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

Antonio González-Pérez,1,2 María Saez,1,2 David Vizcaya,3 Marcus Lind,4 Luis García Rodriguez1

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, overweight (body mass index <25 kg/m2), 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/m2).

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.

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)2–5—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.9 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 m² 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 m², 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. 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 cohorts 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/m²), CVD, cerebrovascular disease, pancreatic disease, liver disorders, eGFR <45 mL/min/1.73 m², 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 765 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 m²), 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 m²), 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/m². 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/m²)**           |       |        |              |                                      |                   |         |
| <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
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 m²: 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 m², 8.06 (3.55 to 18.29) for eGFR 30–44 mL/min/1.73 m², and 25.82 (11.09 to 60.11) for eGFR 15–29 mL/min/1.73 m². 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 remains extremely high, with 1 death among every 20 people each year. This mortality rate was 50% higher than

| 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 m²)† | |       |              |                                     |              |         |
| ≥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.
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, 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 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 and ESRD among people with diabetes or specifically with DKD. 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, 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, smoking, CVD risk factors, cerebrovascular disease, being underweight, pancreatic disease, and liver disorders. Similarly, we confirmed previous reports that being female or being overweight 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.

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 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 biopsy is the gold standard for differentiating DKD from other kidney disease in diabetes. Results of kidney biopsy

| 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 | 12168 | 20.46 | 1.83 (1.41 to 2.38) | <0.01 |
| Age ≥65 years  |  |  |  |  |  |  |
| Matched comparison cohort  | 5149 | 698 | 16317 | 42.78 | 1.0 (reference) |  |
| DKD cohort  | 5149 | 1216 | 16960 | 71.70 | 1.44 (1.30 to 1.60) | <0.01 |
| Male  |  |  |  |  |  |  |
| Matched comparison cohort  | 5251 | 503 | 17391 | 28.92 | 1.0 (reference) |  |
| DKD cohort  | 5251 | 905 | 18088 | 50.03 | 1.39 (1.23 to 1.57) | <0.01 |
| Female  |  |  |  |  |  |  |
| Matched cohort subcohort  | 3165 | 298 | 10831 | 27.51 | 1.0 (reference) |  |
| DKD cohort  | 3165 | 560 | 11040 | 50.73 | 1.68 (1.44 to 1.97) | <0.01 |

*Adjusted for all the variables in table 1.

DKD, diabetic kidney disease.
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               |           |                                      |              |         |               |         |
| 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/m²)**   |           |                                      |              |         |               |         |
| <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
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 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, who are more disproportionately affected by CVD than people without diabetes. Third, although the majority of people with type 2 diabetes will have their renal function assessed regularly, the likely inclusion of some without consistent renal function

| Variable                      | CV deaths | Incidence rate per 1000 person-years | HR* (95% CI) | P value | SHR* (95% CI) | P value |
|-------------------------------|-----------|--------------------------------------|--------------|---------|---------------|---------|
| 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) | 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) | 1.0 (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 m²)†  |           |                                      |              |         |               |         |
| ≥90                           | 16        | 1.47                                 | 1.0 (reference) | 1.0 (reference) | 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.
### 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 1.65) | 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/m²)**                 |       |                                      |              |                  |              |               |
| <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 m²)†**|       |                                      |              |                  |              |               |
| ≥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†
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

| 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.
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, and use of renal replacement therapy is projected to increase dramatically, with an estimated 4.3 million people needing this treatment worldwide by 2030. 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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ORCID iD
Antonio González-Pérez http://orcid.org/0000-0001-9771-5962

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