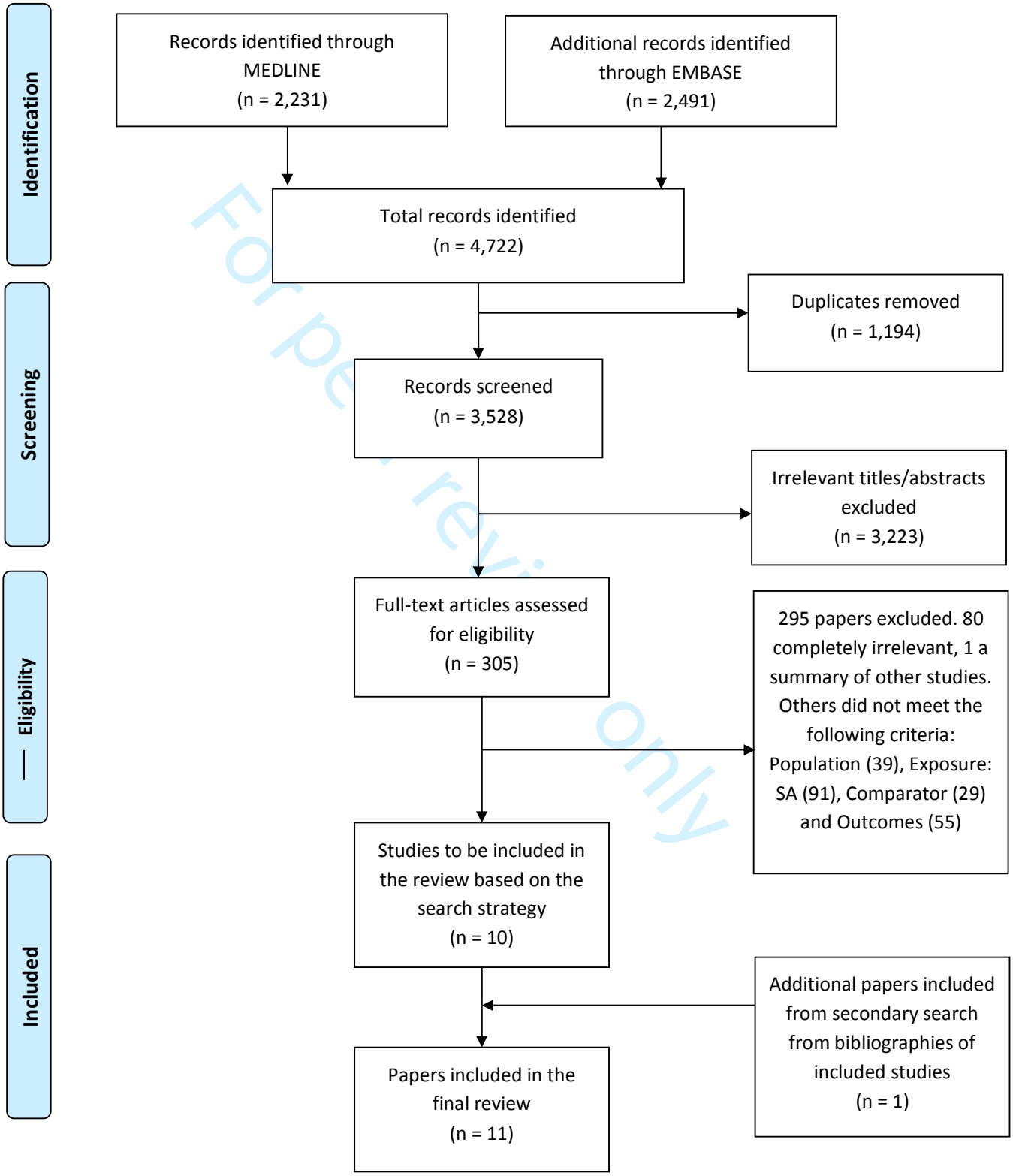

Table 1: Data extraction of studies included in systematic review

Study & year published	Country	Design	Method and Description	Number of Participants & Ethnic Group	Age description	Duration of Study	Key Outcomes
Studies involving a control group							
Swerdlow et al[9] 2004	UK	Prospective Cohort Study	**South Asian Ethnicity** South Asians identified by computer algorithm (SANGRA) followed by a clerical check by an individual with expertise in this area. Patients with IDDM diagnosed <30 years **Method** SMRs calculated, comparing mortality in the cohort to the corresponding mortality rates in the general population	Non South Asian : 23, 326 South Asian: 424	N/A	1972 – 1999	**Mortality** The Standardised Mortality Ratios (SMR) for South Asian patients diagnosed <30 years were 3.9(95% CI 2.0-6.9) in men and 10.1 (5.6-16.6) in women, and in the corresponding non-South Asians were 2.7 (2.6-2.9) in men and 4.0 (3.6-4.3) in women.
Mehta et al[10] 2011	UK	Cross-sectional study	**South Asian (SA) Ethnicity** Ethnicity was categorised as SA or white European (WE) based on patient record documentation or by analysis of their name using a validated name recognition software 'Nam Pechan' supplemented by a visual inspection of surnames and forenames. **Method** Patient characteristics and other data were extracted from the clinical workstation (CWS), a clinical database of patients attending a specialist outpatient diabetes clinic in Leicestershire.	WE: 1,169 SA: 163	**Mean age (years)** WE: 45.3 SA: 41.9	2003-2005	**South Asian (n = 163)** / **White European (n = 1169)** / **p Value** **Number of comorbidities (n (%))** 0: 114 (69.9) / 878 (75.1) / 0.166 1: 36 (22.1) / 235 (20.1) ≥2: 13 (8.0) / 56 (4.8) **Macrovascular (n (%))** CVD: 25 (15.3) / 132 (11.3) / 0.133 Ischaemic heart disease: 20 (12.3) / 97 (8.3) / 0.093 Peripheral vascular disease: 3 (1.8) / 31 (2.7) / 0.790 Cerebrovascular disease: 6 (3.7) / 21 (1.8) / 0.130 TIA: 0 / 2 (0.2) / 1.000 **Microvascular (n (%))** Retinopathy: 63 (38.7) / 561 (48.0) / 0.025 Neuropathy: 24 (14.7) / 325 (27.8) / <0.001 Nephropathy: 22 (13.5) / 118 (10.1) / 0.184 **Glycaemic control (n (%))** / **(n = 163)** / **(n = 1169)** HbA1C < 7%: 19 (12.0) / 193 (17.0) / 0.113 HbA1C ≥7%: 144 (88.0) / 976 (83.0)
Shenoy et al[11] 2004	UK	Retrospective Observational	**South Asian Ethnicity** **Method** Rates of obesity/overweight in white	WE: 112 SA: 38	**Age Group (n)**	N/A	**Demographic Data** 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% v 8.8% respectively for WE/SA).

		Study	Caucasian and South Asian groups, and to correlate these with age, duration of diagnosis, daily insulin requirement, and HbA1c. Included children between the ages of 2 and 18 years and who had been diagnosed more than a year ago.		2-4 yrs (3) 5-9 yrs (33) 10-15 yrs (90) 16-18 yrs (24)		**Obesity in children** No statistically significant differences noted in the rates of overweight or obesity between white Caucasian and South Asian children at any age grouping.
Sivaprasad et al[12] 2012	UK	Cross-sectional study	**Ethnicity** Self-reported ethnicity based on UK census standard (Census 2001): categorised as 'White European', 'African/Afro-Caribbean', 'South Asian', 'Mixed', 'other ethnic group' and 'not known'. **Method** To assess ethnic variations of the prevalence of DR and visual impairment in two multi-racial cohorts in the UK (Yorkshire and South East London)	WE: 2,628 Afro-Caribbean: 344 SA: 120	Mean age of T1DM population: 39.4 yrs	2008-2009	**Ethnic group** / **Prevalence: N (%)** / **Age-standardised prevalence: % (95% CI)** **Any diabetic retinopathy** White Europeans: 1446 (55.0) / 55.0 (53.2, 56.9) African/Afro-Caribbean: 154 (44.8) / 42.8 (37.3, 48.3) South Asian: 64 (53.3) / 54.0 (44.8, 63.2) **Any maculopathy (M1)** White Europeans: 371 (14.1) / 14.1 (12..8, 15.4) African/Afro-Caribbean: 47 (13.7) / 13.1 (9.4, 16.8) South Asian: 17 (14.2) / 16.6 (10.0, 23,2) **CSMO (M1P1)** White Europeans: 171 (6.5) / 6.5 (5.6, 7.4) African/Afro-Caribbean: 35 (10.20 / 10.0 (6.7, 13.3) South Asian: 12 (10.0) / 11.2 (5.4, 16.9) **STDR (R2 or R3 or M1P1)** White Europeans: 318 (12.1) / 12.1 (10.9, 13.3) African/Afro-Caribbean: 53 (15.4) / 15.9 (11.8, 20.0) South Asian: 19 (15.8) / 17.5 (10.6, 24.3)

							CSMO- clinically significant macular oedema; M1- maculopathy P1- macular laser; STDR- sight threatening diabetic retinopathy; R1- mild to moderate non-proliferative diabetic retinopathy; R2- pre-proliferative diabetic retinopathy; R3- Proliferative diabetic retinopathy
Brabar upan et al[13] 2013	UK	Cross-section al study	**Ethnicity** Grouped into White European (WE), Afro-Caribbean (AC) and South Asian (SA) **Method** Data from patients diagnosed with T1DM below 35 years of age, from WE, AC or SA ancestry was obtained from an electronic database in a large multiethnic London diabetes clinic.	642 individuals in total WE: 564 SA: 39 AC: 39	Median age at diagnosis (years) WE: 16.7 AC: 19.4 SA: 19.1	N/A	**Parameters median (IQR)** / **White European (WE)** / **African Caribbean (AC)** / **South Asian (SA)** / **Significant** **BMI (kg/m2)** / 25.0 (22.3-27.7) / 25.7 (22.5-28.9) / 25.3 (22.2-28.5) / NEEDS p Value **Systolic BP (mm/Hg)** / 130 (119-141) / 135 (121-149) / 122 (1120133) / P<0.05 **Diastolic BP (mmHg)** / 75 (69-81) / 80 (72-88) / 73 (67-79) / P<0.05 **HbA1c (%)** / 8.0(7.1-8.9) / 9.1 (7.6-10.7) / 8.3 (7.5-9.2) / P<0.05 **Microalbuminuria (mg/mmol)** / 1.2 (-0.5-3.0) / 3.7 (-44.5-51.9) / 1.2 (-1.4-3.8) / P<0.05 **Total Cholesterol (mmol/L)** / 4.50 (3.90-5.10) / 4.40 (3.90-4.90) / 4.00 (3.2-4.8) **HDL (mmol/L)** / 1.49 (1.21-1.77) / 1.25 (0.95-1.56) / 1.30 (1.47-1.14) / P<0.05 **Triglyceride (mmol/L)** / 0.93 (0.59-1.28) / 0.99 (0.58) / 1.07 (0.76-1.39)
Sarwar et al[14] 2015	UK	Cross sectional Study	**Ethnicity** South Asian and White Caucasian **Method** Data analysed from two centres in the West Midlands (Queen Elizabeth Hospital [QEH] and New Cross Hospital [NCH])	White Caucasian: 278 South Asian: 139	Median age (years) NCH Caucasian: 34 NCH SA: 33.5 QEH Caucasian: 36	N/A	**Characteristic (number of patients)** / **NCH South Asian (80)** / **NCH Caucasian (160)** / **QE South Asian (59)** / **QE Caucasian (118)** **HbA1c (mmol/mol)** / 75 (61.5-88.5) / 76 (63-91) / 66.1 (55.25-81.75) / 70.5 (61-83.6) **Systolic BP (mmHg)** / 121 (113-132) / 125 (115-132) / 130 (120.5-141.5) / 131.5 (120.3-144) **Diastolic BP (mmHg)** / - / - / 86 (80.5—90)* / 82 (77.25-88.75)* **BMI (kg/m2)** / 25.6 (22.55- / 25.7 (22.5-30.4) / 30.9 (22.8-37) / 25 (22.6-28)

					QEH SA: 36		28.4) **Total Cholesterol (mmol/L)** 4.7(3.9-5.45) 4.6 (4-5.3) 4.45 (3.8-5.45) 4.1 (3.7-4.95) **HDL (mmol/L)** 1.3 (1.0-1.6)* 1.4 (1.2-1.65)* - - **Cholesterol/ HDL** 3.6 (2.9-4.5)* 3.2 (2.7-4.0)* - - **Creatinine level (µmol/L)** 75 (66-87) 78 (69-87) - - **eGFR (ml/min/ 1.73m2)** 97.3 (82.2-109.9) 91.2 (79.3-103.9) - - **Albumin/ Creatinine ratio (mg/mmol)** 2.4 (0.7-3.6) 2.5 (0.75-3.5) - - *P value <0.05
Thomas et al[15] 2012	South Africa	Retrospective observational study	**Ethnicity** Caucasian, Indigenous African, Asian and mixed race. No description of how ethnicity identified. **Method** Retinal photography was conducted using a non-mydriatic digital camera without mydriasis and graded by one of three senior graders.	Caucasian: 1247 Indigenous African: 117 Asian: 118 Mixed race: 49	Mean age (yrs) Caucasian: 35.7 Indigenous African: 36.3 Asian: 32.2 Mixed race: 32.6	2001-2010	**Diabetic Retinopathy (DR)** **Any DR (n=541)** **RDR (n=142)** **Crude OR (95% CI)** **Adjusted OR (95% CI)** **Crude OR (95% CI)** **Adjusted OR (95% CI)** **Caucasian (1,247)** 1.00 1.00 1.00 1.00 **Indigenous African (117)** 0.71 (0.46-1.09) 1.72 (1.00-2.97) 0.95 (0.49-1.84) 3.40 (1.40-8.26) **Asian (118)** 1.10 (0.74-1.63) 2.02 (1.23-3.29) 1.05 (0.54-2.04) 2.07 (0.90-4.75) **Mixed race (49)** 1.01 (0.56-1.84) 1.29 (0.62-2.69) 1.10(0.42-2.88) 1.06 (0.36-3.18)
Omar et al[16] 1984	South Africa	Cross-sectional analysis	**Ethnicity** 2 groups: Indians and Blacks. No methodology for ethnicity identification provided	Blacks: 92 Indians: 41	Mean age at onset (yrs)	Not mentioned	**Complications** **Blacks** **Indians** **Total** **Keto-acidosis** 53 (58%) 22 (54%) 75 (56%) **Neuropathy peripheral** 20 (22%) 13 (32%) 33 (25%) 4 (4%) 2 (5%) 6 (5%)

			Method Patients from King Edward VIII Hospital in Durban fulfilling WHO diagnostic criteria for insulin dependent diabetes mellitus. Both case records obtained and a physical examination performed to assess complications.		Blacks: 17 Indians : 23.5		**autonomic** **Retinopathy** 13 (14%) 9 (22%) 22 (17%) **Nephropathy** 3 (3%) 3 (7%) 6 (5%) **Triopathy** 1 (1%) 2 (5%) 3 (2%) **Ischaemic heart disease** - - - **Hypertension** 4 (4%) 2 (5%) 6 (5%) **Cataracts** 5 (5%) 2 (5%) 7 (5%) **Tuberculosis** 6 (7%) 1 (2%) 7 (5%)
Asmal et al[17] 1981	South Africa	Cross-sectional analysis	**Ethnicity** 2 groups: Indians and Blacks. No methodology for ethnicity identification provided **Method** Clinic patients who fulfilled the following criteria: age of diagnosis of diabetes <35 years, development of symptoms +/- ketosis in the absence of insulin therapy, and duration of diabetes of at least 12 months. Case records examined, clinical assessments and biochemical tests carried out	Blacks: 52 Indian: 38	Mean age at onset (years) Blacks: 21.8 Indian: 18.0	4 weeks	**Basic Biochemical Data** **Indians** **Blacks** **Glucose (mmol/l)** 15.80 ± 1.50 14.20 ± 1.50 **Growth hormone (ng/ml)** 3.00 ± 0.76 1.76 ± 0.41 **Cortisol (µg/dl)** 16.20 ± 1.47 15.80 ± 1.40 **Cholesterol (mmol/l)** 5.17 ± 0.32 4.78 ± 0.26 **Triglyceride (mmol/l)** 2.81 ± 0.97 2.27 ± 0.83 **Creatinine (µg/dl)** 68.90 ± 4.10 79.40 ± 6.70 **Complications** Chronic complications associated with micro-angiopathy were detected in 12 Indians (33%) and 2 Blacks (4%). Commonest complication was neuropathy found in 19% of Indian diabetics and in 4% of Black diabetics. 2 Indians had evidence of diabetic triopathy.
Ismail et al[18] 2001	Malaysia	Cross Sectional study	**Ethnicity** 3 groups: Indian, Malay and Chinese. Each ethnic group identified by appearance, language and religion. **Method** Patients recruited from 7 centres throughout Peninsular Malaysia. Blood taken for lipid levels, clinical history and physical examination performed. T1DM defined as acute symptoms associated with heavy ketonuria (>3+) or ketoacidosis at diagnosis, or continuous treatment with insulin within 1 year of diagnosis.	Indian: 154 Malay: 297 Chinese: 128	Mean age (years) All: 28.8 Indian: 29.1 Chinese: 29.8 Malay: 27.7	June 1997-June 1998	**Demographic Features** **Malay (n = 297)** **Chinese(n=128)** **Indian (n=154)** **BMI (kg/m2)** 26.8 ± 4.9 25.4 ± 4.5 25.5 ± 4.3 **Waist-hip ratio** A: 0.88 ± 0.06 A: 0.88 ± 0.07 A: 0.89 ± 0.06 M: 0.91 ± 0.06 M: 0.90 ± 0.06 M: 0.93 ± 0.06 F: 0.86 ± 0.06 F: 0.85 ± 0.07 F: 0.85 ± 0.06 **HbA1c (%)** 8.8 (8.6-9.1) 8.0 (7.7-8.3) 8.5 (8.2-8.8) **Lipid Profiles (mmol/L, mean +/- SEM)** **Total Cholesterol** : Indians (5.74 +/- 1.25), Chinese (5.64 +/- 1.42), Malay (5.58 +/- 1.38) **LDL Cholesterol :** Indians (3.89 +/- 1.20), Chinese (3.52 +/- 1.22), Malay (3.48 +/- 1.12) **HDL Cholesterol** (mean[95% CI]) : Indians (1.28 [1.19-1.38]), Chinese (1.57 [1.48-1.67]), Malay (1.37 [1.28-1.46]) **Triglycerides** (mean[95% CI]): Indians (1.02 [0.9-1.16]), Chinese (0.82 [0.74-0.91)], Malay (1.11 [0.99-1.23])

Omar et al[19] 1984	South Africa	Cross sectional analysis	**Ethnicity** 2 groups: Indians and Africans **Method** Classification of diabetes based on criteria by National Diabetes Data Group and WHO expert committee. T1DM patients had always depended on insulin for control of symptoms and prevention of basal ketosis. All patients diagnosed <35 years of age	African T1DM: 86 Indian T1DM: 40	Mean age of onset (range) African: 23.5 (1-35) yrs Indian: 17 (1-35)	2 year period	**Clinical characteristics of T1DM patients** **Characteristic** — **Africans (n=86)** — **Indians (n=40)** **Male: Female** — 21: 25 — 17: 24 **Mean % ideal body weight** — 106 (68-153) — 91 (71-136) **Mean duration of disease (years)** — 3.8 (1-27) — 5.4 (1-22) **Mean age of onset** — 23.5 (1-35) — 17 (1-35)

Table 2: Summary of Findings

	Findings in the SA population when compared to the specified ethnicity (e.g. SA have the same BMI as WE, but higher HbA1c)		
	WE	**AC**	**Chinese**
BMI	→	→	
HbA1c	↑	↓	↑
SBP	↓	↓	
DBP	→	→	
HDL	↓	↑	↓
Total Chol	→	→	→
Smoking	↓		
Retinopathy	→	→	→
Nephropathy	→	↓	
Neuropathy	↓	→	
CVD	→	→	
Mortality	↑		

Results

Risk Factors

Body Mass Index (BMI)

Six studies explored BMI and general weight measurements as an outcome: three comparing SA with WE only, one comparing with WE and AC, one comparing with AC only, and one comparing to Malay and Chinese. The three papers comparing SA to only WE demonstrated no statistically significant difference in BMI[10, 11, 14]. Mehta et al[10] in the UK showed a mean BMI (kg/m^2) of 27.5 in SA (n=163) compared with 27.4 in WE (n=1169) (p=0.835)[2]. Similarities in BMI (kg/m^2) between SA and WE have previously been reported in two different centres (median BMI 25.6 vs. 25.7 respectively and 30.9 vs. 25 respectively) [14] The results were not significant due to the small number of participants. Shenoy et al[11] 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[13] in the UK showed no statistically significant difference in BMI (kg/m^2) in SA (n=39) compared to WE (n=565) and AC (n=38) (median 25.3 vs. 25.0 vs. 25.7 respectively). Omar et al[19] in South Africa also showed no difference between SA (n=40) and AC (n=86) in mean % ideal body weight (91 vs. 106 respectively).

Lastly, a study by Ismail et al[18] in Malaysia showed that there was no difference in BMI (kg/m^2) when comparing SA to Malay and Chinese (mean 22.0 vs. 22.3 vs. 22.0 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 AC with T1DM. However SA males compared to 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 AC, one comparing to AC only and one comparing with Malay and Chinese. Mehta et al[10] 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[13] in the UK who demonstrate SA (n=39) having higher HbA1c (%) levels (median 8.3) compared to WE (n=565) (median 8.0) but lower than AC (n=38) (median 9.1) (p<0.05). Another UK study analysed SA and WE at two different hospitals[14] 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 in[11] the UK found no significant difference in metabolic control between WE (n=112) and SA (n=38) children (median HbA1c 8.4% v 8.8% respectively). Thomas et al[15] in South Africa also found no statistically significant differences between SA (n=118), WE (n=1247) and AC (n=117) in HbA1c (%) levels (8.7 vs. 8.2 vs. 9.5 respectively). A study by Asmal et al[17] in South Africa showed that SA (n=38) had similar mean glucose concentrations (mmol/l) to AC (n=52) (15.80 vs. 14.20 respectively).

Ismail et al[18] in Malaysia showed that SA (n=76) have significantly higher HbA1c (%) levels compared to 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 to WE, Malay and Chinese but lower than AC ethnic groups.

Blood Pressure

Four studies determined blood pressure/hypertension as an outcome: two comparing SA with WE only, one comparing with WE and AC and one comparing to AC only. The three papers with a WE group all showed that SA have lower blood pressure than the comparator groups. Mehta et al[10] in the UK, showed a significantly lower systolic blood pressure in SA (n=163) compared with WE (n=1169) (mean value 136.4 vs. 141.6 mmHg respectively; p=0.004). However, there was no difference in diastolic blood pressure between SA (mean 75.4 vs. 75.4 mmHg respectively; p=0.41). Brabarupan et al[13] in the UK also showed that SA (n=39) compared with WE (n=565) and AC (n=38) had a lower systolic blood pressure (median 120 vs. 130 vs. 135 mmHg respectively; p<0.05) and a lower diastolic blood pressure (median 73 vs. 75 vs. 80 mmHg respectively, p<0.05). We have previously noted that there was no significant difference in systolic blood pressure (mmHg) between SA and WE (median 121 vs. 125 respectively and 130 vs. 131.5 respectively in two different centres) in a UK population[14]. Another study reported that SA (n=59) had a higher diastolic blood pressure (mmHg) than WE (n=118) (median 86 vs. 82 respectively, p<0.05). Lastly, Omar et al[16] in South Africa showed absence of difference between SA (n=41) and AC (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 AC, 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 AC, one comparing to AC only and one comparing to Malay and Chinese. A UK study has previously shown that SA (n=80) have lower levels of HDL (mmol/L) (median1.3 vs. 1.4 respectively, p<0.05) and higher cholesterol/HDL ratio (median 3.6 vs. 3.2 respectively, p<0.05) than WE (n=160)[14]. There were no statistically significant differences in the levels of total cholesterol (mmol/L) in SA compared to WE (median 4.7 vs. 4.6 respectively and 4.45 vs. 4.1 respectively). Another UK study[13] also showed that SA (n=39) had lower levels of HDL (mmol/L) compared with WE (n=565) but higher levels than AC (n=38)(median 1.30 vs. 1.49 vs. 1.25 respectively, p<0.05). They also demonstrate absence of difference in total cholesterol levels ((mmol/L) between SA, WE and AC (median 4.00 vs. 4.50 vs. 4.40 respectively) and triglyceride levels (mmol/L) (median 1.07 vs. 0.93 vs. 0.99 respectively). Mehta et al[10] in the UK also show similar levels of total cholesterol (mmol/L) in SA (n=163) (mean value 4.6) compared to WE (n=1169) (mean value 4.8) (p=0.132).

Ismail et al[18] in Malaysia demonstrate that SA (n=76) compared with Malay (n=102) and Chinese (91) had no statistically significant differences in total cholesterol (mmol/L) levels (mean 5.74 vs. 5.58 vs. 5.64 respectively) and LDL cholesterol (mmol/L) levels (mean 3.89 vs. 3.48 vs. 3.52 respectively). SA had significantly lower HDL cholesterol (mmol/L) compared with Chinese (mean 1.28 vs. 1.57 respectively, p<0.01) and significantly higher triglyceride levels (mmol/L) (mean 1.02 vs. 0.82

respectively, p<0.03). Lastly, Asmal et al[17] in South Africa found that SA (n=38) compared to AC (n=52) had no statistically significant differences in cholesterol levels (mmol/L) (mean 5.17 vs. 4.78 respectively) and triglyceride levels (mmol/L) (2.81 vs. 2.27 respectively).

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

Smoking Status

Only one paper examined the prevalence of smoking in SA with T1DM. Mehta et al[10] in the UK demonstrated significantly lower prevalence of smokers in the SA group (n=28/163, 17%) compared to the WE group (n=359/1169, 30.7%) (p<0.001).

Microvascular Disease

Retinopathy

Four studies examined retinopathy; one comparing SA with WE only, two comparing to WE and AC, and one comparing to AC only. The most relevant study by Sivaprasad[12] et al investigated retinopathy in T1DM in the UK cohort consisting of 2,626 WE, 344 AC 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 AC with T1DM in the age-standardised prevalence of maculopathy [95% confidence interval] (16.6% [10 – 23.2] vs. 14.1% [12.8-15.4] vs. 13.1% [9.4-16.8] respectively), clinically significant macular oedema (11.2% [5.4-16.9] vs. 6.5% [5.6-7.4] vs. 10.0% [6.7-13.3] respectively), sight threatening diabetic retinopathy (17.5% [10.6-24.3] vs. 12.1% [10.9-13.3] vs. 15.9% [11.8-20.0] respectively) and any diabetic retinopathy (54.0% [44.8-63.2] vs. 55.0% [53.2-56.9] vs. 42.8% [37.3-48.3] respectively).

Thomas et al[15], in South Africa, reported that SA (n=118) were at increased risk of any diabetic retinopathy (Odds ratio 2.02 95% CI 1.23-3.29) when compared with WE (n=1,247), after adjustment for age at diagnosis, sex, duration of diabetes, HbA1c, hypertension, and smoking status. Mehta et al[10] in the UK showed that SA (n=163) compared to WE (n=1,169) had decreased prevalence of retinopathy (38.7% vs. 48.0% respectively, p=0.025). Lastly, Omar et al[16], a South African study, compared SA (n=41) to AC (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 AC 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 AC, and two papers comparing to AC only. The largest study, by Mehta et al[10] in the UK, did not show any differences between SA (n=163) and WE (n=1,169) 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 (µmol/L) (median 76 vs. 78 respectively), albumin/creatinine ratio

(mg/mmol) (median 2.4 vs. 2.5 respectively) and eGFR (ml/min/1.73^2) (median 97.3 vs. 91.2 respectively)[14]. Brabarupan et al[13] in the UK showed no difference in the prevalence of microalbuminuria (mg/mmol) between SA (n=39) and WE (n=565) (median 1.2 vs. 1.2 respectively), however, AC (n=38) had significantly higher levels (median 3.7) ($p<0.05$). There were two studies in South Africa comparing SA to AC. The first by Omar et al[16] showed in their cohort of SA (n=41) and AC (n=92) there was absence of difference in the prevalence of nephropathy (7% vs. 3% respectively). Asmal et al[17] also showed no statistically relevant difference between SA (n=38) and AC (n=52) in creatinine levels (µmol/L) (mean 68.90 vs. 79.40 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 to AC.

Neuropathy

Three studies included neuropathy as an outcome in SA: one comparing to WE only and two comparing to AC only. The most relevant study, Mehta et al[10] in the UK, showed that SA (n=163) compared to WE (n=1,169) have a lower prevalence of neuropathy (14.7% vs. 27.8% respectively, $p<0.001$). Omar et al[16] compared SA (n=41) to AC (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[17] in South Africa showed increased prevalence of neuropathy in SA (n=38) compared to AC (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 AC.

Macrovascular Disease

Two studies reported cardiovascular outcomes: one comparing to WE only and the other comparing to AC only. The largest of these studies, by Mehta et al[10] in the UK, did not show evidence of difference between SA (n=163) and WE (n=1,169) with T1DM in prevalence of cardiovascular disease (15.3% vs. 11.3% respectively, p=0.133). Sub-analysis 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 to 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 AC in South Africa. Omar et al[16] showed that none of their participants in either the SA (n=41) or AC group (n=92) had peripheral vascular 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 AC populations do not differ.

Mortality

Only one study examined the association of SA ethnicity on mortality in people with T1DM. Swerdlow et al[9] in a UK study investigated mortality of SA patients compared to 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 23,326 non-SA there were 1,293 deaths (5.5%). Mortality in SA and non-SA with T1DM was calculated independently by comparing with the general population mortality using Standardized Mortality Ratios (SMR). Compared to the reference population, the SMR for SA patients were 3.9 (95% CI 2.0-6.9) in men and 10.1 (6.6-16.6) in women. The SMR for the corresponding non-SA were 2.7 (2.6-2.9) in men and 4.0 (3.6-4.3) in women. No details are provided as to the age of death in these patients. The most common cause of death in SA patients was cardiovascular disease (29.6%) and renal disease (14.8%). The 'other' causes of death accounted for 8 deaths (29.6%) and included septicaemia, 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 to the reference population in the UK. SA females were in particular affected, with a SMR that was over twice that of the non-SA female T1DM population. The commonest cause of death was cardiovascular disease.

Discussion

This is the first systematic review to examine the differences in risk factors, 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 to a largely WE reference population. Female SAs were in particular affected, with a SMR that was over twice that of the non-SA female T1DM population. The commonest cause of death is cardiovascular disease.

Overall, the studies suggest that cardiovascular disease itself is no more common in SA T1DM compared to 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. Whilst 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 to 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 factors for cardiovascular disease of smoking and systolic BP are lower than in WE.

Most studies also suggest SA have higher HbA1c levels than WE[24], Malay and Chinese but lower than AC ethnic groups. Despite this, rates of retinal and nephropathic microvascular disease were the same as the WE population and some (neuropathy) even lower. Compared to AC, 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 outcomes: cardiovascular disease, retinopathy, neuropathy and BMI.

Strengths and weaknesses

There are a number of weaknesses with the analysis. The quality of the studies were poor with the majority of studies being retrospective observational or cross-sectional. It was also not possible to undertake a meta-analysis of the combined studies because the results were heterogeneous in nature. Furthermore, the methodology of how outcomes were assessed was not consistently reported, and the numbers of SA in each study were small. 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. Firstly, 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[25], 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. Culturally tailored programmes, as have been attempted for T2DM, may also be required for T1DM[26]. In addition, we may require more stringent control of other

cardiovascular risk factors such as lipids and blood pressure, though this needs to be formally addressed. Secondly, 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 risk factors and outcomes. These outcomes should include those mentioned above, and in particular cardiovascular disease, but also outcomes such as peripheral vascular disease, depression and bone fractures that have not previously been addressed.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; KK (Co-Chair) PS and PN are members of the South Asian Health Foundation Working group on Diabetes.

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The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: no additional data available.

Contributorship Statement

Dr Komil N Sarwar: involvement in the design of the work, data collection, data analysis, writing the paper, drafting and revision of the paper

Dr Phoebe Cliff: involvement in the design of the work, data collection, data analysis, helped with drafting and revision of the paper

Dr Ponnusamy Saravanan: involvement in the design of the work, reviewed all drafts of the paper, helped with revision of the paper

Professor Kamlesh Khunti - involvement in the design of the work, reviewed all drafts of the paper,

helped with revision of the paper

Dr Krishnarajah Nirantharakumar - responsible for the conception and design of the work, reviewed all drafts of the paper, helped with revision of the paper

Dr Parth Narendran - responsible for the conception and design of the work, reviewed all drafts of the paper, helped with revision of the paper

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Appendix 1: Search Strategy

Embase

1	type 1 diabetes.mp. or exp insulin dependent diabetes/	95641
2	ethnicity.mp. or exp ethnic group/ or exp race/ or exp ethnicity/ or exp "ethnic or racial aspects"/	288124
3	exp ethnic difference/	27336
4	exp South Asian/	27829
5	Sri Lanka.mp. or exp Sri Lanka	7081
6	Bangladesh.mp. or exp Bangladesh	13584
7	India.mp. or exp India	156225
8	Pakistan.mp. or exp Pakistan	22629
9	Nepal.mp. or exp Nepal	8792
10	Bhutan.mp. or exp Bhutan	507
11	maldives.mp. or exp Maldives	268
12	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	499040
13	**1 and 12**	**2491**

Medline

1	exp Diabetes mellitus, Type 1/ or type 1 diabetes.mp.	72398
2	insulin dependent diabetes.mp.	19957
3	exp ethnic groups/ or ethnicity.mp	158001
4	ethnic differences.mp.	6985
5	ethnic aspects.mp.	30
6	racial differences.mp.	5002
7	race.mp.	77099
8	racial groups.mp.	2853
9	racial aspects.mp.	34
10	South Asian*.mp.	3740
11	exp sri lanka/ or sri lanka*.mp	6443
12	exp bangladesh/ or bangladesh*.mp	11009
13	exp india/ or india*.mp.	164014
14	exp pakistan/ or pakistan*.mp.	17599
15	exp nepal/ or nepal*.mp.	7799
16	exp bhutan/ or bhutan*.mp.	468
17	maldives.mp.	195
18	1 or 2	82700
19	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	405983
20	**18 and 19**	**2231**

Appendix 2: Quality Assessment

Study	Design	Grading of study design	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
Swerdlow et al[9]	Prospective Cohort Study	Selection: 4/4 stars Comparability: 0/2 stars Outcome: 3/3 stars	**South Asian Ethnicity** Identified by computer algorithm (SANGRA) followed by a clerical check by an individual with expertise in this area. Sensitivity of 89-96% and specificity of 94-98%.	**Inclusion Criteria** Age at diagnosis of diabetes <30 years. Some identified in a national register of childhood cases assembled by the BDA from 1972-1986 and remainder from various geographical registers for parts of the UK during 1972-1993. Ages at diagnosis varied. Total cohort of 23, 752 with T1DM.	Age distributions of person-years were similar between the 2 groups	**Type of analysis** Standardised mortality ratios compared using chi squared test. **Power calculation** Not reported	**Follow up** Till 31st December 1999, or the date of death, 85th birthday, emigration or other loss of follow up. **Lost to Follow up** 1 South Asian and 151 non South Asians lost to follow up through emigration. 50 non South Asians lost to follow up in other ways. **Outcome** Mortality assessed in the same way in both groups.	**Effect of differences at baseline** No differences in age distributions. However, differences in comorbidities not reported. May be significant in mortality rates.	1. Assumption that people diagnosed <30 years had T1DM and those diagnosed >30 years had T2DM. 2. Ethnic makeup of the non- South Asian group not reported (assumed Caucasian). 3. Small number of deaths in South Asian group.
Mehta et al[10]	Cross-sectional study	Selection: 1/5 stars Comparability: 2/2 stars Outcome: 3/3 stars	**South Asian Ethnicity** Ethnicity identified based on that given in the patient's record or by use of name recognition software 'Nam Pechan' supplemented by a visual inspection of surnames and forenames.	**Inclusion Criteria** Diabetes patients attending a specialist outpatient diabetes clinic in Leicestershire, UK, between 2003 and 2005. Methodology of patients being classified as T1DM or T2DM not reported.	Age (3.4 years) Duration of diabetes (5.9 years) Smoking (13.7%)	**Type of analysis** Documented **Power calculation** Not reported	**Outcome** Baseline data and comorbidities data collected in the same way in both groups. Classification the same in both groups.	**Effect of differences at baseline** Younger age of onset and shorter duration of diabetes in South Asians may have led to under-representation of comorbidities in South Asians with T1DM.	1.Cross sectional design so causation cannot be established 2.Data from one hospital, not generalizable 3.Did not comment on frequency of attendance for blood glucose monitoring so relationship between HbA1c and comorbidity not clear
Shenoy et al[11]	Retrospective Observational Study	Selection: 1/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Children with T1DM between the ages of 2 and 18 years and who had been diagnosed more than a year ago.	Not reported	**Type of analysis and power calculation** Not reported	**Outcome** Obesity assessed in both groups. No methodology given so unclear if bias in between two groups.	**Effect of differences at baseline** Possibly multiple considering characteristics not described	1.No methodology given 2.No description of statistical analysis used 3.No data on South Asians vs. non-South Asians

									given in the results
Sivaprasad et al[12]	Cross-sectional study	Selection: 1/5 stars Comparability: 1/2 stars Outcome: 3/3 stars	**South Asian Ethnicity** Self-reported ethnicity recorded at the time of screening according to the codes used in the Census 2001.	**Inclusion Criteria** All subjects in the diabetic screening register of West Yorkshire and South East London programmes were included in this study. Coverage of diabetic people in the respective regions: 95% in West Yorkshire and 81% in South East London	Not reported	**Type of analysis** Documented **Power calculation** Not reported	**Outcome** Diabetic screening and retinopathy assessment same in both groups.	**Effect of differences at baseline** Possibly multiple considering characteristics not described	1.Records of patients that were not obtainable or exempt from diabetic screening (12%) did not have ethnicity data so South Asians may have been under-represented 2.Did not assess factors like BP, glycaemic control
Braparupan et al[13]	Cross-sectional retrospective study	Selection: 1/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Subjects with T1DM diagnosed below 35 years of age from a London diabetes clinic. From white European, Afro-Caribbean or South Asian ancestry.	Not applicable	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in both groups. No methodology given so unclear if bias in the way outcomes measured in both groups.	**Effect of differences at baseline** Groups not matched for age and gender.	1.Abstract only so full methodology and results not available 2.Groups not matched for age and gender
Sarwar et al[14]	Retrospective case-controlled study	Selection: 0/5 stars Comparability: 2/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Patients with T1DM in 2 centres in the West Midlands	Patients matched for age and gender	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in both groups. No methodology given so unclear if bias in the way outcomes measured in both groups.	**Factors not included in the study** Methodology not given so bias may be introduced with the two centres	1. Abstract only
Thomas et al[15]	Retrospective observational study	Selection: 1/5 stars Comparability: 2/2 stars Outcome: 3/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Subjects classified as having T1DM or T2DM on clinical assessment according to the American Diabetes Association classification of diabetes.	Age (4.1 years) Duration of diabetes (4 years)	**Type of analysis** Documented **Power calculation** Not reported	**Period of study** 2001-2010 with baseline characteristics being obtained at the time of initial presentation. **Outcome** Same outcome measures in 2 groups but data collected from 2001-2010 so may be discrepancies between people being screened at the beginning and the end of the study. **Drop out or withdrawals**	**Effect of differences at baseline** Younger age of onset and shorter duration of diabetes in South Asians may have led to under-representation of retinopathy	1.Study carried out in private hospital whereas most of diabetic South Africans use public health system so not generalizable 2.Lack of dilation prior to obtaining images may have led to underreporting of

							None reported	in South Asians with T1DM.	retinopathy
Omar et al[16]	Cross-sectional study	Selection: 0/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Patients with onset of IDDM <35 years at King Edward Hospital in Durban. Diagnosis of IDDM based on the criteria recommended by WHO.	Age at onset (6.5 years) Duration of diabetes (1.6 years)	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in 2 groups, however details not given as to when measurements were taken and by whom and if standardised for both groups.	**Effect of differences at baseline** Older age of onset and longer duration of diabetes in South Asians may have led to over-representation of complications in this group.	1.No statistical methods were used to compare the two groups
Asmal et al[17]	Cross-sectional study	Selection: 0/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Clinic patients who fulfilled the following criteria: age of diagnosis of diabetes <35 years, development of symptoms +/- ketosis in the absence of insulin therapy, and duration of diabetes of at least 12 months. Patients with known alcoholic pancreatitic diabetes were not included.	Current age (2.9 years) Age of onset (3.8 years)	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in 2 groups, however details not given as to when measurements were taken and by whom and if standardised for both groups.	**Effect of differences at baseline** Younger age and age of onset in South Asians may have led to a mis-representation of biochemical data in this group	1.No statistical methods were used to compare the two groups
Ismail et al[18]	Cross Sectional study	Selection: 2/5 stars Comparability: 0/2 stars Outcome: 3/3 stars	**South Asian Ethnicity** Identified by their appearance, language and religion	**Inclusion Criteria** T1DM defined as acute symptoms associated with heavy ketonuria (>3+) or ketoacidosis at diagnosis, or continuous treatment with insulin within 1 year of diagnosis. All diagnosed < 40 years	Similar baseline characteristics	**Type of analysis** Documented **Power calculation** Not reported	**Outcome** Same outcome measures in 2 groups	**Effect of differences at baseline** No differences	1.Clinic-based and not a population-based study. Those attending hospital may have more severe diabetes. 2.Conducted in public hospital where majority of patients cannot afford lipid-lowering therapy.
Omar et al[19]	Cross sectional study	Selection: 0/5 stars Comparabi	**South Asian Ethnicity**	**Inclusion Criteria** Onset of diabetes mellitus <35 years. Classification	Duration of diabetes (1.6 years)	**Type of analysis** Documented	**Outcome** Same outcome measures in 2 groups	**Effect of differences at baseline**	1. No outcomes apart from age of onset, duration of

		lity: 0/2 stars Outcome: 2/3 stars		of IDDM and NIDDM based on the criteria recommended by the National Diabetes Data Group and WHO Expert Committee on Diabetes Mellitus. IDDM patients had always depended on insulin for control of symptoms and prevention of basal ketosis		**Power calculation** Not reported		Not relevant as this is a purely descriptive analysis	disease and body weight. Limited information provided by study

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	23-24
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25-28
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	25-28
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology
Keywords:	Type 1 Diabetes Mellitus, Ethnicity, South Asian

Title Page

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

Authors: Komil N Sarwar (Foundation Doctor)[1], Phoebe Cliff (Foundation Doctor)[1], Ponnusamy Saravanan (Associate Clinical Professor)[2], Kamlesh Khunti (Professor of Primary Care Diabetes and Vascular Medicine)[3], Krishnarajah Nirantharakumar (Senior Clinical Lecturer)[1], Parth Narendran (Reader in Diabetes Medicine)[1]

Institution(s) of origin: University of Birmingham, Edgbaston, Birmingham, England, B152TT[1]
University of Warwick, Coventry, England, CV4 7AL[2]
University of Leicester, University Road, Leicester, England LE1 7RH[3]

Corresponding author: Dr Krishnarajah Nirantharakumar

Public Health, Epidemiology and Biostatistics, University of Birmingham, Edgbaston Birmingham, B15 2TT, UK

Telephone: 44 (0)121 414 8344

Fax: +44 (0)121 414 6217

Email: k.nirantharan@bham.ac.uk

Conflicts of Interest: KK (Co-Chair) PS and PN are members of the South Asian Health Foundation Working group on Diabetes.

Keywords: Type 1 Diabetes Mellitus, Ethnicity, South Asian

Word Count: 3993

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

Komil N Sarwar, Phoebe Cliff, Ponnusamy Saravanan, Kamlesh Khunti, Krishnarajah Nirantharakumar, Parth Narendran

Abstract

Objective. To explore the association of South Asian (SA) ethnicity on comorbidities, microvascular and macrovascular complications, and mortality compared to 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 4, 722 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 to 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 to White Europeans (WE), mainly contributed to by excess cardiovascular disease. SA have significantly higher HbA1c, lower HDL and lower rates of neuropathy compared to WE. There were no differences in rates of retinopathy and nephropathy. Compared to 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 BMI. Furthermore, SA have higher HbA1c levels than Malay and Chinese and higher waist-hip ratio and lower HDL levels compared to Chinese only.

Conclusion. Our analysis highlights ethnic disparity in macrovascular outcomes that is so evident for Type 2 Diabetes Mellitus (T2DM) 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

- 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 SA group, the largest ethnic group globally with all other indigenous ethnic groups.

Weaknesses

- The quality of the studies were poor with the majority of studies being retrospective observational or cross-sectional.
- It was also not possible to undertake a meta-analysis of the combined studies because the results were heterogeneous in nature.
- 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[1].Type 2 Diabetes Mellitus is 2-3 times more common in SA than in the WE population in the United Kingdom[2], 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[2,4]. These differences have not been explored in people with T1DM.

Willi et al[5] 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 to white or Hispanic participants. A recent systematic review[6] identified 16 studies in the current literature that showed racial/ethnic minority youth with T1DM having higher HbA1c compared to Caucasian youth. As the majority of these studies are conducted in the United States of America, their primary focus was on the black and Hispanic ethnic groups and youth with T1DM.

SA comprise 20% of the global population[2] and 7% of the UK population[7]. Furthermore, the incidence of T1DM appears to be similar in SA as in the background population[7]. 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 to 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 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 on-going 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 to 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 (Appendix 2). The Newcastle-Ottawa Quality Assessment Scale for observational studies was used for quality assessment[8].

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.

Patient Involvement: Patients were not involved.

Results

The initial search identified 4,722 papers. After removing duplicates (1,194), the remaining 3,528 titles and abstracts were screened. After excluding 3,223 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 1 paper (Figure 1). A total of 11 studies were therefore included: 6 studies were from the United Kingdom, 4 from South Africa and 1 from Malaysia. Nine of the papers were full length papers and 2 were abstracts. Of the included articles, 1 was a prospective cohort study, 2 were retrospective analysis of observational data and 8 studies were cross-sectional analyses. The results are summarised in Table 1 and Table 2.

Table 1: Data extraction of studies included in systematic review

Study & year published	Country	Design	Method and Description	Number of Participants & Ethnic Group	Age description	Duration of Study	Key Outcomes
Papers assessing T1DM comorbidities							
Brabarupan et al[9] 2013	UK	Cross-sectional study	**Ethnicity** Grouped into White European (WE), African and South Asian (SA) **T1DM** Diagnosis of T1DM and diagnosed <35 years of age **Method** Data from patients from WE, African or SA ancestry was obtained from an electronic database in a large multi-ethnic London diabetes clinic.	642 individuals in total WE: 564 SA: 39 African: 39	Median age at diagnosis (years) WE: 16.7 African: 19.4 SA: 19.1	N/A	**Parameters median (IQR)** / **White European (WE)** / **African** / **South Asian (SA)** / **Significant** **BMI (kg/m2)**: 25.0 (22.3-27.7) / 25.7 (22.5-28.9) / 25.3 (22.2-28.5) / NEEDS p Value **Systolic BP (mm/Hg)**: 130 (119-141) / 135 (121-149) / 122 (1120133) / P<0.05 **Diastolic BP (mmHg)**: 75 (69-81) / 80 (72-88) / 73 (67-79) / P<0.05 **HbA1c (%)**: 8.0(7.1-8.9) / 9.1 (7.6-10.7) / 8.3 (7.5-9.2) / P<0.05 **Microalbuminuria (mg/mmol)**: 1.2 (-0.5-3.0) / 3.7 (-44.5-51.9) / 1.2 (-1.4-3.8) / P<0.05 **Total Cholesterol (mmol/L)**: 4.50 (3.90-5.10) / 4.40 (3.90-4.90) / 4.00 (3.2-4.8) **HDL (mmol/L)**: 1.49 (1.21-1.77) / 1.25 (0.95-1.56) / 1.30 (1.47-1.14) / P<0.05 **Triglyceride (mmol/L)**: 0.93 (0.59-1.28) / 0.99 (0.58) / 1.07 (0.76-1.39)
Sarwar et al[10] 2015	UK	Cross sectional Study	**Ethnicity** South Asian and White Caucasian **T1DM** Coding of T1DM from the clinical database of two centres – no diagnostic criteria included **Method** Data analysed from two centres in the West Midlands (Queen Elizabeth Hospital [QEH] and New Cross Hospital [NCH])	White Caucasian: 278 South Asian: 139	Median age (years) NCH Caucasian: 34 NCH SA: 33.5	N/A	**Characteristic (number of patients)** / **NCH South Asian (80)** / **NCH Caucasian (160)** / **QE South Asian (59)** / **QE Caucasian (118)** **HbA1c (mmol/mol)**: 75 (61.5-88.5) / 76 (63-91) / 66.1 (55.25-81.75) / 70.5 (61-83.6) **Systolic BP (mmHg)**: 121 (113-132) / 125 (115-132) / 130 (120.5-141.5) / 131.5 (120.3-144)

					QEH Caucasian: 36 QEH SA: 36		**Diastolic BP (mmHg)**	-	-	86 (80.5—90)*	82 (77.25-88.75)*
							BMI (kg/m2)	25.6 (22.55-28.4)	25.7 (22.5-30.4)	30.9 (22.8-37)	25 (22.6-28)
							Total Cholesterol (mmol/L)	4.7(3.9-5.45)	4.6 (4-5.3)	4.45 (3.8-5.45)	4.1 (3.7-4.95)
							HDL (mmol/L)	1.3 (1.0-1.6)*	1.4 (1.2-1.65)*	-	-
							Cholesterol/ HDL	3.6 (2.9-4.5)*	3.2 (2.7-4.0)*	-	-
							Creatinine level (µmol/L)	75 (66-87)	78 (69-87)	-	-
							eGFR (ml/min/ 1.73m2)	97.3 (82.2-109.9)	91.2 (79.3-103.9)	-	-
							Albumin/ Creatinine ratio (mg/mmol)	2.4 (0.7-3.6)	2.5 (0.75-3.5)	-	-
							*P value <0.05				
Shenoy et al[11] 2004	UK	Retrospective Observational Study	**Ethnicity** South Asian and Caucasian **T1DM** Children coded as T1DM in a centre in Leicestershire – no diagnostic criteria included **Method** Rates of obesity/overweight in white Caucasian and South Asian groups, and to correlate these with age, duration of diagnosis, daily insulin requirement, and HbA1c. Included children between the ages of 2 and 18 years and who had been diagnosed more than a year ago.	WE: 112 SA: 38	**Age Group (n)** 2-4 yrs (3) 5-9 yrs (33) 10-15 yrs (90) 16-18 yrs (24)	N/A	**Demographic Data** 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% v 8.8% respectively for white Caucasian/South Asian). **Obesity in children** No statistically significant differences noted in the rates of overweight or obesity between white Caucasian and South Asian children at any age grouping.					

Asmal et al[12] 1981	South Africa	Cross-sectional analysis	**Ethnicity** 2 groups: Indians and Black African. **T1DM** Clinic patients who fulfilled the following criteria: age of diagnosis of diabetes <35 years, development of symptoms +/- ketosis in the absence of insulin therapy, and duration of diabetes of at least 12 months. **Method** Case records examined, clinical assessments and biochemical tests carried out	Black African: 52 Indian: 38	Mean age at onset (years) Blacks: 21.8 Indian: 18.0	4 weeks	**Basic Biochemical Data** **Indians** / **Black African** **Glucose (mmol/l)** 15.80 ± 1.50 / 14.20 ± 1.50 **Growth hormone (ng/ml)** 3.00 ± 0.76 / 1.76 ± 0.41 **Cortisol (µg/dl)** 16.20 ± 1.47 / 15.80 ± 1.40 **Cholesterol (mmol/l)** 5.17 ± 0.32 / 4.78 ± 0.26 **Triglyceride (mmol/l)** 2.81 ± 0.97 / 2.27 ± 0.83 **Creatinine (µg/dl)** 68.90 ± 4.10 / 79.40 ± 6.70 **Complications** Chronic complications associated with micro-angiopathy were detected in 12 Indians (33%) and 2 Blacks (4%). Commonest complication was neuropathy found in 19% of Indian diabetics and in 4% of Black diabetics. 2 Indians had evidence of diabetic triopathy.
Ismail et al[13] 2001	Malaysia	Cross Sectional study	**Ethnicity** 3 groups: Indian, Malay and Chinese. Each ethnic group identified by appearance, language and religion. **T1DM** T1DM defined as acute symptoms associated with heavy ketonuria (>3+) or ketoacidosis at diagnosis, or continuous treatment with insulin within 1 year of diagnosis. **Method** Patients recruited from 7 centres throughout Peninsular Malaysia. Blood taken for lipid levels, clinical history and physical examination performed.	Indian: 154 Malay: 297 Chinese: 128	Mean age (years) All: 28.8 Indian: 29.1 Chinese: 29.8 Malay: 27.7	June 1997-June 1998	**Demographic Features** **Malay (n = 297)** / **Chinese(n=128)** / **Indian (n=154)** **BMI (kg/m2)** 26.8 ± 4.9 / 25.4 ± 4.5 / 25.5 ± 4.3 **Waist-hip ratio** A: 0.88 ± 0.06 / A: 0.88 ± 0.07 / A: 0.89 ± 0.06 M: 0.91 ± 0.06 / M: 0.90 ± 0.06 / M: 0.93 ± 0.06 F: 0.86 ± 0.06 / F: 0.85 ± 0.07 / F: 0.85 ± 0.06 **HbA1c (%)** 8.8 (8.6-9.1) / 8.0 (7.7-8.3) / 8.5 (8.2-8.8) **Lipid Profiles (mmol/L, mean +/- SEM)** **Total Cholesterol** : Indians (5.74 +/- 1.25), Chinese (5.64 +/- 1.42), Malay (5.58 +/- 1.38) **LDL Cholesterol :** Indians (3.89 +/- 1.20), Chinese (3.52 +/- 1.22), Malay (3.48 +/- 1.12) **HDL Cholesterol** (mean[95% CI]) : Indians (1.28 [1.19-1.38]), Chinese (1.57 [1.48-1.67]), Malay (1.37 [1.28-1.46]) **Triglycerides** (mean[95% CI]): Indians (1.02 [0.9-1.16]), Chinese (0.82 [0.74-0.91)], Malay (1.11 [0.99-1.23])
Omar et al[14] 1984	South Africa	Cross sectional analysis	**Ethnicity** Indians and Africans **T1DM** Classification of diabetes based on criteria by National Diabetes Data Group and WHO expert committee. T1DM patients had always depended on insulin for control of symptoms and prevention of basal ketosis. All patients diagnosed <35 years of age	African T1DM: 86 Indian T1DM: 40	Mean age of onset (range) African: 23.5 (1-35) yrs Indian:	2 year period	**Clinical characteristics of T1DM patients** **Characteristic** / **Africans (n=86)** / **Indians (n=40)** **Male: Female** 21: 25 / 17: 24 **Mean % ideal body weight** 106 (68-153) / 91 (71-136) **Mean duration of disease (years)** 3.8 (1-27) / 5.4 (1-22) **Mean age of onset** 23.5 (1-35) / 17 (1-35)

					17 (1-35)		
Papers assessing T1DM complications							
Swerdlow et al[15] 2004	UK	Prospective Cohort Study	**Ethnicity** Grouped into South Asians and non-South Asians. South Asians identified by computer algorithm (SANGRA) followed by a clerical check by an individual with expertise in this area. **T1DM** Patients with IDDM diagnosed <30 years **Method** SMRs calculated, comparing mortality in the cohort to the corresponding mortality rates in the general population	Non South Asian : 23, 326 South Asian: 424	N/A	1972 – 1999	**Mortality** The Standardised Mortality Ratios (SMR) for South Asian patients diagnosed <30 years were 3.9(95% CI 2.0-6.9) in men and 10.1 (5.6-16.6) in women, and in the corresponding non-South Asians were 2.7 (2.6-2.9) in men and 4.0 (3.6-4.3) in women.
Mehta et al[16] 2011	UK	Cross-sectional study	**Ethnicity** Ethnicity was categorised as SA or white European (WE) based on patient record documentation or by analysis of their name using a validated name recognition software 'Nam Pechan' supplemented by a visual inspection of surnames and forenames. **T1DM** Patient coded as having T1DM in the clinical database of a specialist outpatient diabetes clinic in Leicestershire, UK – no diagnostic criteria included **Method** Patient characteristics and other data were extracted from the clinical workstation (CWS), a clinical database of patients attending a specialist outpatient diabetes clinic in Leicestershire.	WE: 1,169 SA: 163	**Mean age (years)** WE: 45.3 SA: 41.9	2003-2005	**South Asian (n = 163)** / **White European (n = 1169)** / **p Value** **Number of comorbidities (n (%))** 0: 114 (69.9) / 878 (75.1) / 0.166 1: 36 (22.1) / 235 (20.1) ≥2: 13 (8.0) / 56 (4.8) **Macrovascular (n (%))** CVD: 25 (15.3) / 132 (11.3) / 0.133 Ischaemic heart disease: 20 (12.3) / 97 (8.3) / 0.093 Peripheral vascular disease: 3 (1.8) / 31 (2.7) / 0.790 Cerebrovascular disease: 6 (3.7) / 21 (1.8) / 0.130 TIA: 0 / 2 (0.2) / 1.000 **Microvascular (n (%))** Retinopathy: 63 (38.7) / 561 (48.0) / 0.025 Neuropathy: 24 (14.7) / 325 (27.8) / <0.001 Nephropathy: 22 (13.5) / 118 (10.1) / 0.184 **Glycaemic control (n (%))** / **(n = 163)** / **(n = 1169)** HbA1C < 7%: 19 (12.0) / 193 (17.0) / 0.113 HbA1C ≥7%: 144 (88.0) / 976 (83.0)
Sivaprasad	UK	Cross-section	**Ethnicity** Self-reported ethnicity based on UK census	WE: 2,628	Mean age of	2008-2009	

et al[17] 2012		al study	standard (Census 2001): categorised as 'White European', 'African', 'South Asian', 'Mixed', 'other ethnic group' and 'not known'. **T1DM** Patients coded as T1DM in the database of the local DR screening service – no diagnostic criteria included **Method** To assess ethnic variations of the prevalence of DR and visual impairment in two multi-racial cohorts in the UK (Yorkshire and South East London)	African: 344 SA: 120	T1DM population: 39.4 yrs		**Ethnic group** / **Prevalence: N (%)** / **Age-standardised prevalence: % (95% CI)** **Any diabetic retinopathy** White Europeans: 1446 (55.0) / 55.0 (53.2, 56.9) African: 154 (44.8) / 42.8 (37.3, 48.3) South Asian: 64 (53.3) / 54.0 (44.8, 63.2) **Any maculopathy (M1)** White Europeans: 371 (14.1) / 14.1 (12..8, 15.4) African: 47 (13.7) / 13.1 (9.4, 16.8) South Asian: 17 (14.2) / 16.6 (10.0, 23,2) **CSMO (M1P1)** White Europeans: 171 (6.5) / 6.5 (5.6, 7.4) African: 35 (10.20 / 10.0 (6.7, 13.3) South Asian: 12 (10.0) / 11.2 (5.4, 16.9) **STDR (R2 or R3 or M1P1)** White Europeans: 318 (12.1) / 12.1 (10.9, 13.3) African: 53 (15.4) / 15.9 (11.8, 20.0) South Asian: 19 (15.8) / 17.5 (10.6, 24.3) CSMO- clinically significant macular oedema; M1- maculopathy P1- macular laser; STDR- sight threatening diabetic retinopathy; R1- mild to moderate non-proliferative diabetic retinopathy; R2- pre-proliferative diabetic retinopathy; R3- Proliferative diabetic retinopathy
Thomas et al[18] 2012	South Africa	Retrospective observational study	**Ethnicity** Caucasian, Indigenous African, Asian and mixed race. **T1DM** Classified as having T1DM on clinical assessment according to the American Diabetes Association classification of diabetes	Caucasian: 1247 Indigenous African: 117 Asian:	Mean age (yrs) Caucasian: 35.7 Indigenous African	2001-2010	**Diabetic Retinopathy (DR)** **Any DR (n=541)** / **RDR (n=142)** **Crude OR (95% CI)** / **Adjusted OR (95% CI)** / **Crude OR (95% CI)** / **Adjusted OR (95% CI)** **Caucasian (1,247)**: 1.00 / 1.00 / 1.00 / 1.00

			Method Retinal photography was conducted using a non-mydriatic digital camera without mydriasis and graded by one of three senior graders.	118 Mixed race: 49	: 36.3 Asian: 32.2 Mixed race: 32.6		**Indigenous African (117)** **Asian (118)** **Mixed race (49)**	0.71 (0.46-1.09) 1.10 (0.74-1.63) 1.01 (0.56-1.84)	1.72 (1.00-2.97) 2.02 (1.23-3.29) 1.29 (0.62-2.69)	0.95 (0.49-1.84) 1.05 (0.54-2.04) 1.10(0.42-2.88)	3.40 (1.40-8.26) 2.07 (0.90-4.75) 1.06 (0.36-3.18)
Omar et al[19] 1984	South Africa	Cross-sectional analysis	**Ethnicity** 2 groups: Indians and Black African. **T1DM** Patients with onset of IDDM <35 years at King Edward Hospital in Durban. Diagnosis of IDDM based on the criteria recommended by WHO. **Method** Both case records obtained and a physical examination performed to assess complications.	Black African: 92 Indians: 41	Mean age at onset (yrs) Blacks: 17 Indians: 23.5	Not mentioned	**Complications** **Keto-acidosis** **Neuropathy** **peripheral** **autonomic** **Retinopathy** **Nephropathy** **Triopathy** **Ischaemic heart disease** **Hypertension** **Cataracts** **Tuberculosis**	**Black African** 53 (58%) 20 (22%) 4 (4%) 13 (14%) 3 (3%) 1 (1%) - 4 (4%) 5 (5%) 6 (7%)	**Indians** 22 (54%) 13 (32%) 2 (5%) 9 (22%) 3 (7%) 2 (5%) - 2 (5%) 2 (5%) 1 (2%)	**Total** 75 (56%) 33 (25%) 6 (5%) 22 (17%) 6 (5%) 3 (2%) - 6 (5%) 7 (5%) 7 (5%)

Table 2: Summary of Findings

	Findings in the SA population when compared to the specified ethnicity (e.g. SA have the same BMI as WE, but higher HbA1c)		
	WE	**African**	**Chinese**
BMI	→	→	
HbA1c	↑	↓	↑
SBP	↓	↓	
DBP	→	→	
HDL	↓	↑	↓
Total Chol	→	→	→
Retinopathy	→	→	→
Nephropathy	→	↓	
Neuropathy	↓	→	
CVD	→	→	
Mortality	↑		

Results

Comorbidities

Body Mass Index (BMI)

Six studies explored 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[10, 11, 16]. Mehta et al[16] in the UK showed a mean BMI (kg/m^2) of 27.5 in SA (n=163) compared with 27.4 in WE (n=1169) (p=0.835). Similarities in BMI (kg/m^2) between SA and WE have previously been reported in two different centres (median BMI 25.6 vs. 25.7 respectively and 30.9 vs. 25 respectively)[10]. The results were not significant due to the small number of participants. Shenoy et al[11] 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[9] in the UK showed no statistically significant difference in BMI (kg/m^2) in SA (n=39) compared to WE (n=565) and Africans (n=38) (median 25.3 vs. 25.0 vs. 25.7 respectively). Omar et al[14] in South Africa also showed no difference between SA (n=40) and Africans (n=86) in mean % ideal body weight (91 vs. 106 respectively).

Lastly, a study by Ismail et al[13] in Malaysia showed that there was no difference in BMI (kg/m^2) when comparing SA to Malay and Chinese (mean 22.0 vs. 22.3 vs. 22.0 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 to 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[16] 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[9] in the UK who demonstrate SA (n=39) having higher HbA1c (%) levels (median 8.3) compared to 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[10] 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 in[11] the UK found no significant difference in metabolic control between WE (n=112) and SA (n=38) children (median HbA1c 8.4% v 8.8% respectively). Thomas et al[18] 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[12] in South Africa showed that SA (n=38) had similar mean glucose concentrations (mmol/l) to Africans (n=52) (15.80 vs. 14.20 respectively).

Ismail et al[13] in Malaysia showed that SA (n=76) have significantly higher HbA1c (%) levels compared to 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 to 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[16] in the UK, showed a significantly lower systolic blood pressure in SA (n=163) compared with WE (n=1169) (mean value 136.4 vs. 141.6 mmHg respectively; p=0.004). However, there was no difference in diastolic blood pressure between SA (mean 75.4 vs. 75.4 mmHg respectively; p=0.41). Brabarupan et al[9] 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 vs. 130 vs. 135 mmHg respectively; p<0.05) and a lower diastolic blood pressure (median 73 vs. 75 vs. 80 mmHg respectively, p<0.05). We have previously noted that there was no significant difference in systolic blood pressure (mmHg) between SA and WE (median 121 vs. 125 respectively and 130 vs. 131.5 respectively in two different centres) in a UK population[10]. However, we reported that SA (n=59) had a higher diastolic blood pressure (mmHg) than WE (n=118) (median 86 vs. 82 respectively, p<0.05)[10]. Lastly, Omar et al[19] 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 (mmol/L) (median1.3 vs. 1.4 respectively, p<0.05) and higher cholesterol/HDL ratio (median 3.6 vs. 3.2 respectively, p<0.05) than WE (n=160)[10]. There were no statistically significant differences in the levels of total cholesterol (mmol/L) in SA compared to WE (median 4.7 vs. 4.6 respectively and 4.45 vs. 4.1 respectively). Another UK study[9] also showed that SA (n=39) had lower levels of HDL (mmol/L) compared with WE (n=565) but higher levels than Africans (n=38)(median 1.30 vs. 1.49 vs. 1.25 respectively, p<0.05). They also demonstrate absence of difference in total cholesterol levels ((mmol/L) between SA, WE and Africans (median 4.00 vs. 4.50 vs. 4.40 respectively) and triglyceride levels (mmol/L) (median 1.07 vs. 0.93 vs. 0.99 respectively). Mehta et al[16] in the UK also show similar levels of total cholesterol (mmol/L) in SA (n=163) (mean value 4.6) compared to WE (n=1169) (mean value 4.8) (p=0.132).

Ismail et al[13] in Malaysia demonstrate that SA (n=76) compared with Malay (n=102) and Chinese (91) had no statistically significant differences in total cholesterol (mmol/L) levels (mean 5.74 vs. 5.58 vs. 5.64 respectively) and LDL cholesterol (mmol/L) levels (mean 3.89 vs. 3.48 vs. 3.52 respectively). SA had significantly lower HDL cholesterol (mmol/L) compared with Chinese (mean 1.28 vs. 1.57

respectively, p<0.01) and significantly higher triglyceride levels (mmol/L) (mean 1.02 vs. 0.82 respectively, p<0.03). Lastly, Asmal et al[12] in South Africa found that SA (n=38) compared to Africans (n=52) had no statistically significant differences in cholesterol levels (mmol/L) (mean 5.17 vs. 4.78 respectively) and triglyceride levels (mmol/L) (2.81 vs. 2.27 respectively).

In summary, SA have lower HDL levels compared to 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[17] investigated retinopathy in T1DM in the UK cohort consisting of 2,626 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% confidence interval] (16.6% [10 – 23.2] vs. 14.1% [12.8-15.4] vs. 13.1% [9.4-16.8] respectively), clinically significant macular oedema (11.2% [5.4-16.9] vs. 6.5% [5.6-7.4] vs. 10.0% [6.7-13.3] respectively), sight threatening diabetic retinopathy (17.5% [10.6-24.3] vs. 12.1% [10.9-13.3] vs. 15.9% [11.8-20.0] respectively) and any diabetic retinopathy (54.0% [44.8-63.2] vs. 55.0% [53.2-56.9] vs. 42.8% [37.3-48.3] respectively).

Thomas et al[18], in South Africa, reported that SA (n=118) were at increased risk of any diabetic retinopathy (Odds ratio 2.02 95% CI 1.23-3.29) when compared with WE (n=1,247), after adjustment for age at diagnosis, sex, duration of diabetes, HbA1c, hypertension, and smoking status. Mehta et al[16] in the UK showed that SA (n=163) compared to WE (n=1,169) had decreased prevalence of retinopathy (38.7% vs. 48.0% respectively, p=0.025). Lastly, Omar et al[19], 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[16] in the UK, did not show any differences between SA (n=163) and WE (n=1,169) 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 (µmol/L) (median 76 vs. 78 respectively), albumin/creatinine ratio (mg/mmol) (median 2.4 vs. 2.5 respectively) and eGFR (ml/min/1.73^2) (median 97.3 vs. 91.2 respectively)[10]. Brabarupan et al[9] in the UK showed no difference in the prevalence of microalbuminuria (mg/mmol) between SA (n=39) and WE (n=565) (median 1.2 vs. 1.2 respectively), however, Africans (n=38) had significantly higher levels (median 3.7) (p<0.05). There were two

studies in South Africa comparing SA to Africans. The first by Omar et al[19] 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[12] also showed no statistically relevant difference between SA (n=38) and Africans (n=52) in creatinine levels (µmol/L) (mean 68.90 vs. 79.40 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 to 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[16] in the UK, showed that SA (n=163) compared to WE (n=1,169) have a lower prevalence of neuropathy (14.7% vs. 27.8% respectively, p<0.001). Omar et al[19] 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[12] in South Africa showed increased prevalence of neuropathy in SA (n=38) compared to 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[16] in the UK, did not show evidence of difference between SA (n=163) and WE (n=1,169) with T1DM in prevalence of cardiovascular disease (15.3% vs. 11.3% respectively, p=0.133). Sub-analysis 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 to 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[19] showed that none of their participants in either the SA (n=41) or African group (n=92) had peripheral vascular 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[15] in a UK study investigated mortality of SA patients compared to 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 23,326 non-SA there were 1,293 deaths (5.5%). Mortality in SA and non-SA with T1DM was calculated independently by comparing with the general population mortality using Standardized Mortality Ratios (SMR). Compared to the reference population, the SMR for SA patients were 3.9 (95% CI 2.0-6.9) in men and 10.1 (6.6-16.6) in women. The SMR for the corresponding non-SA were 2.7 (2.6-2.9) in men and 4.0 (3.6-4.3) in women. No details are provided as to the age of death in these patients. The most common cause of death in SA patients was cardiovascular disease (29.6%) and renal disease (14.8%). The 'other' causes of death accounted for 8 deaths (29.6%) and included septicaemia, 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 to the reference population in the UK. SA females were in particular affected, with a SMR that was over twice that of the non-SA female T1DM population. The commonest 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 to 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 commonest cause of death is cardiovascular disease.

Overall, the studies suggest that cardiovascular disease itself is no more common in SA T1DM compared to WE. The study by Mehta et al[16] 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. Whilst 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 to 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[20], 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 to 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 to native SA thought to be secondary to urbanisation and lifestyle[21]. 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. Firstly, the ethnic disparity in mortality that has previously been described in T2DM[22] 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[23], 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 to WE and have advocated lower cut-offs for BMI in SA; BMI> 23 overweight and BMI>25 obese[1, 24]. These culturally tailored programmes that have been attempted for T2DM may also be required for T1DM[25].

In addition, we may require more stringent control of other comorbidities such as hyperlipidaemia and hypertension[26], though this needs to be formally addressed. Secondly, 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.

Figure Legends

Figure 1: Flowchart demonstrating Study Selection

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; KK (Co-Chair) PS and PN are members of the South Asian Health Foundation Working group on Diabetes.

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The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: no additional data available.

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Contributorship Statement

Dr Komil N Sarwar: involvement in the design of the work, data collection, data analysis, writing the paper, drafting and revision of the paper

Dr Phoebe Cliff: involvement in the design of the work, data collection, data analysis, helped with

drafting and revision of the paper

Dr Ponnusamy Saravanan: involvement in the design of the work, reviewed all drafts of the paper, helped with revision of the paper

Professor Kamlesh Khunti - involvement in the design of the work, reviewed all drafts of the paper, helped with revision of the paper

Dr Krishnarajah Nirantharakumar - responsible for the conception and design of the work, reviewed all drafts of the paper, helped with revision of the paper

Dr Parth Narendran - responsible for the conception and design of the work, reviewed all drafts of the paper, helped with revision of the paper

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Figure 1: Flowchart demonstrating Study Selection

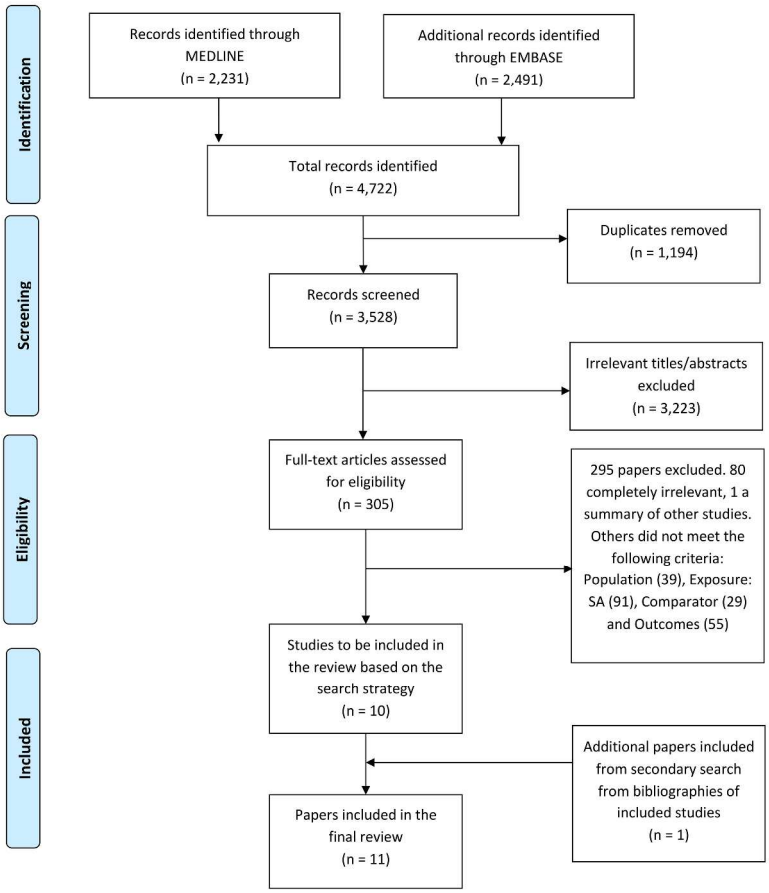

Figure 1: Flowchart demonstrating Study Selection

297x419mm (300 x 300 DPI)

Appendix 1: Search Strategy

Embase

1	type 1 diabetes.mp. or exp insulin dependent diabetes/	95641
2	ethnicity.mp. or exp ethnic group/ or exp race/ or exp ethnicity/ or exp "ethnic or racial aspects"/	288124
3	exp ethnic difference/	27336
4	exp South Asian/	27829
5	Sri Lanka.mp. or exp Sri Lanka	7081
6	Bangladesh.mp. or exp Bangladesh	13584
7	India.mp. or exp India	156225
8	Pakistan.mp. or exp Pakistan	22629
9	Nepal.mp. or exp Nepal	8792
10	Bhutan.mp. or exp Bhutan	507
11	maldives.mp. or exp Maldives	268
12	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	499040
13	**1 and 12**	**2491**

Medline

1	exp Diabetes mellitus, Type 1/ or type 1 diabetes.mp.	72398
2	insulin dependent diabetes.mp.	19957
3	exp ethnic groups/ or ethnicity.mp	158001
4	ethnic differences.mp.	6985
5	ethnic aspects.mp.	30
6	racial differences.mp.	5002
7	race.mp.	77099
8	racial groups.mp.	2853
9	racial aspects.mp.	34
10	South Asian*.mp.	3740
11	exp sri lanka/ or sri lanka*.mp	6443
12	exp bangladesh/ or bangladesh*.mp	11009
13	exp india/ or india*.mp.	164014
14	exp pakistan/ or pakistan*.mp.	17599
15	exp nepal/ or nepal*.mp.	7799
16	exp bhutan/ or bhutan*.mp.	468
17	maldives.mp.	195
18	1 or 2	82700
19	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	405983
20	**18 and 19**	**2231**

Appendix 2: Quality Assessment

Study	Design	Grading of study design	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
Braparupan et al[9]	Cross-sectional retrospective study	Selection: 1/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Subjects with T1DM diagnosed below 35 years of age from a London diabetes clinic. From white European, Afro-Caribbean or South Asian ancestry.	Not applicable	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in both groups. No methodology given so unclear if bias in the way outcomes measured in both groups.	**Effect of differences at baseline** Groups not matched for age and gender.	1.Abstract only so full methodology and results not available 2.Groups not matched for age and gender
Sarwar et al[10]	Retrospective case-controlled study	Selection: 0/5 stars Comparability: 2/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Patients with T1DM in 2 centres in the West Midlands	Patients matched for age and gender	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in both groups. No methodology given so unclear if bias in the way outcomes measured in both groups.	**Factors not included in the study** Methodology not given so bias may be introduced with the two centres	1. Abstract only
Shenoy et al[11]	Retrospective Observational Study	Selection: 1/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Children with T1DM between the ages of 2 and 18 years and who had been diagnosed more than a year ago.	Not reported	**Type of analysis and power calculation** Not reported	**Outcome** Obesity assessed in both groups. No methodology given so unclear if bias in between two groups.	**Effect of differences at baseline** Possibly multiple considering characteristics not described	1.No methodology given 2.No description of statistical analysis used 3.No data on South Asians vs. non-South Asians given in the results
Asmal et al[12]	Cross-sectional study	Selection: 0/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Clinic patients who fulfilled the following criteria: age of diagnosis of diabetes <35 years, development of symptoms +/- ketosis in the absence of insulin therapy, and duration of diabetes of at least 12 months. Patients with known alcoholic pancreatitic diabetes were not included.	Current age (2.9 years) Age of onset (3.8 years)	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in 2 groups, however details not given as to when measurements were taken and by whom and if standardised for both groups.	**Effect of differences at baseline** Younger age and age of onset in South Asians may have led to a mis-representation of biochemical data in this group	1.No statistical methods were used to compare the two groups

Ismail et al[13]	Cross Sectional study	Selection: 2/5 stars Comparability: 0/2 stars Outcome: 3/3 stars	**South Asian Ethnicity** Identified by their appearance, language and religion	**Inclusion Criteria** T1DM defined as acute symptoms associated with heavy ketonuria (>3+) or ketoacidosis at diagnosis, or continuous treatment with insulin within 1 year of diagnosis. All diagnosed < 40 years	Similar baseline characteristics	**Type of analysis** Documented **Power calculation** Not reported	**Outcome** Same outcome measures in 2 groups	**Effect of differences at baseline** No differences	1.Clinic-based and not a population-based study. Those attending hospital may have more severe diabetes. 2.Conducted in public hospital where majority of patients cannot afford lipid-lowering therapy.
Omar et al[14]	Cross-sectional study	Selection: 0/5 stars Comparability: 0/2 stars Outcome: 2/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Patients with onset of IDDM <35 years at King Edward Hospital in Durban. Diagnosis of IDDM based on the criteria recommended by WHO.	Age at onset (6.5 years) Duration of diabetes (1.6 years)	**Type of analysis and power calculation** Not reported	**Outcome** Same outcome measures in 2 groups, however details not given as to when measurements were taken and by whom and if standardised for both groups.	**Effect of differences at baseline** Older age of onset and longer duration of diabetes in South Asians may have led to over-representation of complications in this group.	1.No statistical methods were used to compare the two groups
Swerdlow et al[15]	Prospective Cohort Study	Selection: 4/4 stars Comparability: 0/2 stars Outcome: 3/3 stars	**South Asian Ethnicity** Identified by computer algorithm (SANGRA) followed by a clerical check by an individual with expertise in this area. Sensitivity of 89-96% and specificity of 94-98%.	**Inclusion Criteria** Age at diagnosis of diabetes <30 years. Some identified in a national register of childhood cases assembled by the BDA from 1972-1986 and remainder from various geographical registers for parts of the UK during 1972-1993. Ages at diagnosis varied. Total cohort of 23, 752 with T1DM.	Age distributions of person-years were similar between the 2 groups	**Type of analysis** Standardised mortality ratios compared using chi squared test. **Power calculation** Not reported	**Follow up** Till 31st December 1999, or the date of death, 85th birthday, emigration or other loss of follow up. **Lost to Follow up** 1 South Asian and 151 non South Asians lost to follow up through emigration. 50 non South Asians lost to follow up in other ways. **Outcome** Mortality assessed in the same way in both groups.	**Effect of differences at baseline** No differences in age distributions. However, differences in comorbidities not reported. May be significant in mortality rates.	1. Assumption that people diagnosed <30 years had T1DM and those diagnosed >30 years had T2DM. 2. Ethnic makeup of the non- South Asian group not reported (assumed Caucasian). 3. Small number of deaths in South Asian group.
Mehta et al[16]	Cross-sectional study	Selection: 1/5 stars Comparabi	**South Asian Ethnicity** Ethnicity	**Inclusion Criteria** Diabetes patients attending a specialist	Age (3.4 years) Duration of diabetes (5.9	**Type of analysis** Documented	**Outcome** Baseline data and comorbidities data collected in the same way in both	**Effect of differences at baseline**	1.Cross sectional design so causation cannot

		lity: 2/2 stars Outcome: 3/3 stars	identified based on that given in the patient's record or by use of name recognition software 'Nam Pechan' supplemented by a visual inspection of surnames and forenames.	outpatient diabetes clinic in Leicestershire, UK, between 2003 and 2005. Methodology of patients being classified as T1DM or T2DM not reported.	years) Smoking (13.7%)	**Power calculation** Not reported	groups. Classification the same in both groups.	Younger age of onset and shorter duration of diabetes in South Asians may have led to under-representation of comorbidities in South Asians with T1DM.	be established 2.Data from one hospital, not generalizable 3.Did not comment on frequency of attendance for blood glucose monitoring so relationship between HbA1c and comorbidity not clear
Sivaprasad et al[17]	Cross-sectional study	Selection: 1/5 stars Comparability: 1/2 stars Outcome: 3/3 stars	**South Asian Ethnicity** Self-reported ethnicity recorded at the time of screening according to the codes used in the Census 2001.	**Inclusion Criteria** All subjects in the diabetic screening register of West Yorkshire and South East London programmes were included in this study. Coverage of diabetic people in the respective regions: 95% in West Yorkshire and 81% in South East London	Not reported	**Type of analysis** Documented **Power calculation** Not reported	**Outcome** Diabetic screening and retinopathy assessment same in both groups.	**Effect of differences at baseline** Possibly multiple considering characteristics not described	1.Records of patients that were not obtainable or exempt from diabetic screening (12%) did not have ethnicity data so South Asians may have been under-represented 2.Did not assess factors like BP, glycaemic control
Thomas et al[18]	Retrospective observational study	Selection: 1/5 stars Comparability: 2/2 stars Outcome: 3/3 stars	**South Asian Ethnicity**	**Inclusion Criteria** Subjects classified as having T1DM or T2DM on clinical assessment according to the American Diabetes Association classification of diabetes.	Age (4.1 years) Duration of diabetes (4 years)	**Type of analysis** Documented **Power calculation** Not reported	**Period of study** 2001-2010 with baseline characteristics being obtained at the time of initial presentation. **Outcome** Same outcome measures in 2 groups but data collected from 2001-2010 so may be discrepancies between people being screened at the beginning and the end of the study. **Drop out or withdrawals** None reported	**Effect of differences at baseline** Younger age of onset and shorter duration of diabetes in South Asians may have led to under-representation of retinopathy in South Asians with T1DM.	1.Study carried out in private hospital whereas most of diabetic South Africans use public health system so not generalizable 2.Lack of dilation prior to obtaining images may have led to underreporting of retinopathy
Omar et al[19]	Cross sectional study	Selection: 0/5 stars Comparabi	**South Asian Ethnicity**	**Inclusion Criteria** Onset of diabetes mellitus <35 years. Classification	Duration of diabetes (1.6 years)	**Type of analysis** Documented	**Outcome** Same outcome measures in 2 groups	**Effect of differences at baseline**	1. No outcomes apart from age of onset, duration of

		lity: 0/2 stars Outcome: 2/3 stars		of IDDM and NIDDM based on the criteria recommended by the National Diabetes Data Group and WHO Expert Committee on Diabetes Mellitus. IDDM patients had always depended on insulin for control of symptoms and prevention of basal ketosis		**Power calculation** Not reported		Not relevant as this is a purely descriptive analysis	disease and body weight. Limited information provided by study