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Incidence and risk factors for mortality and end-stage renal disease in people with type 2 diabetes and diabetic kidney disease: a population-based cohort study in the UK

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ABSTRACT

Introduction We aimed to determine the incidence of, and risk factors for all-cause/cardiovascular disease (CVD) mortality, and end-stage renal disease (ESRD) among people with type 2 diabetes with/without diabetic kidney disease (DKD) in the UK general population.

Research design and methods We undertook a population-based cohort study using primary care UK electronic health records. We followed 8413 people with type 2 diabetes and DKD and a matched comparison cohort of people with type 2 diabetes without DKD. Risk factors for all-cause/CVD mortality (using both cohorts) and ESRD (DKD cohort only) were evaluated by estimating HRs with 95% CIs using Cox regression.

Results In the DKD cohort (mean age 66.7 years, 62.4% male), incidence rates per 1000 person-years were 50.3 (all-cause mortality), 8.0 (CVD mortality) and 6.9 (ESRD). HRs (95% CIs; DKD vs comparison cohort) were 1.49 (1.35 to 1.64) for all-cause mortality and 1.60 (1.24 to 2.05) for CVD mortality. In general, higher all-cause mortality risks were seen with older age, underweight (body mass index <20 kg/m^2), reduced renal function, and cardiovascular/liver disease, and lower risks were seen with being female or overweight. In the DKD cohort, higher risks of ESRD were seen with reduced renal function at baseline, high material deprivation, cancer and non-insulin glucose-lowering drugs, and a lower risk was seen with overweight (≥25 kg/m^2).

Conclusions Annually, one death will occur among every 20 people with type 2 diabetes and DKD. The identified risk factors in this study will help identify people with type 2 diabetes at most risk of death and progression of kidney disease, and help to direct effective management strategies.

SIGNIFICANCE OF THIS STUDY

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ Reductions in the proportion of people with diabetic kidney disease (DKD) progressing to end-stage renal disease (ESRD) have been small, and mortality among people with DKD remains strikingly high.

WHAT ARE THE NEW FINDINGS?

⇒ In people with type 2 diabetes and DKD, reduced renal function, high material deprivation, cancer and non-insulin glucose-lowering drugs were associated with a higher ESRD risk.
⇒ Being overweight could confer a lower ESRD risk, although this result should be interpreted with caution.
⇒ Our results highlight the importance of screening for the presence of DKD in primary care.

HOW MIGHT THESE RESULTS CHANGE THE FOCUS OF RESEARCH OR CLINICAL PRACTICE?

⇒ The identified risk factors in this study will help identify people with type 2 diabetes at most risk of death and progression of kidney disease and help to direct effective management strategies.
⇒ Reduction of all-cause mortality observed with the use of glucagon-like peptide-1 receptor agonists should be further investigated in randomized controlled trials.

INTRODUCTION

The global prevalence of diabetes continues to increase with projections of a rise from 9.3% in 2019 to 10.9% by 2045, largely driven by ageing populations and lifestyle changes.[1] About 30%–40% of people with diabetes will develop diabetic kidney disease (DKD)[2 3]—kidney disease caused by diabetes itself, and the leading cause of overall chronic kidney disease (CKD).[4 5] In addition, about 30% of people with type 2 diabetes will progress to end-stage renal disease (ESRD),[6] and renal replacement therapy among these persons estimated to account for 3%–5% of national European healthcare budgets.[7]

Cardiovascular (CV) complications are a major cause of mortality in people with diabetes, and those with DKD have a particularly high risk of these complications.

Ten-year cumulative all-cause mortality in people with diabetes and CKD has been estimated to be 31.1%, compared with 11.5% in people with diabetes but without CKD, and 7.7% in people without either condition.[8] There is mounting evidence that people with DKD face an increased risk of death,[9] which does not seem to depend on the DKD subphenotype.[10] While last two decades have seen a significant decline in the development of CV disease (CVD) and associated death among people with diabetes, reductions in progression to ESRD have been much smaller.[11] Moreover, because of the high prevalence of diabetes, the burden of both diabetes-related CVD and renal complications remains high,[12] and despite the effectiveness of current DKD management strategies, mortality among people with DKD remains strikingly high.[13] Among the literature on this topic, relatively few studies have focused on the incidence and risk factors of major clinical outcomes specifically among the DKD population. There is therefore a need to better understand the epidemiology of CV/renal outcomes and mortality among this high-risk group of people with diabetes. We aimed to determine the incidence of, and risk factors for all-cause and CV mortality, and development of stage 5 CKD/ESRD in a population-based cohort study of people with type 2 diabetes with/without DKD.

RESEARCH DESIGN AND METHODS

Study design and data source

We conducted a population-based cohort study using data from the IQVIA Medical Research Data UK (IMRD-UK), formerly The Health Improvement Network. This study builds on previously published work, and information on the IMRD-UK, the source population, inclusion criteria, DKD/CKD definitions and protocol approval can be found elsewhere.[14] Briefly, between January 1, 2002 and December 31, 2014, 114 056 individuals without CKD and with newly diagnosed diabetes were followed and incident cases of CKD and DKD (defined using the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical criteria)[15] and CKD were identified. Thus, individuals with DKD included those with a specific DKD diagnostic code recorded in the database, those with at least two albumin-to-creatinine ratio (ACR) measurements greater than 300 mg/g (recorded more than 90 days apart), and also those with CKD (two or more measurements of estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 more than 90 days apart) with evidence of proteinuria (ACR greater than 30 mg/g, albuminuria greater than 20 mg/L, or proteinuria diagnostic code). In this current study, we followed up the incident cases DKD with type 2 diabetes and a matched comparison cohort of people with diabetes without DKD to determine the incidence of, and risk factors, for all-cause/CV mortality, and followed the DKD cohort separately for development of stage 5 CKD/ESRD.

DKD and non-DKD comparison cohort

The study entry date for this present study was the date of DKD onset. To establish a comparison cohort of people with type 2 diabetes but without DKD, we matched each member of the DKD cohort 1:1 to a randomly selected individual free of DKD on the date of diabetes diagnosis, and of the same sex, age, type of diabetes and year of diabetes onset. Once selected, people in the comparison cohort entered the study on the same date as their matched partner. As the sequential random sampling process to select individuals in the comparison cohort was performed without replacement, individuals in a matched pair were no longer eligible to become part of a future matched pair. This method avoided selection bias that can be introduced when using information on future events to obtain cohorts, although it resulted in a smaller cohort than would have been identified otherwise. After this process, there were 8416 members of the DKD cohort matched to an equal number of individuals in the comparison cohort; 10 individuals in total were <18 years of age.

Follow-up to mortality outcomes

We followed up the DKD and comparison cohorts from study entry until death or the end of follow-up (December 31, 2015), whichever came first. Deaths due to CVD were ascertained by entries for CVD as the reported cause of death or, if this was missing, by recorded entries for at least one of the following in the 90 days before the date of death (in the absence of a record of cancer in the year before the date of death): ischemic heart disease, cardiac surgery, heart failure, and cerebrovascular disease. For these people, we subsequently manually reviewed their electronic primary care record to confirm whether their death was CV related or non-CV related.

Follow-up to identify stage 5 CKD/ESRD

In a separate follow-up of the DKD cohort, we identified those with a coded entry for stage 5 CKD/ESRD during their period of observation, that is, follow-up ended at the date of stage 5 CKD/ESRD, death or the end of the study period, whichever came first. After excluding people already classified as stage 5 CKD/ESRD on the date of first DKD diagnosis (ie, prevalent cases), 9175 people remained eligible for this follow-up. We defined stage 5 CKD as a recorded eGFR of <15 mL/min/1.73 m^2, and ESRD as a coded entry of dialysis or kidney transplant.

Covariates

We extracted information from the database on person demographics (including the Townsend material deprivation score),[16] comorbidities, lifestyle factors, healthcare use and medication use. Details of these variables have been described previously.[14] For this present study, we determined comorbidities (including renal function, glycemic control and lifestyle factors) anytime before study entry using the most recent value/status for the latter. Codes used to identify comorbidities can be found

in online supplemental tables 1–11. Healthcare use (general practitioner (GP) visits, referrals to secondary care, and hospitalizations) and medication use (including antidiabetic drugs) were determined from prescriptions issued in the year before study entry.

Statistical analyses

Crude incidence rates of all-cause mortality/CV mortality were calculated for the DKD and comparison cohorts by dividing the number of deaths/CV deaths by the respective total person-years follow-up. Crude incidence rates of stage 5 CKD/ESRD were calculated similarly for the DKD cohort. Incidence rates were stratified by age (<65 years and ≥65 years) and sex. Associations between having DKD and all-cause mortality/CV mortality were estimated by calculating HRs with 95% CIs using multivariable Cox proportional hazard regression adjusted for confounders. Associations between other person characteristics, and all-cause mortality/CV mortality were also investigated. In the analysis of CV mortality and stage 5/ESRD, we used both Cox proportional hazard regression and Fine and Gray regression.[17] The latter enables the estimation of subdistribution HRs accounting for competing risks from causes other than the cause being analyzed (ie, accounting for non-CV deaths in the CV mortality analysis, and accounting for all-cause death in the stage 5 CKD/ESRD analysis).

RESULTS

All-cause mortality

Baseline characteristics of the DKD and comparison are shown in table 1 for the cohort combined, and in online supplemental table 12 for the cohorts separately. The mean age of both cohorts was 66.7 years, and 62.4% were male. A total of 2266 people died during follow-up: 1465 in the DKD cohort over a mean follow-up of 3.5 years, and 801 in the comparison cohort over a mean follow-up of 3.4 years. The crude all-cause mortality rate in the DKD cohort was almost double the rate in the comparison cohort at start of follow-up (50.3 vs 28.4 per 1000 person-years). The corresponding crude HR (DKD vs comparison cohort) of 1.77 (95% CI: 1.62 to 1.93) was slightly attenuated after adjusting for confounders; adjusted HR 1.49 (95% CI: 1.35 to 1.64). Older age was strongly related to all-cause mortality; the mortality rate was 2.9 per 1000 person-years in people aged <40 years, increasing to 17.3 per 1000 person-years (for 50–64 years), and 91.4 per 1000 person-years (for 75–89 years). Compared with people aged 40–49 years, the risk of death was increased twofold in those aged 50–64 years, fourfold in those aged 65–74 years, and eightfold in those aged 75–89 years. Other variables strongly associated with a higher risk of all-cause mortality were smoking, being underweight (body mass index (BMI) <20 kg/m^2), CVD, cerebrovascular disease, pancreatic disease, liver disorders, eGFR <45 mL/min/1.73 m^2, use of mineralocorticoid receptor antagonists (MRAs) in the year before study entry, and a high number of GP visits/at least one hospitalization in the year before study entry. We also found clear evidence that being female and being overweight were associated with a lower risk of all-cause mortality.

As shown in table 2, the higher risk of all-cause mortality associated with having DKD was broadly similar among people aged <65 years and ≥65 years, and among males and females—the point estimates being higher among the younger age group and females. Reductions in all-cause mortality were also seen with use of glucagon-like peptide-1 (GLP-1) receptor agonists (a 50% lower risk of death, adjusted HR 0.51, 95% CI: 0.27 to 0.95), and metformin (adjusted HR 0.90, 95% CI: 0.83 to 0.99), while insulin was associated with a higher risk of death (adjusted HR 1.37, 95% CI: 1.15 to 1.63) (online supplemental table 13).

CV mortality

Of the 2266 people who died during follow-up, 336 died from CVD (233 in the DKD cohort and 103 in the comparison cohort). The crude CV mortality rate in the DKD cohort was more than double the rate in the comparison cohort (8.0 vs 3.7 per 1000 person-years). Associations between person characteristics (DKD and comparison cohort combined) and CV mortality are shown in table 3. The DKD cohort had a 60% higher risk of CV mortality compared with the comparison cohort when using either the Cox regression model (adjusted HR 1.60, 95% CI: 1.24 to 2.05) or the Fine and Gray model (adjusted HR 1.56, 95% CI: 1.21 to 2.00). Older age, a high level of material deprivation (Townsend index), hypertension, atrial fibrillation, cerebrovascular disease, reduced renal function (eGFR <60 mL/min/1.73 m^2), and a high level of GP visits/use of MRA in the year before DKD diagnosis were also strongly associated with higher risks of CV mortality. We found moderate evidence for a higher risk of CV mortality among people with glycemic control at >8% during some point in the year before study entry, for heart failure, and for chronic obstructive pulmonary disease.

Stage 5 CKD/ESRD among people with DKD

Among 9175 people with type 2 diabetes and DKD without stage 5 CKD/ESRD at study entry, 213 developed stage 5 CKD/ESRD during follow-up; a crude incidence rate of 6.93 per 1000 person-years. Associations between person characteristics and risk of ESRD are shown in table 4 and online supplemental table 14. We found strong evidence that higher level of material deprivation, cancer, reduced renal function (<60 mL/min/1.73 m^2), a high level of GP visits, and use of oral antidiabetic drug use in the year before DKD diagnosis were associated with higher risks of developing stage 5 CKD/ESRD. Our results provided statistical evidence that being overweight was associated with a lower risk of developing stage 5 CKD/ESRD, although significance was not reached in the Fine and Gray analysis for those with a BMI of ≥30 kg/m^2. Further, subdividing individuals

Table 1 HRs (95% CIs) for the association between DKD, and other person characteristics, and risk of all-cause mortality among people with type 2 diabetes

Variable	N	Deaths	Person–years	Mortality rate per 1000 person-years	HR* (95% CI)	P value
Subcohort						
Comparison	8416	801	28222	28.4	1.0 (reference)	
DKD	8416	1465	29128	50.3	1.49 (1.35 to 1.64)	<0.01
Age (years)						
<40	282	3	1038	2.9	0.36 (0.11 to 1.18)	0.09
40–49	1240	32	4708	6.8	1.0 (reference)	
50–64	5012	317	18326	17.3	2.29 (1.59 to 3.31)	<0.01
65–74	5624	667	19631	34.0	4.02 (2.79 to 5.80)	<0.01
75–89	4674	1247	13646	91.4	8.30 (5.73 to 12.01)	<0.01
Sex						
Male	10502	1408	35478	39.7	1.0 (reference)	
Female	6330	858	21871	39.2	0.84 (0.77 to 0.92)	<0.01
Smoking						
Non-smoker	5434	536	19914	26.9	1.0 (reference)	
Smoker	2204	292	7487	39.0	1.62 (1.39 to 1.88)	<0.01
Ex-smoker	7450	1039	28048	37.0	1.07 (0.95 to 1.19)	0.26
Missing	1744	399	1901	209.9	7.14 (6.22 to 8.20)	<0.01
Alcohol (units/week)						
Non–drinker	3686	554	12341	44.9	1.0 (reference)	
1–2	5528	676	18116	37.3	0.96 (0.85 to 1.08)	0.47
3–15	4198	537	14702	36.5	1.00 (0.89 to 1.14)	0.95
16–24	900	95	3211	29.6	0.89 (0.71 to 1.12)	0.33
≥25	1077	138	3719	37.1	1.16 (0.95 to 1.41)	0.14
Missing	1443	266	5261	50.6	1.21 (1.04 to 1.41)	0.01
BMI (kg/m^2)						
<20	271	112	730	153.4	1.60 (1.30 to 1.98)	<0.01
20–24	2266	492	7282	67.6	1.0 (reference)	
25–29	5622	749	19643	38.1	0.71 (0.63 to 0.80)	<0.01
≥30	8560	873	29330	29.8	0.72 (0.64 to 0.81)	<0.01
Missing	113	40	364	109.8	1.79 (1.29 to 2.49)	<0.01
Townsend index (quintile)						
1st (least deprivation)	3396	412	11523	35.8	1.0 (reference)	
2nd	3446	463	11578	40.0	1.03 (0.90 to 1.17)	0.70
3rd	3549	481	12191	39.5	1.08 (0.94 to 1.23)	0.27
4th	3415	501	11797	42.5	1.10 (0.96 to 1.26)	0.16
5th (most deprivation)	2572	355	8836	40.2	1.07 (0.93 to 1.24)	0.35
Missing	454	54	1424	37.9	0.94 (0.71 to 1.26)	0.69
Glycemic control quality†						
Always ≤8%	10619	1462	36119	40.5	1.0 (reference)	
At some point >8%	4359	478	13999	34.2	1.06 (0.95 to 1.18)	0.30
Missing	1854	326	7232	45.1	1.14 (1.01 to 1.30)	0.04
Comorbidities						
Hypertension	11563	1639	39180	41.8	1.02 (0.92 to 1.13)	0.68

Continued

Table 1 Continued

Variable	N	Deaths	Person–years	Mortality rate per 1000 person-years	HR* (95% CI)	P value
Hyperlipemia	5598	717	19176	37.4	0.90 (0.82 to 0.99)	0.03
Heart failure	944	303	2573	117.8	1.33 (1.15 to 1.54)	<0.01
IHD	3455	693	11383	60.9	1.18 (1.07 to 1.30)	<0.01
Atrial fibrillation	1607	446	4632	96.3	1.24 (1.10 to 1.40)	<0.01
Cerebrovascular disease	1598	399	4857	82.2	1.35 (1.21 to 1.51)	<0.01
COPD	1466	356	4150	85.8	1.68 (1.49 to 1.89)	<0.01
Peptic ulcer disease	1286	242	4022	60.2	1.10 (0.96 to 1.26)	0.17
Pancreatic disease	283	60	877	68.4	1.30 (1.01 to 1.69)	0.04
Liver disorders	734	111	2074	53.5	1.36 (1.12 to 1.66)	<0.01
Cancer	2584	595	7384	80.6	1.61 (1.46 to 1.78)	<0.01
GP visits†						
<12	3619	343	13698	25.0	1.0 (reference)	
12–23	7930	930	27879	33.4	1.21 (1.06 to 1.37)	<0.01
24–35	3337	524	10655	49.2	1.27 (1.09 to 1.47)	<0.01
≥36	1946	469	5117	91.7	1.81 (1.53 to 2.15)	<0.01
Referrals to secondary care†						
None	2282	312	9292	33.6	1.0 (reference)	
1–6	10079	1216	35216	34.5	0.94 (0.83 to 1.07)	0.39
≥7	4471	738	12842	57.5	0.98 (0.84 to 1.15)	0.83
≥1 hospitalization†	3176	627	9311	67.3	1.23 (1.10 to 1.36)	<0.01
Lowest eGFR (mL/min/1.73 m^2)†						
≥90	3354	161	10862	14.8	1.0 (reference)	
60–89	7687	870	26338	33.0	1.09 (0.91 to 1.30)	0.36
45–59	2962	620	10889	56.9	1.20 (0.99 to 1.46)	0.06
30–44	932	303	2993	101.2	1.62 (1.31 to 2.00)	<0.01
15–29	263	99	714	138.6	2.12 (1.62 to 2.78)	<0.01
<15	47	16	136	117.8	2.02 (1.19 to 3.42)	0.01
Missing	1587	197	5418	36.4	1.20 (0.96 to 1.50)	0.11
Medication use†						
ACEI/ARB	11494	1607	39075	41.1	0.95 (0.86 to 1.06)	0.37
MRA	493	148	1189	124.4	1.35 (1.11 to 1.63)	<0.01

*Adjusted for all other variables in the table.
†In the year before study entry.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GP, general practitioner; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist.

in this BMI category did not reveal any particular trend (online supplemental table 15). Associations between BMI category and stage 5 CKD/ESRD did not seem to differ between the sexes (online supplemental tables 16 and 17) and remained virtually unchanged after further adjustment for history of anemia (online supplemental table 18). The largest effect size for development of stage 5 CKD/ESRD was renal function <60 mL/min/1.73 m^2: adjusted HRs (95% CIs) using Cox proportional hazard regression modeling were 5.46 (2.52 to 11.84) for eGFR 45–59 mL/min/1.73 m^2, 8.06 (3.55 to 18.29) for eGFR 30–44 mL/min/1.73 m^2, and 25.82 (11.09 to 60.11) for eGFR 15–29 mL/min/1.73 m^2. Time between diabetes diagnosis and DKD diagnosis was not found to be associated with the risk of stage 5 CKD/ESRD.

DISCUSSION

In this large population-based study, we found that the risk of death among people with type 2 diabetes and DKD

Table 2 All-cause mortality rates per 1000 person-years among people with type 2 diabetes in the DKD and comparison cohorts, and associated HRs (95% CIs; DKD vs comparison)

Subgroup	N	Deaths	Person-years	Mortality rate per 1000 person-years	Adjusted HR* (95% CI)	P value
Age <65 years						
Matched comparison cohort	3267	103	1905	8.65	1.0 (reference)	
DKD cohort	3267	249	12 168	20.46	1.83 (1.41 to 2.38)	<0.01
Age ≥65 years						
Matched comparison cohort	5149	698	16 317	42.78	1.0 (reference)	
DKD cohort	5149	1216	16 960	71.70	1.44 (1.30 to 1.60)	<0.01
Male						
Matched comparison cohort	5251	503	17 391	28.92	1.0 (reference)	
DKD cohort	5251	905	18 088	50.03	1.39 (1.23 to 1.57)	<0.01
Female						
Matched cohort subcohort	3165	298	10 831	27.51	1.0 (reference)	
DKD cohort	3165	560	11 040	50.73	1.68 (1.44 to 1.97)	<0.01

*Adjusted for all the variables in table 1.
DKD, diabetic kidney disease.

remains extremely high, with 1 death among every 20 people each year. This mortality rate was 50% higher than the rate among people with type 2 diabetes without DKD at the start of follow-up after adjusting for other factors and was not significantly different between the sexes; the excess of mortality was slightly greater in younger age groups. Strong evidence was also found for a 60% higher rate of CV death among people with type 2 diabetes and DKD compared with those without DKD.

Other population-based studies have similarly shown that DKD confers a substantially higher mortality risk among people with diabetes,[8 9 18 19] and the annual mortality rate of 64.1 per 1000 per year individuals seen in our study is similar to that reported by Ang *et al*[19] among over 3000 people with DKD in Singapore. Reduced renal function at baseline was an independent risk factor for both CV mortality and ESRD, consistent with previous findings for CV mortality[20–22] and ESRD[20] among people with diabetes[20 21 23 24] or specifically with DKD.[9] We did not find reduced renal function to be associated with increased all-cause mortality as reported by others.[9 20–24] In line with reports from among general populations,[25 26] we found high material deprivation to be associated with elevated risks of CVD mortality and ESRD in our type 2 diabetes cohort, yet no association was seen between material deprivation and all-cause mortality. Several factors previously reported to be independently associated with higher risks of all-cause mortality were confirmed in our study, including older age,[9 23 24] smoking,[23 24 27] CVD risk factors,[23] cerebrovascular disease,[23] being underweight,[24] pancreatic disease,[28] and liver disorders.[29] Similarly, we confirmed previous reports that being female[24] or being overweight[27] was associated with lower risk of death. Age and other traditional CVD risk factors were also associated with a higher risk of CV mortality, while cancer was associated with elevated ESRD risk. We found no evidence for associations between smoking or hyperlipidemia and DKD, and other findings on this topic have been mixed.[30] We found that among patients with DKD, being overweight was associated with slower progression to ESRD, and that this was seen for both sexes and across BMI categories. However, this finding should be interpreted with caution because the general health status of these overweight patients with diabetes and compromised renal function might have been quite different from those who were not overweight. Under these circumstances, adjustment for baseline factors might not have been able to fully account for these differences. The results of the Fine and Gray analysis, with decreasing statistical significance and magnitude of the association, seem to confirm this. Although quality of glycemic control was not associated with either all-cause/CV mortality or ESRD, use of glucagon-like peptide-1 (GLP-1) agonists was associated with a 50% reduced risk of death.

Our population-based sample of people with DKD and a matched non-DKD comparison cohort from a data source representative of the UK population means our findings have good generalizability. The large sample size enabled calculation of precise incidence rates and relative risk estimates, although less powered for ESRD analyses. We explored of a wide range of potential risk factors for mortality and ESRD, including demographics, comorbidities, medications, healthcare use and lifestyle factors. Our study also has its limitations. First, some people may have been missed from inclusion in the DKD cohort because we identified DKD using KDOQI clinical criteria from recorded test results performed during routine clinical practice, yet not everyone with diabetes will necessarily have been tested. Also, KDOQI criteria for DKD identification has its shortcomings because kidney

Table 3 CV mortality rates per 1000 person-years among the DKD and comparison cohorts, and associated HRs (95% CIs; DKD vs comparison)

Variable	CV deaths	Incidence rate per 1000 person-years	HR* (95% CI)	P value	SHR* (95% CI)	P value
Subcohort						
Matched comparison	103	3.65	1.0 (reference)		1.0 (reference)	
DKD	233	8.00	1.60 (1.24 to 2.05)	<0.01	1.56 (1.21 to 2.00)	<0.01
Age (years)						
<40	0	–	–	–	–	–
40–49	4	0.85	1.0 (reference)		1.0 (reference)	
50–64	48	2.62	2.29 (0.82 to 6.42)	0.12	2.18 (0.78 to 6.05)	0.14
65–74	102	5.20	3.68 (1.31 to 10.30)	0.01	3.32 (1.19 to 9.24)	0.02
75–89	182	13.34	7.78 (2.75 to 21.99)	<0.01	6.24 (2.26 to 17.23)	<0.01
Sex						
Male	213	6.00	1.0 (reference)		1.0 (reference)	
Female	123	5.62	0.89 (0.69 to 1.13)	0.33	0.91 (0.71 to 1.15)	0.42
Smoking						
Non-smoker	88	4.42	1.0 (reference)		1.0 (reference)	
Smoker	38	5.08	1.31 (0.88 to 1.96)	0.19	1.18 (0.79 to 1.77)	0.42
Ex–smoker	164	5.85	0.95 (0.72 to 1.25)	0.72	0.98 (0.74 to 1.30)	0.89
Missing	46	24.20	4.98 (3.40 to 7.30)	<0.01	2.14 (1.47 to 3.13)	<0.01
Alcohol (units/week)						
Non-drinker	72	5.83	1.0 (reference)		1.0 (reference)	
1–2	108	5.96	1.09 (0.80 to 1.48)	0.59	1.11 (0.82 to 1.52)	0.50
3–15	89	6.05	1.25 (0.90 to 1.73)	0.19	1.22 (0.87 to 1.70)	0.25
16–24	16	4.98	1.12 (0.64 to 1.97)	0.69	1.13 (0.63 to 2.01)	0.69
≥25	19	5.11	1.18 (0.69 to 2.00)	0.54	1.13 (0.66 to 1.93)	0.65
Missing	32	6.08	1.18 (0.77 to 1.80)	0.44	1.14 (0.74 to 1.76)	0.56
BMI (kg/m^2)						
<20	10	13.70	1.55 (0.77 to 3.09)	0.22	1.37 (0.67 to 2.82)	0.39
20–24	48	6.59	1.0 (reference)		1.0 (reference)	
25–29	121	6.16	1.09 (0.78 to 1.54)	0.61	1.20 (0.85 to 1.70)	0.30
≥30	153	5.22	1.13 (0.80 to 1.59)	0.49	1.25 (0.88 to 1.78)	0.22
Missing	4	10.98	1.84 (0.65 to 5.19)	0.25	1.47 (0.50 to 4.39)	0.48
Townsend index						
1st quintile (least deprivation)	51	4.43	1.0 (reference)		1.0 (reference)	
2nd quintile	71	6.13	1.28 (0.89 to 1.83)	0.19	1.28 (0.89 to 1.84)	0.19
3rd quintile	74	6.07	1.32 (0.92 to 1.89)	0.13	1.30 (0.90 to 1.88)	0.16
4th quintile	73	6.19	1.31 (0.91 to 1.89)	0.15	1.32 (0.92 to 1.91)	0.13
5th quintile (most deprivation)	61	6.90	1.48 (1.01 to 2.18)	0.04	1.50 (1.02 to 2.21)	0.04
Missing	6	4.21	0.84 (0.36 to 1.98)	0.69	0.84 (0.35 to 1.97)	0.68
Glycemic control quality†						
Always ≤8%	216	5.98	1.0 (reference)		1.0 (reference)	
At some point >8%	85	6.07	1.27 (0.98 to 1.65)	0.07	1.24 (0.95 to 1.62)	0.11
Missing	35	4.84	0.86 (0.59 to 1.26)	0.44	0.87 (0.59 to 1.27)	0.47

Continued

Table 3 Continued

Variable	CV deaths	Incidence rate per 1000 person-years	HR* (95% CI)	P value	SHR* (95% CI)	P value
Comorbidities						
Hypertension	266	6.79	1.36 (1.02 to 1.81)	0.03	1.36 (1.03 to 1.81)	0.03
Hyperlipemia	120	6.26	1.00 (0.79 to 1.25)	0.97	1.02 (0.81 to 1.29)	0.86
Heart failure	68	26.43	1.56 (1.11 to 2.19)	0.01	1.46 (1.00 to 2.14)	0.05
IHD	124	10.89	1.30 (1.02 to 1.65)	0.04	1.26 (0.97 to 1.62)	0.08
Atrial fibrillation	100	21.59	1.85 (1.40 to 2.45)	<0.01	1.79 (1.33 to 2.41)	<0.01
Cerebrovascular disease	69	14.21	1.55 (1.18 to 2.05)	<0.01	1.51 (1.14 to 2.00)	<0.01
COPD	52	12.53	1.54 (1.13 to 2.11)	0.01	1.26 (0.91 to 1.74)	0.17
Peptic ulcer disease	37	9.20	1.06 (0.75 to 1.51)	0.73	1.08 (0.75 to 1.55)	0.70
Pancreatic disease	9	10.26	1.31 (0.66 to 2.58)	0.44	1.31 (0.64 to 2.70)	0.46
Liver disorders	12	5.79	0.90 (0.50 to 1.62)	0.73	0.83 (0.46 to 1.51)	0.55
Cancer	66	8.94	1.15 (0.87 to 1.52)	0.32	1.02 (0.76 to 1.36)	0.92
GP visits†						
<12	40	2.92	1.0 (reference)		1.0 (reference)	
12–23	135	4.84	1.40 (0.98 to 2.01)	0.07	1.35 (0.95 to 1.93)	0.10
24–35	82	7.70	1.54 (1.02 to 2.31)	0.04	1.52 (1.00 to 2.29)	0.05
≥36	79	15.44	2.20 (1.40 to 3.47)	<0.01	1.80 (1.12 to 2.89)	0.01
Referrals to secondary care†						
None	43	4.63	1.0 (reference)		1.0 (reference)	
1–6	191	5.42	1.03 (0.73 to 1.44)	0.88	1.03 (0.73 to 1.45)	0.87
≥7	102	7.94	0.83 (0.55 to 1.25)	0.38	0.83 (0.55 to 1.26)	0.38
>1 hospitalization†	94	10.10	1.23 (0.94 to 1.61)	0.14	1.14 (0.86 to 1.52)	0.35
Lowest eGFR (mL/min/1.73 m^2)†						
≥90	16	1.47	1.0 (reference)		1.0 (reference)	
60–89	130	4.94	1.57 (0.91 to 2.72)	0.10	1.62 (0.93 to 2.83)	0.09
45–59	104	9.55	1.81 (1.02 to 3.20)	0.04	1.91 (1.07 to 3.42)	0.03
30–44	46	15.37	2.07 (1.11 to 3.87)	0.02	1.99 (1.04 to 3.80)	0.04
15–29	14	19.59	2.63 (1.22 to 5.65)	0.01	2.10 (0.93 to 4.72)	0.07
<15	0	0	–		–	
Missing	26	4.80	1.81 (0.94 to 3.49)	0.08	1.80 (0.93 to 3.49)	0.08
Medication use†						
ACEI/ARB	253	6.47	0.88 (0.67 to 1.16)	0.36	0.88 (0.67 to 1.16)	0.36
MRA	39	32.79	2.10 (1.40 to 3.13)	<0.01	2.07 (1.33 to 3.22)	<0.01

*Adjusted for all the other variables in the table.
†In the year before study entry.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GP, general practitioner; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist; SHR, subdistribution HR.

biopsy is the gold standard for differentiating DKD from other kidney disease in diabetes. Results of kidney biopsy are, if available, rarely recorded in primary care records. Additionally, evidence from the UK Prospective Diabetes Study that up to 40% of people with type 2 diabetes and reduced eGFR never develop albuminuria[31] suggests that our operational definition of DKD may have missed some patients. Second, CV deaths are likely to have been underestimated because cause of death was not recorded in the majority (>80%) of cases. Some studies have reported that CVD accounts for half of all deaths among people with type 2 diabetes,[32] who are more disproportionately affected by CVD than people without diabetes.[33] Third, although the majority of people with type 2 diabetes will

Table 4 Incidence rates of stage 5 CKD/ESRD per 1000 person-years among the DKD cohort, and HRs (95% CIs) for associations between person characteristics and risk of stage 5 CKD/ESRD

Variable	N	Incidence rate per 1000 person-years	Person-years	Stage 5 CKD/ESRD	HR* (95% CI)	SHR* (95% CI)
Age (years)						
<40	158	0	594	0	–	–
40–49	635	4.16	2402	10	1.0 (reference)	1.0 (reference)
50–64	2597	5.10	9404	48	0.77 (0.38 to 1.56)	0.76 (0.36 to 1.61)
65–74	3028	7.71	10502	81	0.88 (0.43 to 1.80)	0.82 (0.38 to 1.79)
75–89	2757	9.45	7827	74	0.84 (0.40 to 1.79)	0.68 (0.30 to 1.54)
Sex						
Male	5744	6.80	19114	130	1.0 (reference)	1.0 (reference)
Female	3431	7.15	11614	83	0.85 (0.63 to 1.16)	0.90 (0.66 to 1.23)
BMI (kg/m^2)						
<20	148	17.75	394	7	1.49 (0.65 to 3.41)	1.41 (0.64 to 3.13)
20–24	1195	11.62	3614	42	1.0 (reference)	1.0 (reference)
25–29	2941	5.90	10005	59	0.58 (0.39 to 0.88)	0.61 (0.40 to 0.93)
≥30	4835	6.30	16511	104	0.64 (0.44 to 0.95)	0.68 (0.46 to 1.00)
Missing	56	4.92	203	1	0.34 (0.05 to 2.57)	0.32 (0.05 to 2.05)
Townsend index (quintile)						
1st (least deprivation)	1672	4.76	5464	26	1.0 (reference)	1.0 (reference)
2nd	1844	6.62	6044	40	1.33 (0.81 to 2.20)	1.34 (0.81 to 2.20)
3rd	1891	6.55	6415	42	1.49 (0.91 to 2.44)	1.43 (0.87 to 2.36)
4th	1961	8.68	6682	58	1.95 (1.22 to 3.12)	1.88 (1.18 to 2.99)
5th (most deprivation)	1545	7.60	5265	40	1.76 (1.06 to 2.93)	1.71 (1.03 to 2.84)
Missing	262	8.15	859	7	1.79 (0.77 to 4.19)	1.84 (0.80 to 4.23)
Glycemic control quality†						
Always ≤8%	5634	6.80	18819	128	1.0 (reference)	1.0 (reference)
At some point >8%	2933	6.51	9371	61	1.07 (0.76 to 1.50)	1.05 (0.76 to 1.47)
Missing	608	9.46	2538	24	1.30 (0.82 to 2.07)	1.21 (0.75 to 1.95)
Comorbidities						
Hypertension	6609	7.49	22155	166	1.21 (0.85 to 1.72)	1.22 (0.86 to 1.74)
Hyperlipemia	3154	5.74	10623	61	0.76 (0.56 to 1.03)	0.77 (0.57 to 1.04)
Heart failure	691	14.30	1818	26	1.50 (0.93 to 2.44)	1.38 (0.86 to 2.20)
IHD	2105	9.03	6753	61	1.17 (0.84 to 1.62)	1.14 (0.82 to 1.59)
Cancer	1539	13.76	4287	59	1.99 (1.45 to 2.73)	1.75 (1.27 to 2.42)
Lowest eGFR (mL/min/1.73 m^2)†						
≥90	1594	1.51	5281	8	1.0 (reference)	1.0 (reference)
60–89	3390	3.57	11205	40	2.19 (1.00 to 4.79)	2.22 (0.98 to 5.02)
45–59	2314	9.76	8404	82	5.46 (2.52 to 11.84)	5.59 (2.47 to 12.63)
30–44	796	15.68	2487	39	8.06 (3.55 to 18.29)	7.74 (3.30 to 18.16)
15–29	224	47.41	612	29	25.82 (11.09 to 60.11)	23.30 (9.47 to 57.31)
<15	0	0	0	0	–	–
Missing	857	5.48	2740	15	3.92 (1.61 to 9.54)	3.88 (1.55 to 9.70)
GP visits†						
<12	1615	3.51	5986	21	1.0 (reference)	1.0 (reference)
12–23	4085	6.07	14509	88	1.55 (0.95 to 2.53)	1.54 (0.95 to 2.51)
24–35	2067	9.09	6491	59	1.97 (1.15 to 3.38)	1.90 (1.10 to 3.28)
≥36	1408	12.03	3742	45	2.23 (1.22 to 4.09)	1.95 (1.02 to 3.72)
Referrals to secondary care†						

Continued

Table 4 Continued

Variable	N	Incidence rate per 1000 person-years	Person-years	Stage 5 CKD/ ESRD	HR* (95% CI)	SHR* (95% CI)
None	1121	7.50	4536	34	1.0 (reference)	1.0 (reference)
1–6	5252	5.93	18221	108	0.77 (0.51 to 1.15)	0.75 (0.50 to 1.14)
≥7	2802	8.91	7971	71	0.75 (0.46 to 1.21)	0.72 (0.43 to 1.20)
>1 hospitalization†	1940	10.21	5678	58	1.13 (0.80 to 1.59)	1.09 (0.76 to 1.56)
Antidiabetic medication†						
None	1719	5.42	6088	33	1.0 (reference)	1.0 (reference)
1 class of non-insulin glucose-lowering medication	3394	7.64	11525	88	1.80 (1.20 to 2.72)	1.82 (1.20 to 2.75)
2 classes of non-insulin glucose-lowering medication	2475	6.74	8460	57	1.66 (1.04 to 2.63)	1.72 (1.07 to 2.76)
>2 classes of non-insulin glucose-lowering medication	896	6.36	2673	17	2.10 (1.11 to 3.98)	2.14 (1.14 to 4.02)
Insulin	691	9.08	1982	18	2.00 (1.06 to 3.75)	1.96 (1.07 to 3.60)
Other medication†						
ACEI/ARB	6978	7.28	23635	172	1.06 (0.73 to 1.53)	1.12 (0.77 to 1.62)
MRA	370	13.75	873	12	0.94 (0.49 to 1.81)	0.85 (0.43 to 1.65)
Time from diabetes diagnosis to DKD (years)						
0–1	285	7.13	1263	9	1.0 (reference)	1.0 (reference)
1–2	811	7.00	3428	24	0.86 (0.40 to 1.89)	0.89 (0.41 to 1.96)
2–3	1029	8.19	4520	37	0.92 (0.43 to 1.95)	0.96 (0.46 to 2.02)
3–4	1117	7.46	4559	34	0.77 (0.36 to 1.66)	0.75 (0.35 to 1.58)
4–5	1060	6.57	4110	27	0.66 (0.30 to 1.45)	0.64 (0.29 to 1.42)
>5	4873	6.38	12847	82	0.66 (0.31 to 1.38)	0.61 (0.30 to 1.25)

*Adjusted for all the other variables in the table.
†In the year before study entry.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GP, general practitioner; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist; SHR, subdistribution HR.

have their renal function assessed regularly, the likely inclusion of some without consistent renal function testing would have led to some misclassification of renal function at baseline and during follow-up. Fourth, drug use was determined at the start of follow-up, and while this avoids finding spurious associations between chronic medication and survival when drug use is determined around the date of death, drug use may change during follow-up. Glycosylated hemoglobin measurements may also have changed during follow-up. Finally, we were unable to explore ethnicity, family history, physical activity or dietary intake as potential risk factors as this information is not generally recorded in the database.

CVD is the main competing cause of death to ESRD among people with diabetes, thereby highlighting the need for treatments that prevent both adverse CV events and DKD progression. So far, the cornerstone of treatment for DKD management and the prevention of CVD mortality has been control of traditional CVD risk factors, using established therapies such as ACE inhibitors and angiotensin receptor blockers that reduce progression of the disease through lowering blood pressure.[34–36] More recently, two glucose-lowering therapies—sodium-glucose transport protein 2 (SGLT2) inhibitors and GLP-1 receptor agonists—have been shown to reduce both CVD risk (mainly heart failure) and DKD progression. Currently, evidence is stronger for SGLT2 as a cardiorenal reducing class of drugs, including among people with reduced renal function.[37] We were unable to perform a meaningful analysis of SGLT2 inhibitors because relatively few people used these drugs during the current follow-up period. MRAs are another class of drugs being investigated as a possible treatment for DKD. There is some evidence that they decrease the risk of CV events and sudden death in people with reduced eGFR[38] and might therefore have similar beneficial effects in people with DKD. In our study, however, use of MRAs was associated with a twofold higher risk of CV mortality, and a 35% increased risk of all-cause mortality, and no association was seen with ESRD risk. MRAs with

greater selectivity and receptor affinity to those used in practice are currently being investigated for their effects on reducing clinically important CV and renal outcomes in people with DKD.[39]

Our results strongly support continued focus and support to people with type 2 diabetes and DKD in optimizing treatment in clinical practice and continual review of guidelines. The prevalence of DKD is expected to increase alongside increasing prevalence of diabetes,[40] and use of renal replacement therapy is projected to increase dramatically, with an estimated 4.3 million people needing this treatment worldwide by 2030.[41] Considering the high mortality rates among people with DKD, the condition remains a growing public health problem, and there is an explicit need for newer effective treatments to improve cardiorenal outcomes in these people. The independent risk factors for mortality and ESRD identified in this study will help identify people with type 2 diabetes at most risk of death and progression of kidney disease and help to direct effective management strategies.

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