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Prevalence and progression of diabetic nephropathy in South Asians, White Europeans and Afro-Caribbeans with Type 2 diabetes; a systematic review and meta-analysis

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Abstract

Introduction: Diabetic nephropathy remains the most common cause of renal disease in patients diagnosed with type 2 diabetes.

Aims: We conducted a systematic review and meta-analysis of published observational evidence to assess the difference in the prevalence and progression of diabetic nephropathy, and the development of end-stage renal failure in three ethnicities with type 2 diabetes.

Methods: Relevant studies were identified in a literature search of MEDLINE, EMBASE, and reference lists of relevant studies to May 2018. We decided *a priori* that there were no differences in the prevalence and progression of diabetic nephropathy, and the development of end-stage renal failure in the three ethnicities with type 2 diabetes. Pooled relative risks of microalbuminuria by ethnicity were estimated by fitting three random effects meta-analyses models. A narrative synthesis of the nephropathy progression in the studies was done. The review was registered on PROSPERO (registration number CRD42018107350).

Results:

Thirty-two studies with data on 153,827 unique participants were eligible. The pooled prevalence ratio of microalbuminuria in South Asian compared to White Europeans was 1.14 (95% CI: 0.99, 1.32 p=0.065). For African Caribbeans vs South Asians the pooled prevalence ration was 1.08 (95% CI: 0.93, 1.24), p=0.327. Results surrounding renal decline were inconsistent with preponderance towards a high rate of disease progression in South Asians compared to White Caucasians. The estimated pooled incident rate ratio for end stage renal disease was significantly higher in African Caribbeans vs White Europeans 2.75 (95% CI: 2.01, 3.48 p<0.001)

Conclusion: This review did not find a significant link between ethnicity (South Asians, White Europeans and Afro-Caribbeans) and the prevalence of microalbuminuria. However,

the incident rate ratio of end stage renal disease in African Caribbeans compared to White Europeans was significantly higher. Further research is needed to explore the potential non-albuminuric pathways of progression to end stage renal failure.

Introduction

Diabetes is a substantial public health problem and the most common cause of end stage renal disease globally. The relative contribution of type 2 diabetes (T2DM) to the increasing burden of end stage kidney disease has been well established (1) (2). With the rising epidemic of T2DM, obesity and an ageing population, it is anticipated that the burden of renal disease on health systems will increase further.

A migrant is defined as someone who has either changed their usual country of residence or settled in another country such as the US, Europe or Australia or is a descendant of the former (3). Globally migration is increasing, with the number of international migrants reaching 258 million in 2017 (4). 79.6 million originated from Asia. Many of these migrants were of South Asian origin with 17 million originating from India alone. 24.7 million of the migrants were of African origin, making Africa the fourth largest contributor in 2017 (4).

The 2011 UK Census demonstrated an increase in the ethnic minority population. South Asian and Afro-Caribbean migrants comprise about 8% and 3% of the total population in the UK, respectively. Together these ethnicities make up more than half of the UK's non-European population (5).

It is well established that South Asian and Afro-Caribbean adults develop T2DM at a much younger age compared to their White counterparts and exhibit a marked predisposition to cardiovascular disease and end-stage renal failure (6) (7). In the UK, a higher incidence of central obesity and vascular disease has been reported in migrant South Asians when compared to White Europeans despite lower levels of cardiovascular risk factors (7) (8). It is likely that higher levels of insulin resistance drive the higher rates of vascular disease and diabetes in this population (9).

A number of studies indicate that the risk for the development and progression of diabetic nephropathy varies among different populations (8) (10) (11). The incidence of end stage kidney disease due to both T1DM and T2DM is higher among South Asians compared to White Europeans (12), (13). However, the literature on diabetic nephropathy in ethnic groups is sparse and varied and it is not clear whether progression or higher levels of urine albumin excretion influence similar rates of e-GFR decline among different ethnic populations despite similar competing risks and therefore may impact rates of prevalence of end stage renal failure.

The objective of this systematic review and meta-analysis was to examine and analyze published evidence on the prevalence of albuminuria, rates of disease progression and end stage renal disease outcomes in White European compared to South Asian and Afro-Caribbean adults with nephropathy due to T2DM. We decided *a priori* that there were no differences in the prevalence and progression of diabetic nephropathy, and the development of end-stage renal failure in various ethnicities with type 2 diabetes.

Methods

Search strategy

Medline (1950 to week 1 May 2018), Embase (1980 to week 1 May 2018), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Renal Group trial register were searched using a broad search strategy to identify all potentially relevant publications for this review. Population search terms, including Medical Subject Heading (MeSH) 'Asian Continental registry group', 'Asians', Indians', 'Pakistanis', 'Bangladeshis', 'Afro-Caribbeans' and 'ethnic minority population' were combined with MeSH terms that covered T2DM, diabetes mellitus, nephropathy, renal disease, end-stage renal disease (ESRD) and albuminuria. Free text terms were also used to optimise search sensitivity. Reference lists were checked to identify any further articles. Studies were not limited to the English language, however none of the relevant studies required translation to the English language.

Study selection

Only studies comparing the ethnicities; White Europeans, South Asians and Afro-Caribbeans, in whichever combination, in adult T2DM patients with diabetic nephropathy were included. Where studies compared ethnicities other than the ones included in our selection criteria, data for South Asians, White Europeans and African Caribbeans was extracted separately. We excluded "American Asians" or "Asians" unless clearly defined, since they may comprise of Arab/ Chinese/ Hmong/ Lebanese/ Turkish/ Bangladeshi/ Filipino/ Indian/ Korean/ Pakistani/ Taiwanese populations and therefore could not be categorized as South Asians or people originating from the Indian subcontinent. We used the term "African Caribbeans" to mean people of African descent wherever they are living in world.

Additionally, those studies that did not differentiate between T1DM and T2DM were only included if the estimated T2DM sample was ≥ 80% of the total sample. Since the review was aimed at identifying three key aspects of diabetic nephropathy, we grouped selected studies under "prevalence", "progression" and "outcomes studies".

Prevalence is defined as the number of cases existing at a given time in a given population usually expressed as a percentage (14). Since the definition of "Diabetic nephropathy" encompasses those with "incipient nephropathy", defined as the presence of microalbuminuria and those with "overt nephropathy", defined as those with macroalbuminuria or overt proteinuria (15), we included all studies that measured either one or both of these outcomes in terms of prevalence of disease. Microalbuminuria and proteinuria were measured using different definitions across the majority of studies. In this review, microalbuminuria was defined as an albumin creatinine ratio (ACR) of >2 mg/mmol and proteinuria as >30 mg/mmol. Prevalence studies carried out in a representative population and examining at least 50 participants or more were included in the review.

Progression studies included all studies that examined the progression/remission of albuminuria or estimated glomerular filtration rate (eGFR) decline. Studies where progression was based on CKD stages (1-5) as defined by the National Kidney Foundation Disease Outcome Quality Initiative working group guidelines on the classification of chronic kidney disease were included. Studies reporting the doubling of serum creatinine, or changes in creatinine clearance over time were also included in this review.

Outcome studies included any studies related to the development of End-Stage Renal Disease (ESRD), when the kidneys permanently fail to work as a result of diabetic nephropathy in patients with T2DM. The review was registered on PROSPERO CRD42018107350.

Methods of the review

The titles and abstracts of all articles identified by the broad literature search were assessed independently by two reviewers (CJ and SS). Studies that did not meet inclusion criteria were discarded. Full texts of selected articles were retrieved and assessed to determine if they met the inclusion criteria. A consensus was reached in case of any inconsistency with involvement of a third (KK). Those studies which met the inclusion criteria were included in the review and data was extracted independently using a standard data extraction form.

Quality scoring of selected studies

We created a quality scoring system ranging from 0 to 6 points based on parameters identified by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (16). We used four pre-defined domains namely: selection criteria, measurement of exposure, objective diagnostic procedure and controlling for confounders to assess the quality of the studies. Six points on the MOOSE reflects the highest study quality. (APPENDIX 1)

Statistical analysis

Pooled relative risks of microalbuminuria by ethnicity were estimated by fitting three random effects meta-analyses models. Heterogeneity between studies was assessed using the I-squared statistics (17). For incidence of ESRD by ethnicity, data from studies was combined in a random effects meta-analysis model. Incidence was reported using incidence rate ratios (IRRs). In some studies the standard error of the IRR was calculated using published formula (18) (19) (20). Studies reporting hazard ratios, which can be assumed to estimations of the IRR, were also included in this review. As the impact of both age and duration of diabetes on the incidence of microalbuminuria may differ by ethnicity, we conducted meta-regression analyses to adjust for both these factors. This was done by extracting data on mean age and duration by ethnicity and calculating the difference in means between ethnic groups for each study. By fitting this difference in means in a meta-regression model, the reported intercept will be the estimated rate ratio for ethnicity when the difference in mean age or duration is zero.

For all meta-analyses models fitted, funnel plots and Egger's tests were carried out to assess for publication bias. Since there was substantial heterogeneity due to large differences in clinical or methodological nature between the studies in terms of the reporting of the progression of diabetes nephropathy, we decided *a priori* not to pool the data on nephropathy progression from the studies in a meta-analysis. Instead, we did a narrative synthesis of the nephropathy progression in the studies. STATA release 15 (Stata Corp, College Station, Texas, USA) was used for all statistical analyses.

Results

The search yielded a total of 2329 articles. 54 articles were retrieved for more detailed evaluation of the full text (Figure 1.1). APPENDIX 1 shows a flow diagram of the search strategy. Applying our inclusion criteria, 22 studies were excluded. 32 studies were identified as being suitable for this review, with the studies collectively reviewing 153,827 patients. The studies identified 84,718 White European participants, 24, 298 South Asian and 19,961 African Caribbean participants.

Among the 32 studies, 18 were conducted in the UK, 3 in Netherlands, 3 in Australia, 7 in the USA and 1 study in Brazil.

Study Quality

Quality scores for 32 studies included in this review are shown in Table 1.2. Overall, the quality of studies was high (median 5, IQR 4-6), with thirteen studies achieving the highest score.

Prevalence of diabetes nephropathy

Data were extracted from 20 studies on prevalence of microalbuminuria in patients with T2DM by ethnic group (Table 1.1). The study by McGill et al. (21) was excluded from the meta-analysis as data was presented as odds of having microalbuminuria rather than the number/percentage of participants affected. The pooled prevalence rate ratio of microalbuminuria in South Asian compared to white European patients with type 2 diabetes was 1.14 (95% CI: 0.99, 1.32 p=0.07) (Fig 2.1). Similarly, for African Caribbeans vs White Europeans the pooled prevalence rate ratio was 1.06 (95% CI: 0.93, 1.20), p=0.35, and for African Caribbeans vs South Asians the pooled prevalence rate ratio was 1.08 (95% CI: 0.93, 1.24), p=0.33 (Fig 2.2). The I-squared value from the three random effects meta-analysis, indicated the amount of variation in the effect sizes attributable to study heterogeneity was moderate to high at 98.70%, 53.00% and 50.10% respectively. After adjusting for differences in mean age and duration of diabetes between ethnic groups in a meta-regression analyses, there was still no statistically significant differences in in the prevalence of microalbuminuria. The estimated prevalence rate ratios in South Asian vs White European was 1.15 (0.99, 1.32) p=0.570, African Caribbeans vs White European was 0.97 (95% CI: 0.63, 1.46) p=0.826, and South Asian vs African Caribbean was 0.95 (0.85, 1.06), p=0.524.

Progression of diabetes nephropathy

Five studies reported the progression of diabetic nephropathy (Table 2). Three studies measured progression of disease in South Asians, White Europeans and Afro Caribbeans (22) (23) (24) whereas two only compared progression in South Asians and White Europeans (25) (26). Three out of the five studies recorded annual eGFR decline (22) (23). The remaining two studies assessed progression of renal disease by recording serial serum creatinine measurements (26), assessing time taken for serum creatinine to double (24) and lastly measuring creatinine clearance over a set period of time (25). In summary, in three of the studies, differences were noted in the progression of renal deterioration among the three ethnic groups, thus confirming the alternative hypothesis. Two studies showed no differences in the progression of renal deterioration. Assessing the annual decline in eGFR, one study found a non-significant decline in Afro-Caribbean's of -2.12 ml/min/1.73m^2 compared to White European's (-1.93 ml/min/1.73m^2) and South Asians (-1.85

ml/min/1.73m^2) (22). The second study reported a significant difference in all three groups with White Europeans demonstrating an annual decline of -0.64 (95% CI -0.68, -0.60), South Asians of -0.77 (-0.81, -0.74) and Afro-Caribbeans of -0.55 (95% CI -0.61, -0.48) (23). Similarly, Chandie-Shaw et al (25) assessed eGFR decline but over a 5-year period. They found a decline of 32 ml/min in South Asians and 22 ml/min in White Europeans (p=0.049). Of the remaining two studies, one study found a mean estimated rise in creatinine (ß) of 5.36 (95% CI, 2.21-8.52) vs 2.22 (95% CI, 1.31-3.14) in White Europeans and 3.14 (95% CI, 0.82-5.46) in Afro-Caribbean's, p<0.05 (24). Finally, Koppiker et al, (26) compared the interaction between creatinine-ethnicity using serum creatinine as a time dependent variable. Results from extended Cox modelling found a risk ratio (95% CI) of 1.00 (0.99, 1.02) between South Asians and White Europeans. A meta-analysis was not performed since measurement of disease progression differed across the studies.

End-Stage Renal Disease

Ten studies reported the incidence of ESRD in the three ethnicities relevant to this review. However, three of the studies where data were extracted were not included in the study; Chandie Shaw et al (27) and Gerchman et al (28) reported odds of having eGFR rather than incidence rates, and Omer Ali (22) reported different clinical outcomes relating to decline in kidney function.

The estimated pooled IRR for ESRD was significantly higher in African Caribbeans vs White Europeans 2.75 (95% CI: 2.01, 3.48 p<0.001) (Fig 3.1). The pooled IRR for South Asians vs Western Europeans (Fig 3.2) was 0.88 (95% CI: -0.18, 1.94), p=0.104, from three studies. Between study heterogeneity was again high, with I-squared values of 86.9% and 76.6% for the two meta-analyses.

All Egger's tests for publication bias were non-significant, and an examination of the funnel plots raised no concerns for the presence of publication bias. The number of studies included in the meta-analyses models were fairly small, and heterogeneity was high.

Discussion

This systematic review and meta-analysis of published prevalence studies showed no significant differences in the prevalence of microalbuminuria in South Asians and Afro-Caribbeans compared to White Europeans with T2DM. Of the 5 studies identified for this review for various markers of renal impairment progression, when comparing the rates of deterioration between south Asians and white Caucasians, the results were inconsistent with preponderance towards a high rate of disease progression in south Asians compared to white Caucasians. This is consistent with previous literature (23) (27) (24). Similarly, an inconsistent pattern of renal disease progression rates was found in studies that compared blacks with white Caucasians, but two (22) (24) out of the three studies identified showed a higher rate in blacks compared to white Caucasians. These results are in keeping with studies assessing the progression of renal disease in non-diabetics. In the observational analysis of combined data from the Third National Health and Nutrition Examination Survey and the US Renal Data System, which includes patients without diabetes, even though the prevalence of CKD was similar among African Americans and among persons of white race/ethnicity, the estimated progression rates among those with CKD were 5-fold higher among African Americans (29). It is acknowledged that some of the differences found in this systematic review for prevalence of microalbuminuria between ethnic groups, may be due to differences in age and duration of diabetes by ethnicity. This was explored through meta-regression analyses, although the analyses that could be carried out were limited as not all studies reported the relevant data. Meta-regression analyses lack power, as only study level data is available. To really understand the complexity of these relationships individual patient data is needed.

With regards to ESRF, there was a significant difference in the IRR between African Caribbeans vs White Europeans. In the African American Study of Kidney Disease and Hypertension (AASK) (30) (31) (32), which did not meet the inclusion criteria of this review, a beneficial effect of RAAS inhibition was noted which is likely to be along the proteinuria axis, as this has been confirmed in other landmark trials (33) (34). Despite these benefits, other studies have shown that African Americans who are treated with RAAS therapy continue to progress during the long term follow ups (35). This progression to ESRF could be occurring across other non-albuminuric pathways that yet remain to be established (36). Other reasons including genetic predisposition (particularly with recent discovery of apolipoprotein L1) (37), obesity, low socioeconomic status, high-risk health behaviours (such as poor diet), and limited access to healthcare could also account for the continuous progression. In our analysis, despite the finding of equivalence in prevalence of albuminuria between the African Caribbeans and White Europeans, the IRR of ESRF was 2.75, suggesting an alternative pathway to ESRF in addition to the albuminuric pathway, probably more predominant in the African Caribbean race.

Whatever the reasons for this disparity, standardized interventions and improved health care delivery in these high-risk individuals is required to reduce the variations in renal outcomes in these populations. In a recent post-hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial looking at the longitudinal change in eGFR, time to development of microalbuminuria, macroalbuminuria, incident CKD, and kidney failure or serum creatinine > 3.3 mg/dL (38), it was noted that even though the mean values of systolic blood pressure, hemoglobin A1c microalbuminura, macroalbuminira and serum creatinine levels were higher in blacks at baseline, both blacks and whites achieved similar rapid improvement of both clinical parameters, which were maintained during study follow-up. This suggests that optimization of the delivery of diabetes care prior to the development of CKD may lead to similar short-term kidney outcomes, irrespective of race.

Strengths and Limitations of the review

The strengths of this systematic review are the use of a broad search strategy performed on multiple databases and the involvement of two independent reviewers for the study selection and the data extraction phases. Limitations in the studies include estimating the prevalence of microalbuminuria and proteinuria using albumin creatinine ratio (ACR) that was reported on the basis of a single random urine sample or an early morning sample. The use of a single ACR value may underestimate microalbuminuria in those with a higher muscle mass, including males and could be affected by variations in diet or physical exercise (39). The presence of selection bias is another limiting factor which can have a considerable impact on prevalence estimates of the different stages of diabetic nephropathy. Different methods for ascertainment of outcomes were also used in the studies, making this a limiting factor during comparisons.

The number of studies in this review was limited because seven of the 22 excluded studies was due to lack of differentiation between the types of diabetes as a cause of underlying diabetic nephropathy. This is an important differentiating feature which has been ignored in these studies. Generally, it is estimated that 20-30% of people with T1DM develop proteinuria, and a large number progress to renal failure (40). Fewer patients with T2DM progress to ESRD but despite this they account for a large majority of patients on renal units. This is largely due to the higher prevalence of T2DM compared to T1DM. Racial differences have also been observed between T1DM and T2DM patients with nephropathy (12).

Conclusion

This systematic review and meta-analysis of published prevalence studies showed that the pooled estimates of microalbuminuria, were numerically higher in South Asians compared to White Europeans, however these results were not statistically significant. This review was able to identify few studies relating to progression of diabetic nephropathy between South Asians and White Europeans. Our results were inconsistent with South Asians and African Caribbeans demonstrating a faster progression than White Europeans in some of the studies, however due to considerable heterogeneity between these studies, no definite conclusion can be drawn on whether disease progression is significantly different in these individuals. This review found a significantly higher IRR of ESRF in African Caribbeans compared to White Europeans. These results have highlighted the need for more research on the potential non-albuminuric pathways of progression to ESRF with a focus on ethnic origin to explore if a correlation between the two exists. This systematic review has also revealed the sparsity in studies looking at the progression of diabetic nephropathy in patients with T2DM. This has highlighted the need for more research studies to determine if ethnic disparities do exist in disease progression and outcomes of T2DM nephropathy which can guide early, targeted interventions and improved health care delivery in these high-risk individuals.

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Duality of Interest

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme.

SS has acted as consultant, advisory board member and speaker for Novo Nordisk, Amgen, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, NAPP and Novartis. He has received research grants Jansen.

MJD has acted as consultant, advisory board member, and speaker for Novo Nordisk, Sanofi, Eli Lilly and Company, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. MJD has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi, and Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

CG, DK WC and CJ have no conflicts of interest

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Fig. 2.1: Difference in the Risk of developing microalbuminuria in South Asian and White European patients with T2DM. CI, confidence interval (bars)

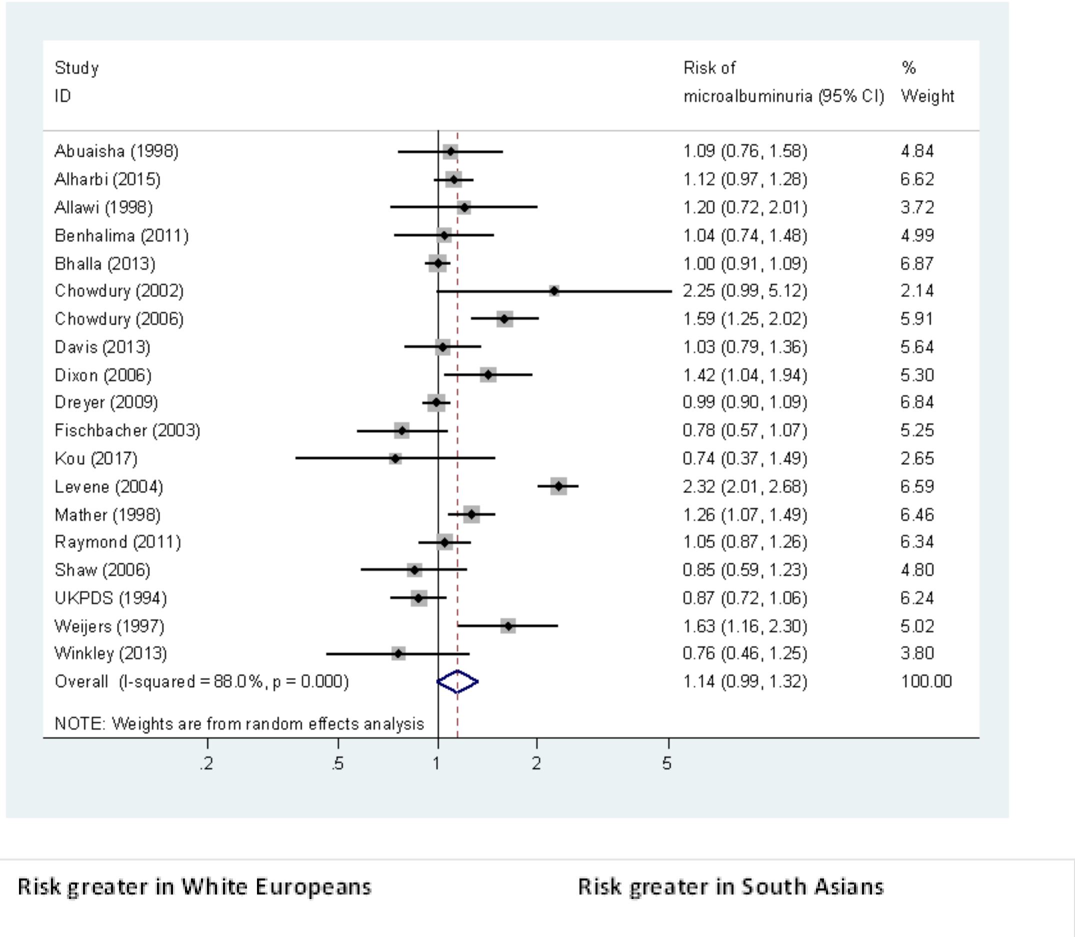
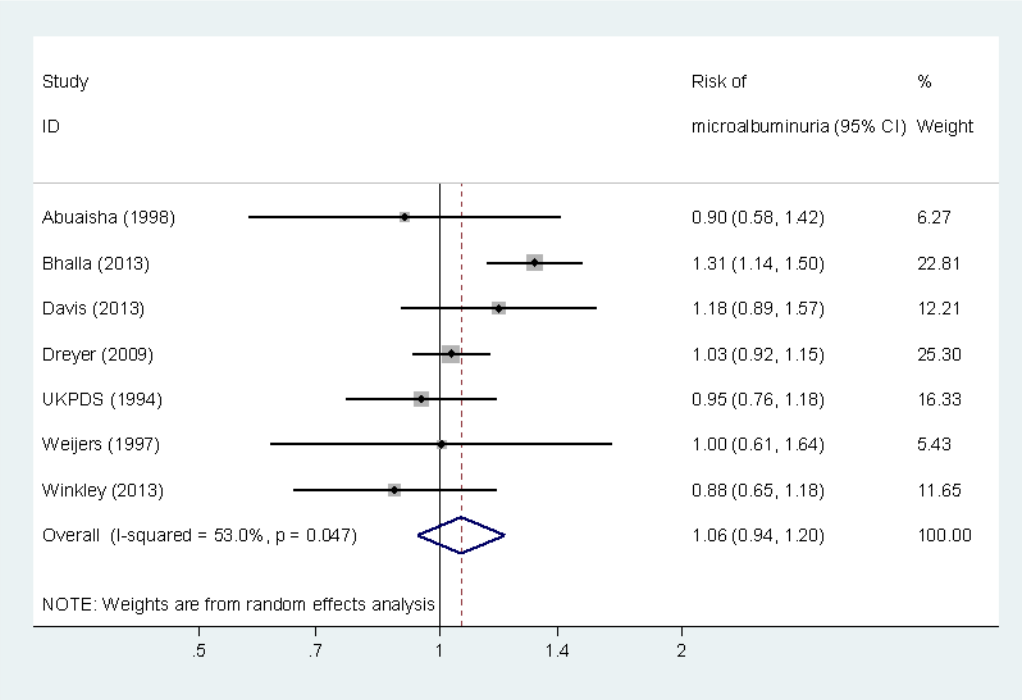
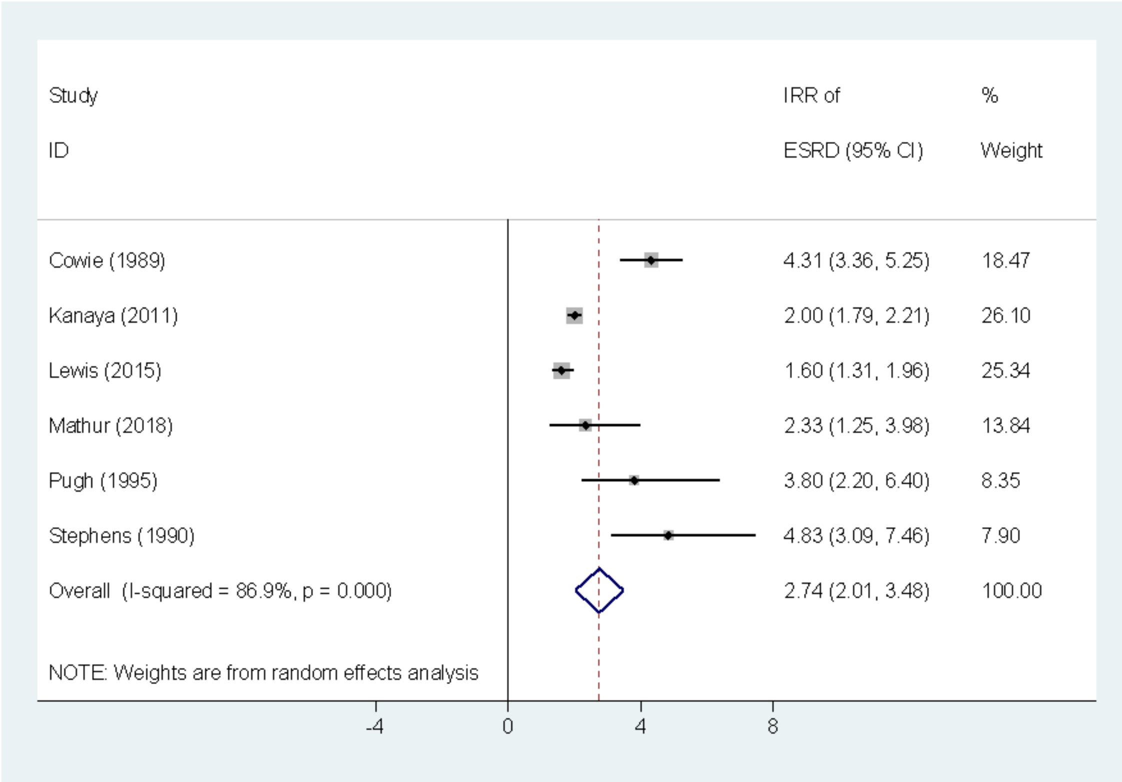


Fig 2.2 Difference in the Risk of developing microalbuminuria in Afro-Caribbean and White European patients with T2DM. CI, confidence interval (bars)



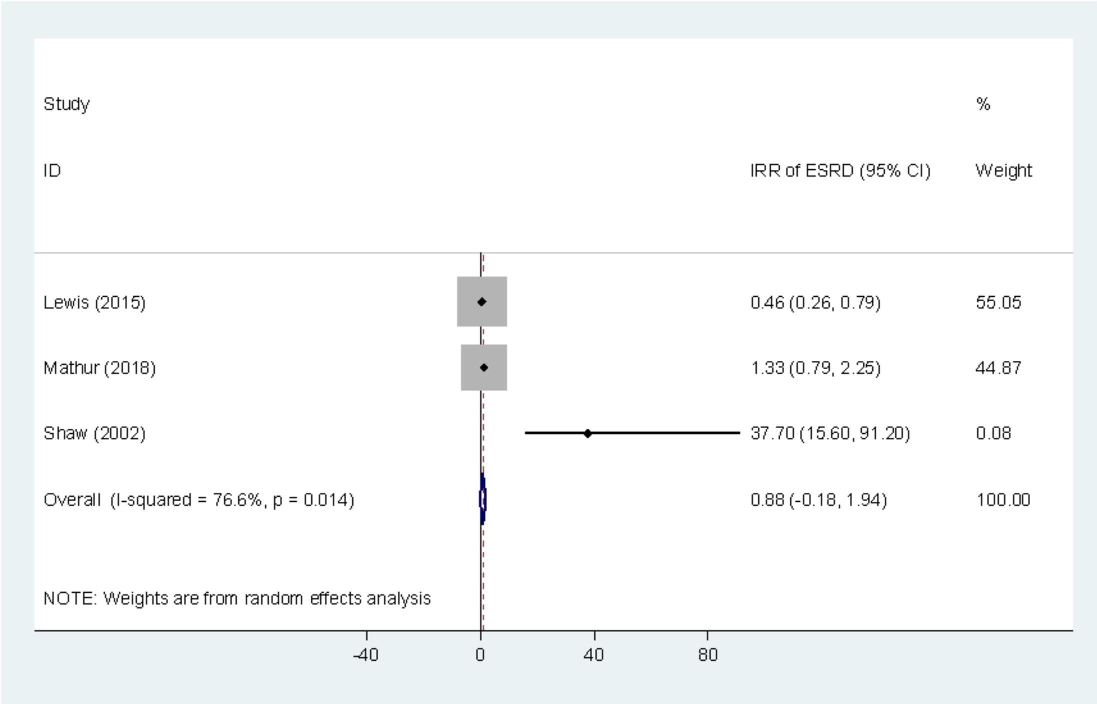
Risk greater in White Europeans   Risk greater in African Caribbeans

Fig 3.1 Difference in the incidence rate of ESRD developing in African Caribbean vs White European patients with T2DM. CI, confidence interval (bars)



IR greater in White Europeans **IR greater in African Caribbeans**

Fig 3.2 Difference in the incidence rate of ESRD developing in South Asian vs White European patients with T2DM. CI, confidence interval (bars)



IR greater in White Europeans **IR greater in South Asians**

Table 3. Meta-regression analyses for prevalence rate ratios of albuminuria

Comparison	*Analysis*	*Predicted RR (95% CI)*	*p-value*	*Number of studies included in the analysis*
South Asian vs Western European	Unadjusted	1.15 (0.99, 1.32)	0.065	19
	Adjusted for difference in mean age	1.08 (0.81, 1.42)	0.570	14
	Adjusted for difference in mean duration	1.25 (1.06, 1.48)	0.015	9
Afro-Caribbean vs Western European	Unadjusted	1.06 (0.93, 1.20)	0.350	7
	Adjusted for difference in mean age	0.97 (0.63, 1.46)	0.826	6
	Adjusted for difference in mean duration	Not enough data to calculate	-	-
South Asian vs Afro-Caribbean	Unadjusted	1.08 (0.93, 1.24)	0.327	7
	Adjusted for difference in mean age	0.95 (0.85, 1.06)	0.238	6
	Adjusted for difference in mean duration	0.95 (0.47, 1.94)	0.524	3

Not enough studies reported mean age and duration by ethnicity, to allow meta-regression models to be fitted for the three meta-analyses investigating incidence.

Table 1.1 Characteristics of prevalence studies in the systematic review.

Study	Mather et al, 1998 (41)	Dixon et al, 2006 (42)	Chowdhury et al, 2002 (43)	Weijers et al, 1997 (44)	McGill et al, 1996 (21)	Kou et al, 2017 (45)	Levene et al, 1994 (46)
Population	Secondary care clinic	Primary care - UKADS	Primary & Secondary clinic	Referred to secondary care	Diabetes centre	Secondary care clinic	Primary care practices
Country	United Kingdom	United Kingdom	United Kingdom	The Netherlands	Australia	Australia	United Kingdom
Race comparisons	SA and WE	SA and WE	SA and WE	SA, WE and AC	SA and WE	SA and WE	SA and WE
No. participants	1472	552	292	1124	1845	204	1362
South Asians, n(%)	889	311	165	167	115	23	308
White Europeans, n(%)	583	241	127	603	896	85	903
Afro-Caribbean's, n (%)	-	-	-	126	-	-	-
Mean age/range, yrs							-
South Asians	58	61	34	52	51	54	
White Europeans	66	66	35	64	59	63	
Afro-Caribbean's	-	-	-	57	-	-	
Gender							-
South Asians males, n	542	160	96	87	71	17	
White Europeans males, n	347	140	72	261	493	51	
Afro-Caribbean's males, n	-	-	-	39	-	-	
BMI, kg/m^2							-
South Asians	27.5	-	26.0	26.8	26.3	27.3	
White Europeans	29.2	-	27.2	29.1	30.8	34.8	
Afro Caribbean's	-	-	-	28.2	-	-	
Mean BP. mmHg							-
South Asians	139/75	145/82	127/80	139/80	132/82	130/76	
White Europeans	143/77	144/76	123/76	147/83	139/81	142/77	
Afro-Caribbean's	-	-	-	145/83	-	-	
Hypertensives, (n)		-	-	-	-	-	-
South Asians	341						

White Europeans	226						
Afro-Caribbean's	-						
Definition of urinary albumin excretion (MA/P)	MA (mg/mmol): ♀ ACR > 4.5 ♂ ACR > 2.5	MA (mg/mmol): ACR 3.5-30.0 P: >30 mg/mmol	MA (µg/min): ACR 20-200 P: >200 µg/min	P: ACR > 30 mg/mmol	MA (µg/min): ACR 50-200 P: ACR>200 µg/min	MA: Abnormal ACR – nil figures	MA (mg/mmol): ♀ ACR > 3.5 ♂ ACR > 2.5 P: >200 µg/min
Urinary estimation method	Early morning sample	Early morning sample	Timed urine collection	Not stated	Timed urine collection	Not stated	Early morning sample
Prevalence of UAE, (n)					-		
South Asians	332	122	30	40		7	271
White Europeans	160	59	10	81		39	253
Afro-Caribbean's	-	-	-	17		-	-
OR for MA (OR, 95% CI), p	P=0.0008		-	-	P=0.7	-	P= 0.39
SA vs WE	1.65 (1.23, 2.21)	2.0 (1.3, 3.2)			0.9 (0.4-1.9)		1.20 (0.78, 1.84)
AC vs WE							

Study	Fischbacher et al, 2003 (47)	Raymond et al, 2011 (48)	Allawi et al, 1998 (49)	Chowdhury et al, 2006 (50)	Bhalla et al, 2013 (10)	Shaw et al, 2006 (25)
Population	Primary care – Newcastle Heart project	Primary care – UKADS	Secondary care clinic	Secondary care clinic	Primary care	Outpatient diabetic clinic
Country	United Kingdom	United Kingdom	United Kingdom	United Kingdom	California	The Netherlands
Race comparisons	SA and WE	SA and WE	SA and WE	SA vs WE	SA, WE and AC	SA and WE
No. participants	1509	1852	236	2074	15,683	304
South Asians, n(%)	684	1486	154	912	1862	149
White Europeans, n(%)	825	492	82	1162	8728	155
Afro-Caribbean's, n (%)	-	-	-	-	457	-
Mean age/range, yrs						-
South Asians	50	49.6	51	52	51	
White Europeans	54	59.3	57	57	63	

Afro-Caribbean's	-	-	-	-	58	
Gender						-
South Asians males, n		727	93	484	1210	
White Europeans males, n		271	52	604	4748	
Afro-Caribbean's males, n		-	-	-	198	
BMI, kg/m^2		-				-
South Asians	27.4		27.4	27.9	27.3	
White Europeans	26.3		28.0	27.2	31.9	
Afro Caribbean's	-		-	-	32.7	
Mean BP. mmHg						-
South Asians	121/70	140/83	136/83	131/81	123/74	
White Europeans	130/75	144/82	140/82	129/79	128/74	
Afro-Caribbean's	-	-	-	-	131/77	
Hypertensives, (n)	-			-		-
South Asians			55		1277	
White Europeans			31		7785	
Afro-Caribbean's			-		414	
Definition of urinary albumin excretion (MA/P)	MA (mg/mmol): ♀ ACR > 3.5 ♂ ACR > 2.5 P: >30 mg/mmol	MA (mg/mmol): ♀ ACR > 3.5 ♂ ACR > 2.5 P: >30 mg/mmol	MA (mg/mmol): ACR> 2	MA (mg/mmol) ♀ ACR > 3.5 ♂ ACR > 2.5 P: albuminuria on dipstick	MA (mg/g)/(µg/min) ACR 30-299 mg/g or 20-199 µg/min P: ACR ≥300mg/24hr or ≥200 µg/min	MA (mg/mmol): ♀ ACR > 3.5 ♂ ACR > 2.5 Or >30mg/24hr
Urinary estimation method	Early morning sample	Random urine sample	Early morning sample	Random urine sample	Random sample	Random/timed sample
Prevalence of UAE, (n)						
South Asians	121	382	40	140	462	42
White Europeans	41	120	17	106	2165	38
Afro-Caribbean's		-	-	-	161	-
OR for MA (OR, 95% CI), p		P=0.1236	-	-		
SA vs WE	0.55 (0.24-1.26)	0.78 (0.57-1.07)				

AC vs WE

Study	Dreyer et al, 2009 (51)	Abuaisha et al, 1998 (52)	UKPDS,1994 (53)	Benhalima et al, 2011 (54)	Winkley et al, 2013 (55)	Alharbi et al, 2014 (56)	Davis et al, 2013 (57)
Population	Primary care	Diabetes centre	Primary care,	Secondary care centre	Primary care practices	Diabetes centre	Primary care - UKPDS
Country	United Kingdom	United Kingdom	UK	United Kingdom	United Kingdom	Australia	United Kingdom
Race comparisons	SA, WE & AC	SA, WE & AC	SA, WE & AC	SA & WE	SA, WE & AC	SA & WE	SA, WE & AC
No. participants	34359	200	5098	648	1506	8484	5102
South Asians, n(%)	13320	54	534	295	164	485	418
White Europeans, n(%)	9617	103	4177	353	767	3608	3543
Afro-Caribbean's, n (%)	6952	43	387	-	575	-	312
Mean age/range, yrs	-						
South Asians		56	47	34	52	51	47
White Europeans		61	52	34	59	60	53
Afro-Caribbean's		58	51	-	52	-	52
Gender	-						
South Asians males, n			362	128	98	302	282
White Europeans males, n			2425	145	472	2085	2065
Afro-Caribbean's males, n			219	-	259	-	179
BMI, kg/m^2	-						
South Asians		27.3	27.2	30.9	29.6	27.7	26.0
White Europeans		30.0	29.5	35.0	32.8	33.3	27.9
Afro Caribbean's		39.3	28.1	-	32.4	-	27.1
Mean BP. mmHg				-			
South Asians	129/76	146/80	126/80		129/81	127/77	124/79
White Europeans	133/76	163/91	137/83		134/81	135/78	137/83
Afro-Caribbean's	135/78	165/85	136/85		135/83	-	134/84
Hypertensives, (n)	-					-	
South Asians		11	121	112			

White Europeans		36	1631	181				
Afro-Caribbean's		14	163	-				
Definition of urinary albumin excretion (MA/P)	P: ≥+1 on urine dipstick or ACR (mg/mmol) >2.5(♂) >3.5 (♀)	MA (µg/min) >10.5	MA mg/l Urine albumin > 50	MA (mg/mmol): ♀ ACR > 3.5 ♂ ACR > 2.5 P: >30 mg/mmol	MA (µg/mg): ACR ≥3	MA: Urine albumin >30mg/l Or ACR >2.5 mg/mmol (♂), 3.5 mg/mmol (♀)	MA mg/l Urine albumin ≥50-299 P: ≥300
Urinary estimation method	Random Urine sample	Timed urine sample	Random urine sample	Not stated	Random urine sample	Spot urine sample	Random urine sample
Prevalence of UAE, (n)							
South Asians	891	30	94	51	16	171	53
White Europeans	650	50	864	58	102	1100	430
Afro-Caribbean's	518	18	75	-	66	-	48
OR for MA (OR, 95% CI), p	-	-	-			-	-
SA vs WE							
AC vs WE							

Data presented as n (%) or Mean ± SD unless stated otherwise; SA=South Asian; WE=White European; AC=Afro-Caribbean; MA=Mircroalbuminuria; P= Proteinuria; UAE=Urinary albumin Excretion OR=Odds Ratio; [a]Age adjusted geometric mean; *Median(range); [b]Mean (range); [†]Mean ± S.E.M

Table 2: Characteristics of studies looking at progression of diabetic nephropathy in the systematic review

Study	**Ali et al, 2013 (22)**			**p**	**Mathur et al, 2018 (23)**			**p**	**Shaw et al, 2006 (25)**			**p**
	SA	**WE**	**AC**		**SA**	**WE**	**AC**		**SA**	**WE**	**AC**	
Total study participants	149	105	75		2732	2447	1095		149	155		
Participants with diabetic nephropathy	149	105	75		2732	2447	1095		42	56		
Age (range), yrs	57.8 (11.4)	61.3 (12.6)	62.4 (11.3)	0.005	65.5 (9.9)	69.5 (9.3)	67.8 (10.0)	<0.001	52	64		0.001
Gender (M), n	98	65	50	0.741	1322	1025	465					
BMI (kg/m^2)									29	29		
Duration of diabetes, yrs	14.0 (12.9)	18.3 (11.6)	13.4 (7.1)	0.013	9.9 (7.7)	7.8 (6.7)	10.8 (8.3)	<0.001				
HbA1c(%)*	8.7 [a]	8.5 [a]	8.8 [a]	0.445	7.9	7.5	7.9	<0.001	8.6	7.8		0.003
Mean BP (mmHg)	137/75	147/76	158/83		133/74	135/74	139/77	<0.001				
Serum creatinine (mmol/l)												
GFR (ml/min)	44.3 (21)	38.1 (19)	39.0 (21)	0.039	51.6 (8.3)	51.2 (8.2)	51.8 (8.1)					
Urine ACR												
Urinary protein excretion (g/24 h)												

Duration of follow-up (months)	67	72	60	0.05	106	110	108	<0.001	60	60		
Annual GFR decline (ml/min/1.73m^2), CI	-1.85[c]	-1.93[c]	-2.12[c]		-0.77 (-0.81, -0.74)[b]	-0.64 (-0.68, -0.60)[b]	-0.55 (-0.61, -0.48)[b]					
GFR decline at follow up (ml/min)									-32	-22		0.049
Rate of creatinine rise/ time, µmol/l/month,(CI)												
Mean slope log creatinine against time												
Doubling of serum creatinine at follow up, (%)												
Mortality, n (%)	12 (8.1)	11 (10.5)	9 (12)		333 (12.2)	460 (18.8)	139 (12.7)	<0.001	10 (6.7)	30 (19.3)		
RRT[+], n					117 (4.3)	56 (2.3)	49 (4.7)	<0.001				
ESRD at follow up, n (%)	58 (38.9)	34 (32.4)	33 (44)									
Lost to follow up (%)									7	7		
Incomplete data, n (%)									16 (11)	17 (11)		

Study	Koppiker et al, 1998 (26)			P	Earle et al, 2001 (24)			p
	SA	WE	AC		SA	WE	AC	

Total study participants	24	15			10	24	11	
Participants with diabetic nephropathy	24	15			10	24	11	
Age (range), yrs	57 (35-70)†	60 (49-73)†		0.1	59	67	68	
Gender (M), n	15	8			9	13	7	
BMI (kg/m^2)					-	-	-	
Duration of diabetes, yrs	11 (4-27)†	12.5 (2-25)†		0.89	14.7	16.2	12.7	
HbA1c(%)	9.5†	9.2†			8.5‡	8.6‡	9.1‡	NS
Mean BP (mmHg)	160/85†	180/90†			154/87	157/83	159/90	NS
Serum creatinine (mmol/l)	273 (93-704)†	270 (200-695)†		0.36	121.6	123.9	146.2	
GFR (ml/min)								
Urine ACR								
Urinary protein excretion (g/24 h)	2.65 (0.1-13.1)†	4.14 (0.6-19.2)†		0.55	1.13	2.07	3.07	
Duration of follow-up (months)	30.5 (2-148)†	16.5 (3-62)†		0.06	37 (19-98)‡	51 (23-92)‡	46 (23-127)‡	NS
GFR decline at follow up (ml/min)								

Rate of creatinine rise/ time, µmol/l/month,(CI)					5.36 (2.21-8.52)	2.22 (1.31-3.14)	3.14 (0.82-5.46)	0.031
Mean slope log creatinine against time	0.030 (0.02-0.04)	0.032 (0.02-0.05)		0.73				
Doubling of serum creatinine at follow up, n (%)					10 (100)	12 (50)	5 (45)	0.025
Mortality, n (%)	9	3						
RRT, n	8	10						
ESRD at follow up, n (%)								
Lost to follow up (%)	0 (0)	3 (20)						
Incomplete data, n (%)_	0 (0)	3 (20)						

Data presented as either n(%) or Mean (SD) unless stated otherwise. SA= South Asian; WE= White European; AC= Afro-Caribbean
†Median (range), ‡Mean (range), *HbA1C units presented as IFCC converted to DCCT using HbA1C units converter (reference diabetes.co.uk); [b]Age-Sex adjusted eGFR progression rate; [c]Adjusted for age, sex, presence/absence of vascular disease, presence/absence of drug treatment, presence/absence of proteinuria at baseline and baseline eGFR; [+]Renal transplant/Dialysis;

Figure1.1:Flowchart of studies

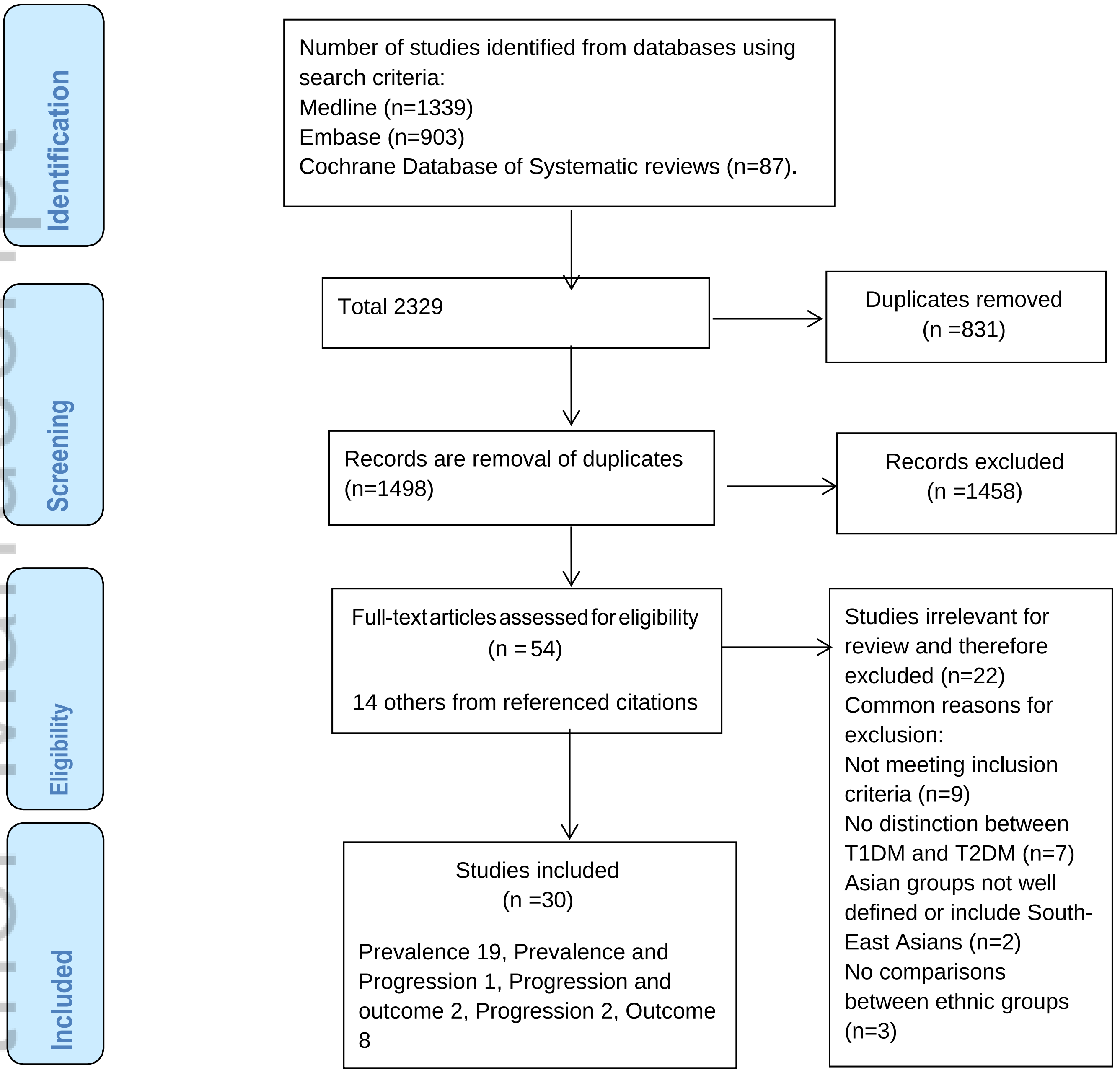


Table 1.2: Quality scoring using MOOSE criteria for studies included in the review

Author, year	Selection criteria	UAE/Progression/ ESRD defined	Type of DM confirmed	Objective diagnostic procedure	Adequate analysis and controlling by confounding	Additional adjustment in analysis	Score (0-6)
Chowdhury et al, 2006	Yes	No	Yes	No	No	No	2
Kou et al, 2017	Yes	No	Yes	No	No	No	2
UKPDS group, 1994	Yes	No	Yes	Yes	No	No	3
Allawi et al, 1988	Yes	No	Yes	Yes	No	No	3
Chowdhury et al, 2002	Yes	Yes	Yes	Yes	No	No	4
Fischbacher et al, 2003	Yes	Yes	No	Yes	Yes	No	4
Abuaisha et al, 1998	Yes	Yes	Yes	Yes	No	No	4
Winkley et al, 2013	Yes	Yes	Yes	Yes	No	No	4
Davis et al,2013	Yes	Yes	Yes	Yes	No	No	4
Alharbi et al,	Yes	Yes	Yes	Yes	No	No	4
Bhalla et al. 2013	Yes	Yes	Yes	No	Yes	No	4
Dreyer et al 2009	Yes	Yes	Yes	Yes	No	No	4
Keane et al, 2003	Yes	Yes	Yes	Yes	No	No	4
Weijers et al, 1997	Yes	Yes	Yes	Yes	Yes	No	5
Benhalima et al 2011	Yes	Yes	Yes	No	Yes	Yes	5
Chandie Shaw et al, 2002	Yes	Yes	Yes	Yes	Yes	No	5

Cowie et al, 1989	Yes	Yes	Yes	Yes	Yes	No	5
Stephen et al, 1990	Yes	Yes	Yes	Yes	Yes	No	5
Pugh et al, 1995	Yes	Yes	Yes	Yes	Yes	No	5
McGill et al, 1996	Yes	Yes	Yes	Yes	Yes	Yes	6
Dixon et al, 2006	Yes	Yes	Yes	Yes	Yes	Yes	6
Mather al, 1998	Yes	Yes	Yes	Yes	Yes	Yes	6
Chandie Shaw et al, 2006	Yes	Yes	Yes	Yes	Yes	Yes	6
Levene et al, 2004	Yes	Yes	Yes	Yes	Yes	Yes	6
Raymond et al, 2011	Yes	Yes	Yes	Yes	Yes	Yes	6
Earle et al, 2001	Yes	Yes	Yes	Yes	Yes	Yes	6
Koppiker et al, 1998	Yes	Yes	Yes	Yes	Yes	Yes	6
Ali et al, 2013	Yes	Yes	Yes	Yes	Yes	Yes	6
Mathur et al, 2018	Yes	Yes	Yes	Yes	Yes	Yes	6
Kanaya et al, 2011	Yes	Yes	Yes	Yes	Yes	Yes	6
Lewis et al, 2015	Yes	Yes	Yes	Yes	Yes	Yes	6
Gerchman et al, 2008	Yes	Yes	Yes	Yes	Yes	Yes	6