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Systematic Review or Meta-analysis

Incidence of chronic kidney disease among people with diabetes: a systematic review of observational studies

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What's new?

- The annual incidence of microalbuminuria and albuminuria is ~ 2–3% in Type 1 diabetes, and ~ 8% in Type 2 or mixed diabetes type populations.
- The incidence of developing eGFR < 60 ml/min/1.73 m^2 is ~ 2–4% per year.
- The annual incidence of end-stage renal disease ranged from 0.04% to 1.8%.

Abstract

Aims The aim was to systematically review published articles that reported the incidence of chronic kidney disease among people with diabetes.

Methods A systematic literature search was performed using MEDLINE, Embase and CINAHL databases. The titles and abstracts of all publications identified by the search were reviewed and 10 047 studies were retrieved.

Results A total of 71 studies from 30 different countries with sample sizes ranging from 505 to 211 132 met the inclusion criteria. The annual incidence of microalbuminuria and albuminuria ranged from 1.3% to 3.8% for Type 1 diabetes. For Type 2 diabetes and studies combining both diabetes types, the range was from 3.8% to 12.7%, with four of six studies reporting annual rates

between 7.4% and 8.6%. In studies reporting the incidence of eGFR < 60 ml/min/1.73 m^2 using the Modification of Diet on Renal Disease (MDRD) equation, apart from one study which reported an annual incidence of 8.9%, the annual incidence ranged from 1.9% to 4.3%. The annual incidence of end-stage renal disease ranged from 0.04% to 1.8%.

Conclusions The annual incidence of microalbuminuria and albuminuria is ~ 2–3% in Type 1 diabetes, and ~ 8% in Type 2 diabetes or mixed diabetes type. The incidence of developing eGFR < 60 ml/min/1.73 m^2 is ~ 2–4% per year. Despite the wide variation in methods and study design, within a particular category of kidney disease, there was only modest variation in incidence rates. These findings may be useful in clinical settings to help understand the risk of developing kidney disease among those with diabetes.

Introduction

Diabetes is a serious global public health problem with increasing prevalence and incidence. In 2015, approximately 415 million people had diabetes worldwide; this number is expected to rise to 642 million by 2040 [1]. This increase in the number of people with diabetes will result in increased numbers of individuals with diabetic complications. Complications impose a large financial burden on patients, their families, healthcare systems and society [2].

Diabetic kidney disease is one of the most frequent complications of both types of diabetes. It occurs in 20–30% of people with Type 1 or Type 2 diabetes [3], and is the leading cause of end-stage renal disease (ESRD) [3–5]. As per the 2014 United States Renal Data System (USRDS) annual report, in 2012, the proportion of new ESRD cases with diabetes as the primary cause differed greatly across countries and ranged from 12% to 66% [6].

People with ESRD are dependent on dialysis or kidney transplantation, both of which are associated with high costs [5]. Data from the 2011 USRDS in the USA showed that the total Medicare costs of reported ESRD was about $12.2 billion in 2000 and this figure rose rapidly to $24.7 billion in 2009 [7]. In addition to financial burden, those with ESRD often report a poor quality of life.

Although there is literature describing the pathophysiology and management of chronic kidney disease (CKD) in diabetes [2,8], there are no systematic reviews investigating the incidence of CKD among people with diabetes across the globe. Even though the burden of CKD among people with diabetes is high and treatment options are expensive, it is not clear to what extent the incidence varies. Given this, there is a strong imperative to understand fully the epidemiology of CKD in diabetes across different countries and diabetes types. The objective of this work was to undertake a systematic review of published studies that reported the incidence of CKD in diabetes. This will help to inform current and future government policy, and may help to identify new opportunities for prevention.

Methods

Literature search

The literature search was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. Studies were identified by searching electronic databases, scanning reference lists of articles and consultation with experts in the field. We systematically searched, MEDLINE and Embase via Ovid and CINAHL databases. The search was last updated on the 26 July 2016.

We used combinations of the following search terms: incidence, mortality, diabetic nephropathies, diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus, diabetes complications, chronic kidney failure, chronic renal insufficiency, chronic kidney disease, glomerular filtration rate, creatinine, albuminuria, microalbuminuria, macroalbuminuria, proteinuria, eGFR, ESKD, ESRD. We used medical subject heading terms (MESH) to identify synonyms and text words in the appropriate syntax of each database. We limited the search to studies written in English, which were conducted in humans only and were published over the period 1990 to 2016. We also searched the references of relevant studies for studies which fit our inclusion criteria (below). The search strategy is shown in Appendix 1.

Study selection criteria

The titles and abstracts of all publications identified by the search were reviewed by two independent reviewers (DNK and DJM) and full texts of all relevant studies (n = 277) were retrieved. Prospective or retrospective cohort studies reporting the incidence of CKD among people with diabetes were included in this review. Studies reporting outcomes for Type 1 diabetes, Type 2 diabetes or both types (referred to as mixed diabetes type population hereafter) combined were considered. We included studies reporting cumulative incidence or incidence rate, with no restriction on the length of follow-up. We only included studies containing at least 500 participants with diabetes, and which reported a diabetes-specific incidence of CKD. We excluded studies: if they were conducted (1) among those < 18 years of age only, or (2) within clinical trial populations or (3) among hospitalized patients; or (4) incidence estimates were only reported graphically or could not be extracted from the presented data. When multiple articles were available from a single study, the most recently published article, or the article with the larger sample size was selected for inclusion.

Data extraction

After identifying articles for inclusion, one reviewer (DNK) extracted data into a standard, pre-formulated form. The standard data extraction form recorded country of the study, year of study initiation, duration of follow-up, study design, study size, participant demographics (age and gender), type of diabetes (Type 1 diabetes, Type 2 diabetes or mixed), average duration of diabetes, definition of kidney disease [microalbuminuria, albuminuria, macroalbuminuria, estimated GFR (eGFR) decline or ESRD], methods of determination, and reported incidence of CKD. A second reviewer (DJM) checked 20% of the extracted data. Disagreements were resolved by discussion among the two authors. Annual incidence rates were calculated from the proportion of new cases using the following formula: $-\ln(1 - S)/t$; where S is the proportion of new cases (number of new cases at follow-up divided by number of cases at risk at baseline) over t years and t is the time of follow-up [10].

Risk of bias assessment in individual studies

An assessment of the risk of bias was conducted on all included studies using the modified Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses (Appendix 2) [11]. This tool includes items that assess representativeness, whether the outcome was present or not at the beginning of the study, the method of assessing outcomes, whether follow-up was long enough for outcomes to occur and the proportion of lost-to-follow-up. Studies were classified as 'high risk of bias' (total score between 0 and 2), 'medium risk of bias (total score between 3 and 5), or 'low risk of bias' (total score between 6 and 7).

Results

The initial search identified 10 047 non-duplicate studies. After screening the titles, we excluded 9011 studies using the inclusion/exclusion criteria. Two hundred and seventy-seven studies were thus identified and reviewed in full-text versions, from which we extracted data from 83 studies. We then excluded another 12 studies where we had more than one publication reporting on the same data, and 71 unique studies remained for inclusion in the systematic review (Fig. 1).

Characteristics of selected studies

The studies identified included 56 prospective and 15 retrospective cohort studies. There were 43 clinic-based, 16 registry-based and 12 population-based studies published between 1994 and 2016, and reported data from 30 different countries in total. More than one third (38%, n = 27) were from the USA [12–38], 22 (31%) were from Europe [39–60], 16 (22.5%) were from Asia [61–76], three were from Canada [77–79] one from Australia [80], one from New Zealand [81] and one from the Middle East [82]. One of the studies from Europe was a multi-country study involving 16 European countries [43]. The sample size of the studies ranged from 505 [82] to 211 132 [36], representing a total population of 821 252 study participants. One registry-based study used the estimated number of people with diabetes as a dominator in determining the incidence of ESRD [77].

In seven studies, participants aged < 18 years were included and there were no age-specific incidence rates for those ≥ 18 years. The mean age of the participants at baseline varied from 19.7 to 76 years. The age of participants was not stated for two studies [77,81]. The mean duration of follow-up varied from 2.3 to 26 years. One study did not state the length of follow-up [24]. More than a third of the studies (40.8%, *n* = 29) were conducted in Type 2 diabetes, 23 (32.4%) in Type 1 diabetes and 19 (26.8%) studies included mixed types of diabetes. The baseline median duration of diabetes varied from 0 to 29 years. Two studies [29,47] recruited study participants at the time of diabetes diagnosis, but 13 studies did not report the baseline duration of diabetes [12,13,27,36,40,50,56,57,71,74,77,78,81]. Characteristics of the 71 included studies are presented in Table S1.

Incidence of microalbuminuria and macroalbuminuria

Twenty-one studies reported the incidence of kidney disease in diabetes using a variety of urine albumin and protein measurement methods. Seven studies used albumin excretion rate (AER), six studies used the albumin-to-creatinine ratio (ACR), two studies used dipsticks for microalbuminuria, and the following were used by one study each: urine albumin concentration, ACR/AER, urine protein concentration and urine protein excretion. Some of the studies used 24 h urine collection; others used timed or spot urine collections (Table 1).

Among the 21 studies, seven reported incident microalbuminuria (AER of 20–200 μg/min or urinary albumin concentration 30–300 mg/24 h). Six studies reported urinary albumin levels based on AER ≥ 20 μg/min or ACR ≥ 30 mg/g. Given this combined definition, we have used the term ‘albuminuria’ to describe the definition of urinary albumin for these six studies. Two studies reported proteinuria based on urinary protein concentration ≥ 0.3 g/l and six studies reported macroalbuminuria (AER ≥ 200 μg/min or ACR ≥ 300 mg/g).

Studies conducted among Type 2 diabetes or a mixed diabetes type population reported a higher annual incidence of microalbuminuria and albuminuria than studies conducted in people with Type 1 diabetes. The annual incidence of microalbuminuria and albuminuria ranged from 1.3% to 3.8% for Type 1 diabetes. For Type 2 diabetes or mixed diabetes type populations, the range was from 3.8% to 12.7%, with four of six studies reporting annual rates between 7.4% and 8.6%.

One study from Iran [82] identified being male, older, longer diabetes duration, poor glycaemic control and hypertension as risk factors for incident microalbuminuria in Type 2 diabetes, but by contrast, Lloyd *et al.* [28], Bjornstad *et al.* [15] and Chaturvedi *et al.* [43] reported no significant differences in men and women in Type 1 diabetes. Another study [46] identified baseline AER, HbA_{1c}, diabetes duration, smoking and HDL-cholesterol as predictors of incident microalbuminuria in Type 1 diabetes. Choi *et al.* [16] reported greater risk of albuminuria in Filipinos, Asian and Black people compared to Caucasians in a mixed diabetes type population.

Two studies reported annual incidence of macroalbuminuria of 1.1% and 1.8% in Type 1 diabetes. The annual incidence ranged from 1.0% to 4.8% in four studies in Type 2 diabetes.

One Italian study [42] identified those who developed incident macroalbuminuria as being older, with a longer duration of diabetes and higher values of cumulative average HbA_{1c} at baseline and baseline microalbuminuria in Type 2 diabetes. Shultis *et al.* [33] reported no significant differences between men and women.

Incidence of eGFR decline

Fifteen studies reported the incidence of CKD in diabetes based on eGFR decline or increased serum creatinine values (Table 2). They used a variety of definitions: eGFR < 60 ml/min/1.73 m^2, plasma creatinine ≥ 2.0 mg/dl, hospital admission for renal disease, and self-reported kidney problems.

In six of the seven studies reporting the incidence of eGFR < 60 ml/min/1.73 m^2 using the MDRD equation, the annual incidence ranged from 1.9% to 4.3%, whereas the seventh [80] reported an annual incidence of 8.9%. Of the seven studies reporting incidence of eGFR < 60 ml/min/1.73 m^2, one was carried out in Type 1 diabetes (2.1%) and one in mixed diabetes type (1.9%); all others were in Type 2 diabetes (2.2–4.3%) (Table S2).

Incident eGFR < 60 ml/min/1.73 m^2 was higher in those with poor glycaemic control [13,65], low baseline eGFR and with albuminuria [63,65], older age, longer duration of diabetes and macrovascular complications at baseline [60,65] and high blood pressure [32,60,65].

Incidence of ESRD among people with diabetes

Forty studies reported the incidence of ESRD in diabetes (Table 3). Almost all used the requirement of renal replacement therapy as a definition for ESRD, with a few other studies defining ESRD from death certificates. Some also used doubling of plasma creatinine or eGFR decline > 50% from baseline as criteria for defining ESRD.

In 35 studies defining ESRD as requiring renal replacement therapy, after excluding two studies conducted in high-risk participants with albuminuria at baseline [48,59] (reporting annual incidences of 4.5% and 4.4%), the annual incidence of ESRD ranged from 0.04% to 1.8%. Figure 2 shows that registry studies tended to report lower incidences than clinic or population-based studies, but neither diabetes type nor geographic region was clearly related to the incidence of ESRD.

Several studies reported a higher incidence of ESRD among men than women [25,48,51], but others [47,53,64] reported no significant differences. Incidence of ESRD was higher among African Americans [20,27,29], native people in Canada [77] and Maoris in New Zealand [81] compared with whites people (Europids). The hazard of ESRD was also reported higher in Latinos, Chinese, Japanese and Pacific Islanders [20]. Studies also identified baseline eGFR and albuminuria [14,25,37,41,67,71,75,76], longer duration of diabetes, poor glycaemic control (higher HbA_{1c}) [25,31,37,48,53,67,76,78], late onset of diabetes in Type 1 diabetes [51], high blood pressure and use of angiotensin-converting enzyme inhibitors [25,79] increased the risk of ESRD. Lower incidence of ESRD was reported among those with diabetes diagnosed in recent years compared to earlier time intervals [25,29,30,47,64,76].

Risk of bias in individual studies

Detailed results of the risk of bias assessment of individual studies according to the modified NOS are reported in Table S3. In summary, 46 (65%) studies scored as ‘low-risk of bias’, 25 and (35%) studies scored ‘moderate risk of bias’. Excluding studies with moderate risk of bias did not materially change the results.

Discussion

In this systematic review, we have shown that the annual incidence of microalbuminuria and albuminuria ranges from 1.3% to 3.8% for Type 1 diabetes. For Type 2 diabetes and combined populations of Type 1 and Type 2 diabetes, the range is from 3.8% to 12.7%, with four of six studies reporting annual rates between 7.4% and 8.6%. Two studies reported annual incidence of macroalbuminuria of 1.1% and 1.8% in Type 1 diabetes. The annual incidence ranged from 1.0% to 4.8% in Type 2 diabetes. In studies reporting the incidence of eGFR < 60 ml/min/1.73 m^2 using the MDRD equation, apart from one study, the annual incidence ranged from 1.9% to 4.3%. The annual incidence rate of ESRD among people with diabetes ranges from 0.04% to 4.5%, but after excluding two studies conducted in a high-risk population, the range narrowed to 0.04–1.8%. Neither diabetes type nor geographic region was clearly related to the incidence of ESRD. This is not consistent with a recent review which reported that the estimated incidence of ESRD in Type 2 diabetes is highest in East Asia and the Pacific [83].

More than half of the included studies were clinic based, almost all of them were from high-income countries, and more than a third were from the USA. Although CKD is expected to be more frequent among people with diabetes in developing countries compared with those in the developed world [84], we could not find any study which met our criteria from low-income countries and thus could not present in data in this regard.

There was a wide variation in methods of assessment and classification of CKD in diabetes. Studies used urinary albumin or protein levels, GFR estimates or the requirement of renal replacement therapy to define it. The definition of ESRD due to diabetes was quite consistent; almost all studies used the requirement of renal replacement therapy. A variety of urine protein level measurements were used in defining CKD, i.e. AER, ACR, dipsticks, urine-albumin concentration, urine-protein concentration and urine-protein excretion. We used the term albuminuria for those six studies that reported albuminuria using AER ≥ 20 μg/min or ACR ≥ 30 mg/g. The definition encompasses both microalbuminuria and macroalbuminuria together. Because of this, we reported them as albuminuria and separated them from microalbuminuria.

Although most cases within the albuminuria category are likely to be microalbuminuria, we believe that it would be misleading to include them with those studies that define albuminuria with greater accuracy. For example, Xu *et al.* [35] reported a cumulative incidence of albuminuria of 33%; 29% and 4% of them in the microalbuminuria and macroalbuminuria range, respectively.

Albuminuria is a clinically useful tool for predicting prognosis and for monitoring response to therapy, but the use of albuminuria as a marker of diabetic kidney disease has considerable limitations. Increased levels of albumin can be caused by episodic hyperglycaemia, high blood pressure, high-protein diet, exercise, fever, urinary tract infection and congestive heart failure [4]. In addition, spontaneous or treatment-induced remission of microalbuminuria is also common among people with diabetes [85]. There were also inconsistencies in the timing of urine sample collections; studies used 24 h, timed or spot urine collections. Some of the studies used a single urine measurement and others used multiple urine measures. However, there were no major differences in incidence between those studies using multiple urine measures over several days and those using a single urine measurement. Two studies [16,68] used a urine dipstick for incident microalbuminuria. A urine dipstick has low sensitivity to detect microalbuminuria, but it was only one of three urine albumin tests that were used in the studies, which reduces its impact, but to an unknown extent. However, the incidences in these two studies were comparable with other similar studies that did not use dipstick.

Although we excluded clinical trial populations, our findings are comparable with some of the findings from clinical trials. We reported that the annual incidence of microalbuminuria and albuminuria is ~ 2% to 3% in Type 1 diabetes. In the primary prevention cohort of the Diabetes Control and Complications Trial (Type 1 diabetes) [86], annual incidences of 2% and 3% in the intensive and conventionally treated groups were reported. We reported that the annual incidence of microalbuminuria and albuminuria was ~ 8% in Type 2 diabetes or in a mixed diabetes type population. However, the UKPDS [87] reported the progression of microalbuminuria to be only 2.0% per year in Type 2 diabetes. Similarly, TECOS [88] reported an annual incidence of 2.7% in the treatment and control groups in Type 2 diabetes, and the ROADMAP study [89] reported an annual incidence of 2.7% in the treatment and 3.2% and control groups in Type 2 diabetes.

We reported Type 2 diabetes and mixed diabetes types together for two reasons. First, the number of studies in each category of CKD becomes too small when separating into the three categories (Type 1 diabetes, Type 2 diabetes and mixed). Second, it is likely that the large majority of participants in the mixed type studies have Type 2 diabetes.

Different guidelines around the world use different definitions for classification and staging CKD, usually a mix of eGFR and markers of kidney damage. This heterogeneity in definitions and differences in study populations makes comparison between studies difficult and might be a possible explanation for the wide variation in incidence of CKD in diabetes. Bruck *et al.* [90] conducted a systematic review on methodology used in studies reporting CKD prevalence in Europe and showed that there was considerable variation in assessment of kidney function across studies. They also highlighted that there were high levels of heterogeneity in the reporting of CKD prevalence. Despite the fact that measurement and studies are inherently different, there is surprisingly modest variation in incidence rates within particular categories of CKD.
It is also important to acknowledge that the competing risk of death may confound the risk for ESRD. However, this was not uniformly addressed in the studies included in the current review. Among 10 studies (all reporting on the incidence of ESRD) that did account for mortality as a competing risk, two [51,59] reported on the difference between findings according to whether the competing mortality risk was accounted for and in neither was there a difference. Thus, the failure to adjust for competing mortality risk in some studies is unlikely to have had a major impact on our findings.

The major strength of the current analysis was the inclusion of a large number of studies and the representation of different parts of the world. However, there are some limitations to note. We did not review articles in non-indexed journals and only included published studies, thus there is a possibility of publication bias. Further, we limited our search to English language papers only, a sample size of 500 and above, and published since 1990, and these criteria may potentially exclude a significant number of studies. Most of the studies included in this review were from clinic-based populations. Clinic-based studies will probably overestimate incidence estimates because participants differ from the general diabetes population in that they usually have more advanced disease. Although 80% of people with diabetes mellitus currently live in low- and middle-income countries, most of the data were retrieved from studies carried out in Western

countries. Thus, the results from our study may not be generalizable to low-income or middle-income countries. Indeed, we identified no studies from India or mainland China, despite these countries accounting for more than one third of all the people with diabetes, globally. Because of the heterogeneity in the definitions used and study population differences, we did not generate pooled estimates for the incidence of CKD in diabetes. Even though we excluded studies containing fewer than 500 participants, more than one third (36.7%) of the studies had fewer than 1000 participants. We did not report the cause of ESRD in people with diabetes because most studies did not differentiate between different types of kidney disease; most simply report the incidence/progression of kidney disease.

In summary, this review highlights that CKD among people with diabetes currently imposes a significant health problem across the globe. The annual incidence of microalbuminuria and albuminuria is ~ 2% to 3% in Type 1 diabetes, and ~ 8% in Type 2 diabetes or mixed diabetes type. The incidence of developing eGFR< 60 ml/min/1.73 m^2 is ~ 2–4% per year. The annual incidence rate of ESRD ranges from 0.04% to 1.8%. Despite the wide variation in methods and study design, there was, within a particular category of kidney disease, only modest variation in incidence rates. Our understanding of the development of CKD/ESRD in diabetes will be further improved if methods of assessment are standardized so that we can compare the incidence rates and progression of kidney disease between populations. Finally, there is an urgent requirement for more studies in developing countries.

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Competing interests

None declared.

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Author contributions

DNK formulated the research question, designed the study, searched the published work, extracted and selected articles, extracted and analysed data, and drafted and revised the report. DJM formulated the research question, designed the study, extracted and analysed data, contributed to conceptualization and discussion and reviewed/edited the manuscript. JES formulated the research question, designed the study, contributed to conceptualization and discussion and reviewed/edited the manuscript. CMR, RCA and ATR contributed to discussion and reviewed/edited the manuscript. All authors read and approved the final manuscript.

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FIGURE 1 Flowchart of study selection for the systematic review. ESRD, end-stage renal disease.

FIGURE 2 Annual incidence rate of ESRD in people with diabetes by diabetes type, study design and region in studies defining ESRD as a requirement of renal replacement therapy. ESRD, end-stage renal disease; T1DM, Type 1 diabetes; T2DM, Type 2 diabetes; US, United States of America; NZ; New Zealand.

Appendix 1

Electronic search strategy used for Medline

1. exp incidence/ or mortality/
2. (incidenc* or mortalit*).tw.
3. 1 or 2
4. exp Diabetes mellitus/ or diabetes mellitus, Type 1/ or diabetes mellitus, Type 2/ or diabetes complications/
5. (diabet* or T1DM or T2DM or IDDM or NIDDM).tw.
6. 4 or 5
7. Kidney failure, chronic/ or Renal Insufficiency, Chronic/ or kidney disease/ or Glomerular Filtration Rate/ or Proteinuria/ or creatinine/
8. ((Kidney* or renal) adj3 diseas*).tw.
9. ((Kidney* or renal) adj3 failure).tw.

10. ((Kidney* or renal) adj1 insufficienc*).tw.

11. (Kidney* adj1 Dysfunction*).tw.

12. (Albuminuria* or microalbuminuria* or macroalbuminuria* or proteinuria* or glomerular filtration rate* or GFR or eGFR or ESKD or ESRD or creatinine).tw.

13. or/7-12

14. 6 and 13

15. exp Diabetic Nephropathies/

16. (diabet* adj1 nephropath*).tw.

17. (Diabet* adj1 Glomeruloscleros*).tw.

18. (Diabet* adj (Kidney* or renal)).tw.

19. or/15-18

20. 14 or 19

21. 3 and 20

22. epidemiological studies/ or exp cohort studies/ or prospective studies/ or retrospective studies/

23. Observational Study/ or longitudinal studies/ or follow-up studies/

24. ((Epidemiolog* or cohort or observation* or prospective or retrospective) adj1 stud*).tw.

25. 22 or 23 or 24

26. 21 and 25

27. exp animals/ not humans.sh.

28. 26 not 27

29. limit 28 to (english language and yr="1990 -Current")

Appendix 2

Modified Newcastle–Ottawa Quality Assessment Scale

Selection

1) Representativeness of the general diabetes population
    a) Truly representative of the general diabetes population *
    b) Somewhat representative of the general diabetes population
    c) Selected group e.g. patient groups

d) No description of the derivation of the cohort

2) Ascertainment of diabetes status
   a) Record linkage/medical record *
   b) Blood test *
   c) Self-report
   d) No description

3) Demonstration that outcome of interest (kidney disease) was not present at start of study
   a) Yes *
   b) No

Comparison

1) Is the incidence rate adjusted/standardized for at least age and sex?
   a. Yes*
   b. No

Outcome

1) Assessment of outcome
   a) Independent blinded assessment *
   b) Record linkage *
   c) Self-report
   d) No description

2) Was follow-up long enough for outcomes to occur
   a) Yes (at least 3 years) *
   b) No

3) Adequacy of follow-up
   a) Complete follow-up - all subjects accounted for *
   b) Subjects lost to follow-up unlikely to introduce bias (lost to follow-up rate < 10%, or description provided of those lost) *
   c) Follow-up rate < 90% and no description of those lost
   d) No statement

*** Studies score 1 point for response marked with an asterisk**

Supporting Information

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

Table S1 Characteristics of studies included in the systematic review

Table S2 Summary of the incidence of CKD in diabetes

Table S3 Risk of bias assessment of included studies using NOS for assessing the quality of non-randomized studies

Table 1 Studies reporting incidence of microalbuminuria and macroalbuminuria

First author, year	Urine measurement method[a]	Time of urine collection	Definitions	Incidence	
				Reported	Annual
			Microalbuminuria		
Amini, 2007 [82]	Urinary albumin concentration	24 h	Microalbuminuria: urinary albumin concentration 30–300 mg/24 h	Microalbuminuria: 82.3 per 1000 person-years (95% CI: 69 to 105) (141.4 per 1000 in men, 66.1 per 1000 in women) (cumulative incidence of 34.9%)	8.6%
Chaturvedi, 2001 [43]	AER	Timed overnight collections	Microalbuminuria: AER: 20–200 µg/min	Microalbuminuria: 12.6% (95% CI: 10.7 to 14.7%) (13.2% in men and 12.1% in women)	1.8%
Esmatjes, 2002 [46]	AER	2 of 3 in 6 months	Microalbuminuria: AER: 20–200 µg/min	Microalbuminuria: 11.6%	2.7% (95% CI: 2.2 to 3.2)
Gordin, 2011 [54]	AER		AER: 20–200 µg/min or 30–300 mg/24 h	148 progressed to normoalbuminuria from 2763 CI: of microalbuminuria: 5.4%	NA*
Lloyd, 1996 [28]	AER	2 or 3 of the timed urine samples	Microalbuminuria: AER 20–200 µg/min in 2 or 3 of the timed urine samples	Microalbuminuria: 14%	3.8%
Potisat, 2013 [68]	Urine dipstick for microalbuminuria, spot urine for albumin/creatinine, and	2 of the 3 morning urine samples	The diagnosis of diabetic nephropathy was established by the nephrologist, based on the presence of microalbuminuria in at least 2 of the 3	DN: 91.1 (95% CI: 78.8, 105.1) per 1000 person-years (cumulative incidence of 27.59%)	8.1%

	spot urine for protein/creatinine		morning urine samples		
Xu, 2008 [35]	ACR	Random morning urine sample	Albuminuria: ACR ≥ 30 mg/g (3.4 mg/mmol) but no definition for microalbuminuria	Microalbuminuria: 29% during the first examination and 19% during the second (4-year interval)	8.6%
			Albuminuria		
Bjornstad, 2014 [15]	AER timed or ACR spot	Timed or spot	AER ≥ 20 µg/min or ACR ≥30 mg/g Albuminuria was defined as microalbuminuria or greater	Albuminuria CI:: 7.6% (9.6% of men and 6.1% of women)	1.3%
Bo, 2012 [40]	AER	2 of 3 in 6 months	Nephropathy: AER > 20 mg/min in at least 2 of 3 urine collections, gross proteinuria or elevated serum Cr levels	Nephropathy: 26.9%	2.2%
Choi, 2011 [16]	Positive dipstick urinalysis (≥ 1) or ACR ≥ 30 mg/g	NS	Albuminuria: ≥ 1 on dipstick testing or ≥ 30 mg/g on ACR confirmed on a second consecutive occasion at least 3 months later	Albuminuria: 35.9 per 1000 person-years (cumulative incidence of 9.3%)	3.8%
Drion, 2012 [45]	ACR	NS	Albuminuria: ACR > 2.5 mg/mmol for men and > 3.5 mg/ mmol for women	Albuminuria: 26.7%	NA[a]
Hsu, 2012 [62]	ACR	2 consecutive urine tests	ACR of ≥ 3.4 mg/mmol (ACR ≥ 30 mg/g) in two consecutive urine tests	Microalbuminuria: 67.4 per 1000 person-years or 36.7%	7.4%
Schimke, 2010 [80]	ACR	First-morning sample	Microalbuminuria: ACR ≥ 3.0 mg/mmol	Microalbuminuria: 99 per 1000 person-years of follow-up (cumulative incidence of 41.3%)	12.7%
Xu, 2008	ACR	Random	Albuminuria: ACR ≥ 30 mg/g	Albuminuria: 33% during the	10%: second

[35]		morning urine sample	(3.4 mg/mmol)	second examination and 23% during the third	6.5%: third
			Macroalbuminuria		
Bruno, 2003 [42]	AER	2 of 3 overnight collection	Overt nephropathy: AER > 200 µg/min in at least two consecutive overnight urine collections	Overt nephropathy: 37.0 per 1000 person-years (95% CI: 32.3 to 42.6) (cumulative incidence of 18.3%) From baseline microalbuminuria to overt nephropathy: 53.6 per 1000 person-years (95% CI: 44.7 to 64.2)	3.8%, 5.1% from baseline microalbuminuria
Horikawa, 2014 [61]	ACR	Spot	Overt nephropathy: ACR >300 mg/g Cr in 2 consecutive samples	Overt nephropathy: 8.70 per 1000 person-years (7.8%)	1%
Lloyd, 1996 [28]	AER	2 or 3 of the timed urine samples	Macroalbuminuria: AER > 200 µg/min in 2 or 3 of the timed urine samples	Macroalbuminuria: 7%	1.8%
Pambianco, 2006 [30]	AER	2 of 3 timed urine collections (24 h, overnight and post clinic)	Overt nephropathy: AER > 200 µg/min in at least 2 of 3 timed urine collections (24 h, overnight and post clinic)	Overt nephropathy: 13.3 per 1000 person-years (11.0–16.0) over 12 years of follow-up (12.6%)	1.1%
Shultis, 2007 [33]	ACR	NS	Macroalbuminuria: ≥ 300 mg/g	The crude incidence of macroalbuminuria: 37.5 cases per 1000 person-years (cumulative incidence of 36.5%)	4.8%

Xu, 2008 [35]	ACR	Random morning urine sample	Albuminuria: ACR ≥ 30 mg/g (3.4 mg/mmol) but no definition for macroalbuminuria	Macroalbuminuria: 4% for the first and second examinations	1%
			Proteinuria or definition not specific to macroalbuminuria		
Esmatjes, 2002 [46]	AER	2 of 3 in 6 months	Macroalbuminuria: AER: > 200 µg/min; Established nephropathy: macroalbuminuria and renal failure (plasma Cr > 124 µmol/l)	Established nephropathy per year: 0.7 (0.5–0.9)%	0.7 (0.5–0.9)%
Hovind, 2003 [50]	AER	24 h	Persistent albuminuria: AER ≥ 300 mg/24 h in at least two of three consecutive samples; Diabetic nephropathy if the following criteria were fulfilled: persistent albuminuria, duration of diabetes > 10 years, presence of diabetic retinopathy, and absence of clinical or laboratory evidence of other kidney or renal tract disease	DN after 20 years of diabetes: 21%	1.2%
Klein, 1997 [22]	Urinary protein concentration	NS	Proteinuria ≥ 0.30 g/l	10-year incidence of gross proteinuria: 36.5%	4.5%
Krakoff, 2003 [24]	Protein to Cr ratio	Spot	Nephropathy (protein to Cr ratio ≥0.5 g/g) in spot urine collection	Nephropathy: 34.18 per 1000 person-years (cumulative incidence of 20.5%)	NA[b]
Shankar, 2007 [32]	Urinary protein excretion	Casual urine specimen	Proteinuria: presence of ≥ 0.3 g/l of protein excretion in a casual urine specimen	Proteinuria: 38.4%	3%

Tuomilehto, 1997 [55]	NA	NA	Diabetic nephropathy was defined as the first hospitalization with a diagnosis of nephropathy (ICD 8 or 9 code)	DN: 6 per 1000 person-years 95% CI: 5 to 6 (cumulative incidence of 8.7%)	0.6%

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; UAE, urinary albumin excretion; DN, diabetic nephropathy; Cr, Creatinine; NA, not applicable; NS, not stated.

[a]The study involves two cohorts with different duration of follow-up; annual cumulative incidence cannot be calculated.

[b]Annual cumulative incidence cannot be calculated because of duration of follow-up is not stated.

Table 2 Studies reporting incidence of estimated GFR decline among people with diabetes

First author, year	Method used for eGFR estimation	Definition of incident CKD or eGFR decline	Incident CKD or eGFR decline	
			Reported	Annual
Incident eGFR < 60 using the MDRD equation				
Bash, 2008 [13]	MDRD	eGFR < 60 ml/min/1.73 m^2 at visit 4 or kidney disease noted during a hospitalization or death	17.0 per 1000 person-years (cumulative incidence of 19.1%)	1.9%
Kim, 2014 [63]	MDRD	CKD stage 3 or greater was defined as GFR < 60 ml/min/1.73 m^2	12.1% progressed to CKD 3 or greater during the follow-up period	4.3%
Luk, 2013 [65]	The abbreviated MDRD Study formula recalibrated	eGFR < 60 ml/min/1.73 m^2	19.7% developed CKD	3%

	for the Chinese population			
Salinero-Fort, 2015 [60]	MDRD	eGFR< 60 ml/min/1.73 m^2 at any visit, and an average successive eGFR of < 60 ml/min/1.73 m^2	Cumulative incidence of 10.23% (95% CI: = 9.12–11.43); 2.48 (95% CI: = 2.19–2.79) cases per 100 patient-years	2.2
Schimke, 2010[80]	MDRD	From baseline eGFR ≥60 to renal impairment(eGFR<60)	Renal impairment (eGFR <60): 74 per 1000 person-years; (cumulative incidence of 31.2%)	8.9%
Shankar, 2007[31]	MDRD	CKD: eGFR < 60 ml/min/1.73m^2	31.7% after 16 years of follow-up	2.1%
Zoppini, 2012[58]	MDRD	eGFR <60 ml/min/1.73m^2 or persistent macroalbuminuria (ACR≥30 mg/mmol in at least two of three consecutive samples)	13.4% developed incident CKD	2.9%
			11.4% developed incident eGFR<60	2.4%
	Incident eGFR < 60 using other eGFR equations or incident CKD using other definitions			
Van Blijderveen, 2014[56]	CKD-EPI	CKD: abnormalities in eGFR, albuminuria, or from medical	71.2 per 1000 person-years, (cumulative incidence of	7.1%

		record	15.1%)	
Yu, 2015 [38]	CKD-EPI	First measurement of an eGFR < 60 ml/min per 1.73 m^2 or sex-specific microalbuminuria (urine albumin-to-creatinine ratio ≥ 25 mg/g for women and ≥ 17 mg/g for men)	Incidence of CKD (eGFR <60 or microalbuminuria): 149.3 cases per 1000 patient-years (95% CI: 140.0, 159.3) Cumulative incidence of 63.1%	23.8%
		Incidence of eGFR < 60 ml/min per 1.73 m^2	Incidence of eGFR < 60 ml/min/1.73 m^2: 116.2 events per 1000 patient-years (95% CI: 105.0, 128.5) in women and 106.5 events per 1000 patient-years (95% CI: 95.3, 118.9) in men. Cumulative incidence of 47.1%	NA[b]
Klein, 1999 [23]	A modification of the Cockroft-Gault formula	A decrease in the estimated annual creatinine clearance of ≥ 3 ml/min/1.73 m^2/year	The 10-year estimated incidence of an annual decrease in the creatinine clearance of ≥ 3 ml/min was 52.5%	7.4%
Gohda, 2012 [18]	eGFR cystatin values	Incident stage 3 CKD defined as estimated GFR	16 per 1000 person-years over 12 years (cumulative	NA[a]

		< 60 ml/min/1.73 m^2	incidence of 11%)	
Bruno, 2003 [41]		Chronic renal failure (2 consecutive plasma Cr values ≥ 2.0 mg/dl at least 2 months apart)	Chronic renal failure: 7.63 (95% CI: 6.06–9.61) per 1000 person-years (cumulative incidence of 5.1%)	0.78%
Kaushik, 2007 [21]		Self-report: as a result of your diabetes, have you ever had any problems with your kidneys or not?	26.2% over a 7-year period	4.3%
Uzu, 2010 [70]	MDRD modified for Japanese for eGFR estimation	Doubling of the serum Cr concentration from baseline	Doubling of the serum Cr concentration from baseline: 11.5%	1.6%
Xue, 2007 [36]		From Medicare claims	CKD or ESRD: 64 per 1000 person-years, (cumulative incidence of 41.5%)	5.4%

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MDRD, modification of diet in renal disease; RRT, renal replacement therapy.

[a]The study involves two cohorts with different duration of follow-up; annual cumulative incidence is not possible to calculate in this study.

[b]Annual cumulative incidence is not possible to calculate in this study

Table 3 Studies reporting incidence of ESRD among people with diabetes

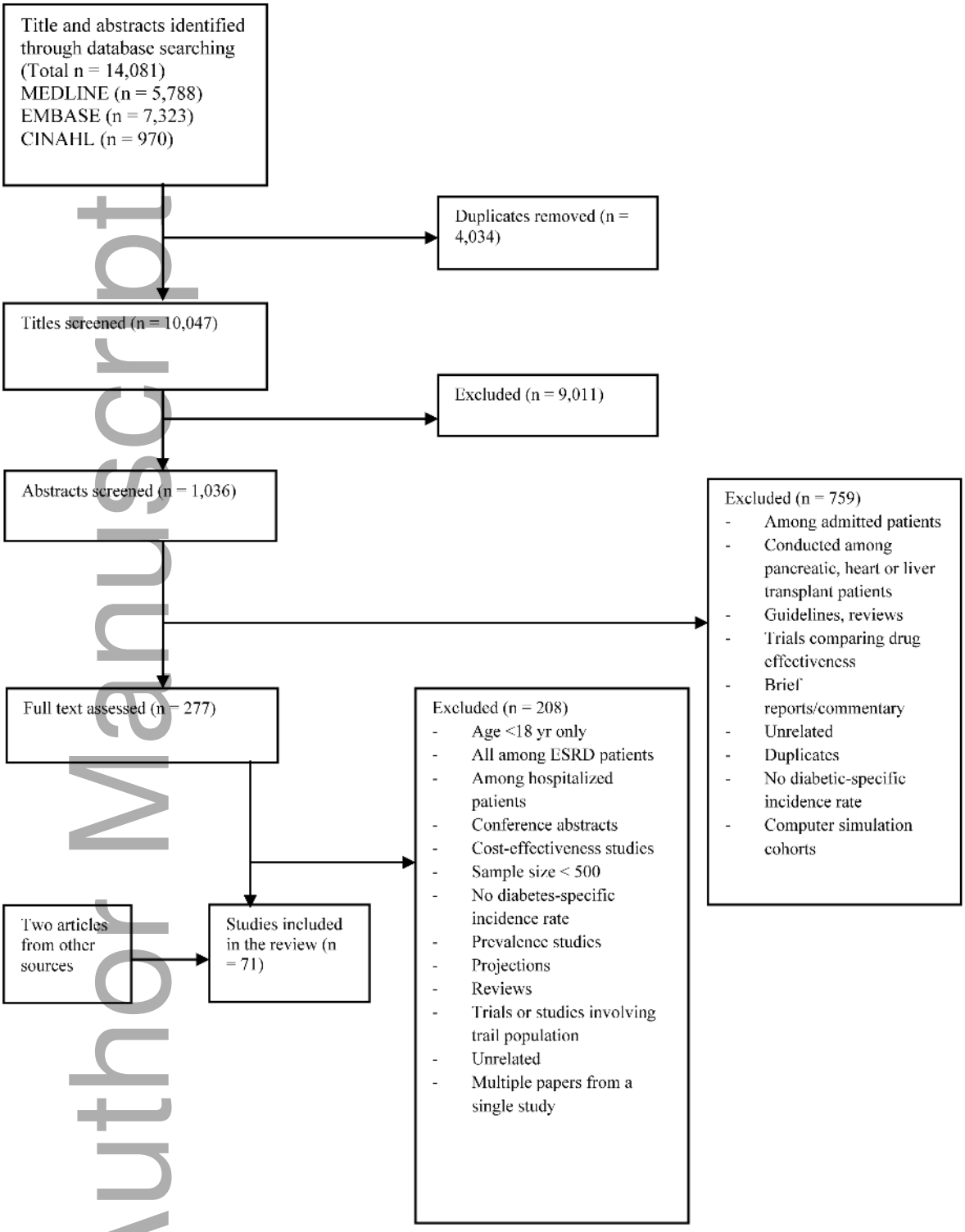
First author, year	Definition of ESRD	Incidence of ESRD	
		Reported	Annual

Andresdottir, 2014 [39]	RRT	7.7%	1.0%
Bash, 2010 [12]	RRT	6.03 (5.12–7.10) per 1000 person-years	0.52%
Berhane, 2011 [14]	RRT	Overall: 11.6 per 1000 person-years From baseline normoalbuminuria: 4.9 (3.8, 6.0) per 1000 person-years From baseline microalbuminuria: 11.5 (8.9, 14.1) per 1000 person-years From baseline macroalbuminuria: 60.2 (50.0, 70.4) per 1000 person-years	1.24%
Bruno, 2003	RRT	1.04 (95% CI: 0.56 to 1.94) per 1000 person-years	1.1%
Costacou, 2011 [17]	RRT	7.3 per 1000 years' exposure to diabetes	1.5%
Currie, 2013 [44]	Renal failure from patient records	Renal complications: 3.4 per 1000 person-years	0.45%
Dyck, 1994 [77]	RRT	0.4%	0.04%
Finne, 2005 [47]	RRT by linking with the Finnish Registry for Kidney Diseases	2.2% (1.9–2.5%) after 20 years and 7.8% (7.1–8.5%) after 30 years of follow-up Incidence rate: 1.8 per 1000 person-years	0.18%
Forsblom, 2011 [48]	RRT	36% OR 51 per 1000 person-years (95%CI: 44.4, 58.5)	4.5%
Fung, 2015 [72]	Using ICD-9 code from medical records	0.8 % (1015/127 822)	0.16
Hadjadj, 2016 [59]	RRT	18.4 (95% CI: 14.2, 22.5) in Type 2 diabetes 47.1 (95%CI: 38.4, 55.9) per 1000 patient-years in Type 1 diabetes	1.77 4.35
Huang, 2014 [19]	RRT	5.04 (4.76, 5.32) per 1000 person-years	0.32%
Joshy, 2009 [81]	RRT	Dialysis/transplantation: 1.37 (1.02, 1.86) per 1000 person-years, (cumulative incidence of 0.5%)	0.13%

Kanaya, 2011 [20]	Record linkage to ESRD treatment registry or Death certificate	5 per 1000 person-years	0.52%
Klein, 1999 [23]	Serum Cr ≥ 2.0 mg/dl or RRT	10-year incidence of renal insufficiency and end-stage renal failure: 14.4%.	1.55%
Lecaire, 2014 [25]	Self-reported history of RRT	25-year incidence of ESRD was 17.9% (95% CI: 14.3–21.5) in males, 10.3% (7.4–13.2) in females, and 14.2% (11.9–16.5) overall	0.6%
Lee, 1994 [26]	RRT or chronic renal failure or if a patient died of chronic renal failure as an underlying or a contributing cause of death (ICD 585–589).	CRF: 15.7 per 1000 person-years OR 16.0% over an average 10-year period of follow-up	1.7%
Lee, 2015 [74]	RRT	41/1427 (0.9%)	0.2
Lin, 2014 [64]	Using ICD-9 code from the National Health Insurance Research Database	Males: 5.6%, females: 5.88%; Overall: 5.52 per 1000 person-years	0.59%
Lipworth, 2012 [27]	Record linkage to USRDS	6.11 per 1000 person-years	0.66%
Liu, 2015 [75]	Linkage with ESRD registry	147 cases of ESRD over 13 020 person-years follow-up. 11.3 per 1000 person-years; cumulative incidence of 6.3% (147/2337)	1.62
Lloyd, 1996 [28]	RRT or a serum Cr >5 mg/dl	Renal failure: 5%	1.3%
Luk, 2014 [66]	Fatal or nonfatal renal failure (code 585 and 586), requirement of dialysis (procedure code 39.95 or 54.98), or eGFR < 15 ml/min/1.73 m^2.	2.2, 6.4, and 8.4 per 1000 person-years in people with Type 1 diabetes, normal-weight people with Type 2 diabetes and overweight people with Type 2 diabetes (cumulative incidence of 6%)	0.67%
Mollsten, 2010 [51]	Start active uremia treatment due to renal failure (GFR < 10–15 ml/min).	0.53 per 1000 person-years	0.05%
Muhlhauser, 2000 [52]	RRT	4.6%	0.46%
Nishimura, 2003 [29]	RRT	13.0% OR 5.21 per 1000 person-years 95% CI: (4.24–6.29)	0.55%
Otani, 2015 [76]	RRT or death from diabetic kidney disease due to refusal	3.4 (2.6 to 4.3) per 1000 person-years; cumulative incidence of 6.5%	0.35

	or no access to dialysis		
Oh, 2011 [67]	RRT	2%	0.38%
Pambianco, 2006[30]	Self-reported RRT or renal failure mentioned in death certificate	Renal failure: 6.3 (5.2–7.4) per 1000 person-years	1.26%
Shankar, 2007 [31]	RRT	6.80%	0.44%
Shultis, 2007 [33]	RRT due to diabetes or death from diabetic nephropathy	9.0 cases per 1000 person-years	1.5%
Shurraw, 2011 [78]	RRT	2%	0.53%
Stadler, 2014 [53]	RRT	8.6% OR 3.35 per 1000 person-years (95% CI:: 2.46–4.23)	0.35%
Suissa, 2006 [79]	RRT	2.13 per 1000 person-years	0.22%
Thomas, 2011 [54]	RRT	4.5%	0.46%
Tong, 2007 [69]	Renal end points were defined as a reduction in eGFR by>50% or progression to eGFR <15 (stage 5) or renal dialysis or death secondary to renal causes	Renal end points: 5%	1.5%
Uzu, 2010 [70]	RRT	ESRD and/or death: 9.5%	1.33%
Van Pottelbergh, 2012 [57]	eGFR dropped < 15 ml/min/1.73 m^2 on one occasion and the mean of the last two measurements was still < 30 ml/min/1.73 m^2.	1.29 per 1000 person-years	0.12%
Wada, 2014 [71]	RRT or half reduction in eGFR	19.8 renal events per 1000 person-years	1.45%
Yu, 2014 [37]	RRT	3.30 per 1000 person-years, 95% CI:: 2.66–4.05	0.25%

CKD, chronic kidney disease; CRF, chronic renal failure; ESRD, eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; CI: confidence interval; IR, incidence rate; RRT, renal replacement therapy, ICD; International Classification of Diseases.



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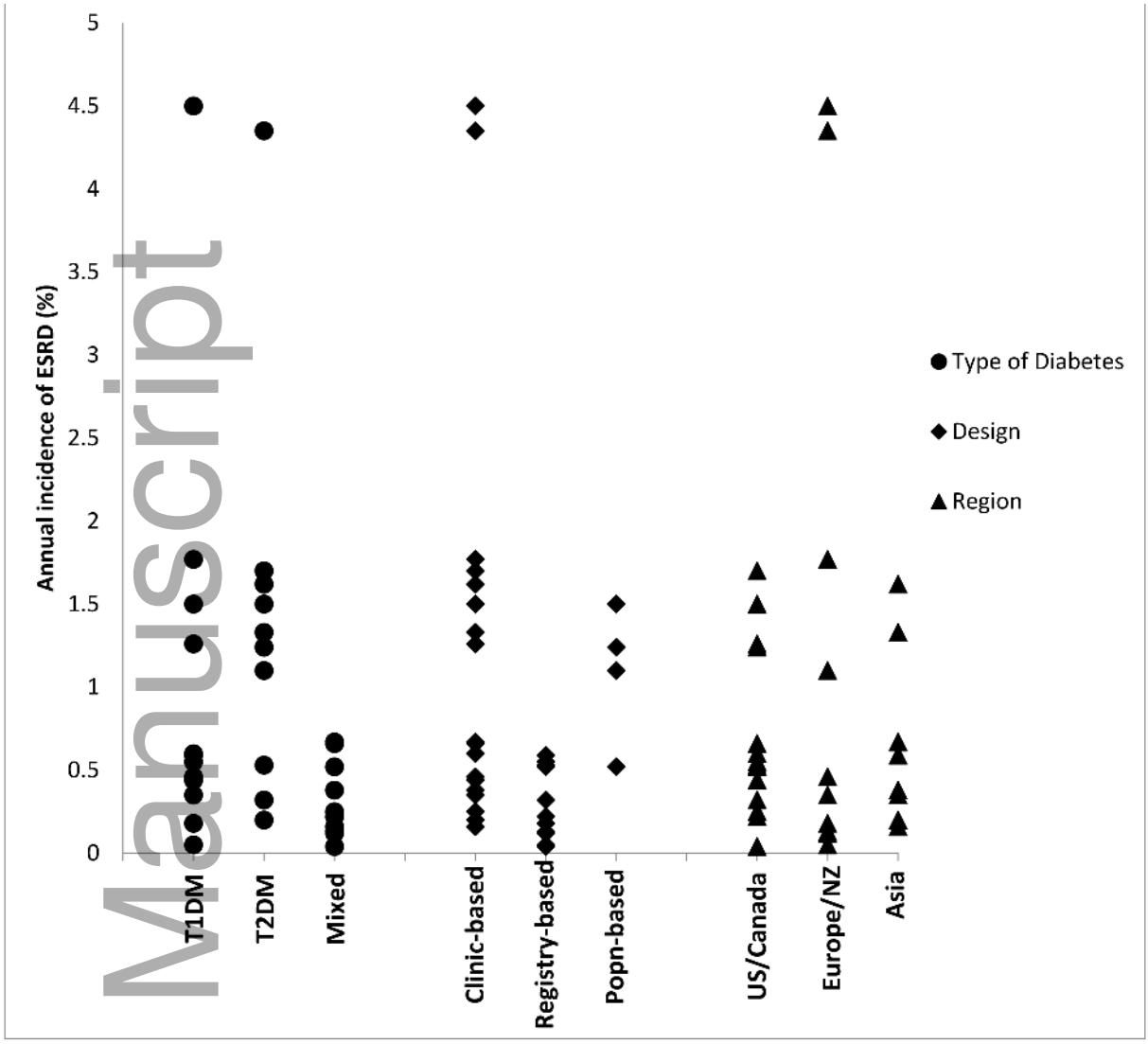

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