The Association Between Age of Onset of Type 2 Diabetes and the Long-term Risk of End-Stage Kidney Disease: A National Registry Study

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

The long-term risk of end-stage kidney disease (ESKD) in type 2 diabetes is poorly described, as is the effect that younger age of diabetes onset has on this risk. Therefore, we aimed to estimate the effect of age of onset on the cumulative incidence of ESKD from onset of type 2 diabetes.

RESEARCH DESIGN AND METHODS

This study included 1,113,201 people with type 2 diabetes registered on the Australian National Diabetes Services Scheme (NDSS) followed from 2002 until 2013. The NDSS was linked to the Australia and New Zealand Dialysis and Transplant Registry and the Australian National Death Index.

RESULTS

Between 2002 and 2013, there were 7,592 incident cases of ESKD during 7,839,075 person-years of follow-up. In the first 10–15 years following the onset of diabetes, the incidence of ESKD was highest in those with an older age of onset of diabetes, whereas over longer durations of diabetes, the incidence of ESKD became higher in those with younger-onset diabetes. After 40 years of diabetes, the cumulative incidence of ESKD was 11.8% and 9.3% in those diagnosed with diabetes at ages 10–29 and 30–39 years, respectively. When death from ESKD without renal replacement therapy was included, the incidence of ESKD remained higher in older-onset diabetes for the initial 20 years, with no clear effect of age thereafter.

CONCLUSIONS

The long-term risk of ESKD in type 2 diabetes is high, which disproportionately affects those with younger onset of diabetes because they are more likely to survive to longer diabetes durations.

One of the most burdensome and costly complications of diabetes is end-stage kidney disease (ESKD) (1,2). People with diabetes are at considerably increased risk for the development of ESKD (3), and diabetic nephropathy (DN) is now the leading cause of ESKD, accounting for one-third of incident cases worldwide (4). Despite this significant burden, estimates of the long-term risk of ESKD for those with type 2 diabetes are scarce.

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The primary limiting factor in the estimation of long-term risk has been that ESKD is a relatively rare event (5). Thus, to generate reliable estimates of ESKD incidence, studies must be of considerable size and duration, and include people with a wide spread of ages of onset of diabetes. Consequently, with the exception of Indigenous populations at very high risk for ESKD (6,7), there has been only one study sufficiently large enough to estimate long-term risk of ESKD. Finne et al. (5) estimated the cumulative risk of ESKD after 20 years of type 2 diabetes at 0.74% using a Finnish national cohort study, defining ESKD as initiation of renal replacement therapy (RRT), and concluded that the risk of ESKD in type 2 diabetes is low. However, one-third of the people in their cohort were diagnosed with diabetes at >70 years of age, and initiation of RRT at onset of ESKD diminishes dramatically with increasing age (8). Furthermore, the study excluded people diagnosed with diabetes at <40 years of age, who may be at increased risk for ESKD, especially at longer durations (6). Thus, the long-term risk of ESKD in type 2 diabetes may be considerably greater than this work would suggest.

Additionally, the relationship between age of onset of type 2 diabetes and risk for ESKD is poorly described. In particular, it is unclear whether the pathophysiology of DN in younger-onset diabetes is somehow different from older-onset diabetes, or whether survival to longer durations of diabetes in this group simply allows more time for DN to progress to ESKD (4). While it is clear that at a given age those with younger-onset diabetes are at higher risk of ESKD (7), when duration of diabetes is controlled for, reports of the effect of age of onset have been inconsistent (5,7). This is probably because noninitiation of RRT and the competing risk of death have not been considered, both of which are highly dependent on age (8,9), and are therefore likely to be especially important in describing the effect of age of onset on long-term ESKD risk (10).

Clearly, more information is needed on the long-term risk of ESKD for people with type 2 diabetes, and the effect that a younger age of diabetes onset has on this risk. Therefore, we linked nationwide diabetes, ESKD, and death registries in Australia to produce a cohort of >1 million people with type 2 diabetes and estimated the incidence of ESKD from the onset of diabetes by age of onset.

RESEARCH DESIGN AND METHODS

Data Sources

The National Diabetes Services Scheme (NDSS) was established by the Australian government in 1987 to deliver diabetes-related products at subsidized prices and provide information to people with diabetes. As such, its clinical data are limited to the date of onset of diabetes, diabetes type, and use of insulin. The NDSS is estimated to include 80–90% of people with diagnosed diabetes in Australia (11). We included as our study population individuals with type 2 diabetes registered on the NDSS as of 1 January 2002 and all new registrants from this date until 31 December 2013. In the NDSS database, diabetes type is classified by a health care practitioner at the time of registration. However, because there is often uncertainty in this diagnosis, especially at the time of diagnosis (when registration is usually completed), certain clinical characteristics were also required to be satisfied for assignment of diabetes type for the current analysis (Supplementary Appendix). Registrants with missing data on age, sex, or type of diabetes were excluded from all analyses ($n = 104$). Registrants diagnosed with diabetes after the age of 79 years were excluded ($n = 61{,}361$), because beyond 79 years the vast majority of ESKD is not treated with RRT (8). Because Aboriginal and Torres Strait Islander Australians are able to access services the NDSS provides through other means and are therefore not well represented on the NDSS, our analysis was restricted to non-Indigenous Australians.

NDSS registrants were matched to the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), Australian Pharmaceutical Benefits Scheme (PBS), and Australian National Death Index (NDI). ANZDATA is a registry for the purpose of collecting data on all patients who undergo kidney transplantation and/or dialysis. All RRT units in Australia contribute to ANZDATA, and very few people have opted out since its inception. Thus, the registry is essentially 100% complete. The PBS is an Australian government program that subsidizes the cost of medicines and collects data on all prescriptions dispensed in Australia under the scheme. In the current analysis, the PBS was used only in the classification of diabetes type. The NDI contains records of all registered deaths in Australia since 1980. This study used data from 1 January 2002 up to and including 31 December 2013. Linkage was performed by the Australian Institute of Health and Welfare, as previously reported (12).

In the primary analysis, ESKD was defined as initiation of RRT; date of onset of ESKD was derived from ANZDATA, and date of death was derived from the NDI. To distinguish between ESKD due to DN and total ESKD in people with diabetes, we used ANZDATA information on primary renal disease to conduct a sensitivity analysis restricted to DN as the listed cause of ESKD. Because some people may not be offered RRT and others may opt out of it, defining ESKD as initiation of RRT (treated ESKD) will underestimate the incidence of ESKD. Therefore, we also estimated the incidence of ESKD including as incident cases individuals who did not initiate RRT, but for whom ESKD was recorded as a cause of death on their death certificate (untreated ESKD). This is possible because survival for those who have ESKD and do not receive RRT is likely to be short (13). ESKD in mortality data were defined as previously described (8). Briefly, an incident case was defined when the underlying cause of death was chronic renal failure (ICD-10 codes N18.0, N18.5, N18.8, and N18.9), hypertensive renal failure (I12.0, I13.1, and I13.2), or unspecified renal failure (N19), or when chronic renal failure (N18.0 and N18.5) was listed as an associated cause of death. Additionally, if the underlying cause of death was listed as diabetes and first contributing cause of death was listed as ESKD, this was also counted as untreated ESKD.

This study was approved by the Alfred Hospital Ethics Committee (Project No.: 15/15) (Melbourne, Victoria, Australia) and the Australian Institute of Health and Welfare Ethics Committee (EO 2015/1/148) (Canberra, Australian Capital Territory, Australia).

Data Analysis

NDSS registrants were followed from 1 January 2002 or date of registration, if later, until onset of ESKD, death, or end of follow-up on 31 December 2013. Incidence rates were calculated by dividing the total number of new cases of ESKD by the total person-years of follow-up in 5-year duration of diabetes intervals. When untreated ESKD was included,

analyses were as above, but date of ESKD onset was defined as the date of death for those with untreated ESKD. Similarly, mortality rates in those without ESKD were estimated by following NDSS registrants from 1 January 2002 or date of registration, if later, until death, onset of ESKD, or end of follow-up on 31 December 2013. Incidence rates were calculated separately based on the age of diabetes onset, which was divided into six categories: 10–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years. If age of diagnosis was unavailable for a participant, age of registration on the NDSS was used. When diagnosis and registration date are both available, the dates are generally similar; however, to determine whether using the registration date instead of the diagnosis date materially affected the results, ESKD incidence rates were estimated using only those with an available diagnosis date (70% of registrants) in a sensitivity analysis.

To estimate the cumulative incidence of ESKD from the onset of diabetes, life table models were constructed that simulate the annual progression of a cohort with diabetes initially free of ESKD and followed from diabetes onset. Separate life tables were constructed for each of the aforementioned categories of age of onset of diabetes. Life tables were truncated at the end of the 5-year duration interval beyond which there were $\leq$10 incident cases of ESKD. These models were based on duration-specific and age-specific transition rates: incidence of ESKD from onset of diabetes and all-cause mortality by attained age in those without ESKD. These transition rates were estimated for each category separately. Analyses were also stratified by sex. Incidence rates were calculated by dividing the total number of new cases of ESKD by total person-years of follow-up in 1-year duration of diabetes intervals. Age-specific mortality rates for each category were estimated using a Gompertz distribution (14) and applied from the midpoint of each category of age of diabetes onset (e.g., in the 40–49 category, mortality rates were applied from age 45), with the exception of the age category 10–29 years, for which rates were applied from age 25 (the mean age of onset in this category). CIs were obtained using 500 bootstrap replicates of each age of onset category. For each bootstrap sample, incidence and mortality rates were estimated, and a life table was constructed; 95% CIs represent the 2.5th and 97.5th centile value of each estimated parameter from these bootstrapped life tables.

Statistical analyses were performed in the Stata 15 statistical software (StataCorp, College Station, TX).

RESULTS

Study Population

The characteristics of the study population are summarized in Table 1 and Supplementary Table 1. This study included 1,113,201 people with type 2 diabetes. The median age of onset was 58.1 years (interquartile range 49.0–66.5). During 7,839,075 person-years of follow-up, there were 7,592 incident cases of treated ESKD and 192,005 deaths without ESKD. There were 5,671 deaths attributed to ESKD in individuals who did not initiate RRT, and the vast majority of these cases were in the older categories of age of onset (Supplementary Table 2).

Incidence of ESKD

Table 2 reports the incidence of treated ESKD at different diabetes duration intervals by age of onset of diabetes. Incidence increased with increasing duration of diabetes. ESKD incidence rates were higher in males than in females (Supplementary Table 3). This sex difference was larger in those with diabetes onset before age 40 years compared with diabetes onset after 40 (Supplementary Table 4). Incidence rates were higher in the older categories of age of onset for the first 10–15 years of diabetes (Supplementary Table 5). However, at longer durations of diabetes the incidence of ESKD became higher in those with younger diabetes onset. At any given age, those with a longer duration of diabetes were at markedly higher risk for ESKD (Supplementary Table 6), and the magnitude of this effect of diabetes duration was substantially more than the effect of age. When untreated ESKD was included (Supplementary Table 7), those older at onset remained at a higher risk of ESKD for the first 20 years of diabetes, beyond which there were no obvious differences in incidence across different categories of age of onset.

Cumulative Incidence of ESKD

During the first 10–15 years of diabetes, younger onset of diabetes afforded some protection against ESKD for a given duration of diabetes (Table 3 and Fig. 1*A*). Over longer durations of diabetes, the cumulative incidence of treated ESKD was highest in those with younger onset of diabetes. In the categories of younger-onset diabetes, males were at a substantially higher risk of ESKD compared with females: in those with diabetes onset before 30 years of age, the risk of ESKD in males was more than twofold that of females after 40 years of diabetes (17.4% and 7.7%, respectively). Figure 1*B* and Supplementary Table 8 show the cumulative incidence of ESKD when untreated ESKD is included. The cumulative incidence was higher in older categories of age of onset of diabetes for the first 20 years of diabetes, beyond which the cumulative incidence became more similar across categories of age of onset.

Sensitivity Analyses

Incidence of treated ESKD was similar when only those who had an available date at diagnosis of diabetes were analyzed (Supplementary Table 9). The difference in incidence rates between categories of age of onset of diabetes was smaller when only those who developed ESKD due to DN are considered (Supplementary Table 10). Additionally, the proportion of ESKD due to DN decreased with increasing age of onset of diabetes (Supplementary Table 2).

CONCLUSIONS

We observed that the incidence of ESKD in type 2 diabetes increases with increasing duration of diabetes as well as age, leading to a complex association of ESKD risk with age of onset of diabetes. During the first 10–15 years of diabetes those with an older age of onset of diabetes were at higher risk for ESKD, with younger age of onset tending to higher risk at longer durations. However, because duration of diabetes is the predominant determinant of ESKD risk and those with younger-onset type 2 diabetes are more likely to survive to longer diabetes durations, younger-onset clearly confers a higher long-term risk of ESKD. The cumulative incidence of ESKD by 40 years of diabetes duration was as high as 11.8% for those with type 2 diabetes diagnosed before age 30 years and 9.3% in those diagnosed aged 30–39.

The incidence of ESKD in this study is noticeably higher than recently published estimates from Finland (5). As mentioned, this may be partly due to their inclusion of elderly individuals with diabetes, who are

Table 1—Participant number, incident treated ESKD, number of deaths in those without treated ESKD, time to ESKD, and diabetes duration at end of follow-up, by age of onset of diabetes and sex

Age of onset of diabetes	Total, *N* (%)	Number with incident ESKD	Number of deaths without ESKD	Person-years of follow-up	Time from diabetes onset to ESKD (years)[a]	Diabetes duration at end of follow-up (years)[a]
Overall	1,113,201 (100)	7,592	192,005	7,839,075	12.1 (6.9–16.7)	8.8 (4.2–14.5)
Males	610,460 (54.8)	4,842	112,802	4,138,175	12.0 (6.8–16.6)	8.2 (3.8–13.9)
Females	502,741 (45.2)	2,750	79,203	3,700,900	12.3 (7.0–16.9)	9.4 (4.5–15.2)
10–29 years	28,403 (2.6)	257	773	250,639	18.4 (13.6–25.0)	14.0 (6.7–18.5)
30–39 years	85,506 (7.7)	736	3,316	709,135	16.3 (12.0–21.2)	11.7 (5.5–17.2)
40–49 years	190,946 (17.2)	1,747	14,182	1,474,328	14.8 (10.2–18.5)	10.2 (4.7–16.3)
50–59 years	316,177 (28.4)	2,336	38,107	2,317,578	12.8 (7.8–16.9)	9.2 (4.4–15.0)
60–69 years	309,387 (27.8)	1,822	67,623	2,044,986	9.4 (5.4–13.2)	8.1 (3.8–13.6)
70–79 years	182,782 (16.4)	694	68,004	1,042,408	4.8 (2.0–8.3)	6.7 (3.3–10.9)

[a]Expressed as median (interquartile range).

far less likely to initiate RRT at the onset of ESKD. Consistent with this, when only those with diabetes onset before 60 years in their study are considered, estimates of cumulative ESKD are comparable. Similarly, results in our study are commensurate with a population-based study from Canada (15), although the Canadian study included both type 1 and 2 diabetes. Most other estimates of the incidence of ESKD from onset of type 2 diabetes are derived from Indigenous populations, in whom the risk of ESKD is considerably higher (6,7,15). The concordance of our estimates with those previously published in non-Indigenous populations supports the generalizability of our results to other high-income nations. It is therefore apparent and not unexpected that the risk of ESKD is high over long durations of type 2 diabetes.

We observed that in type 2 diabetes, as is the case for type 1 diabetes (16–18), diabetes duration is the predominant determinant of ESKD risk. Our results suggest that the incidence of ESKD may be higher in type 2 than type 1 diabetes, especially beyond 20 years' duration (16–18), which may be partly explained by poorer glycemic control in type 2 diabetes (19,20), as well as by a greater prevalence of hypertension and dyslipidemia (21), major risk factors for progression of chronic kidney disease (4). Indeed, Luk et al. (22) found the higher incidence of ESKD in type 2 diabetes was largely driven by obesity, hypertension, and dyslipidemia, and several studies have documented an increase in vascular complications in younger-onset type 2 compared with type 1 diabetes (23).

To a lesser extent than duration, age of onset of diabetes also affected ESKD risk. Incidence of ESKD was higher at a given duration in those diagnosed later in life for the first 10–15 years of diabetes. This may be partly related to the well-established increasing risk for ESKD from any cause with increasing age (8). Indeed, other causes of ESKD were more common in those older at onset of diabetes, and the effect of age on ESKD incidence is smaller when only those who developed ESKD due to DN are considered. However, it should be noted that assigning a single cause for ESKD becomes increasingly difficult with increasing age due to the frequent presence of multiple risk factors. The association with age is also consistent with observations that those diagnosed with diabetes later in life are more likely to present with nephropathy at diagnosis of diabetes (24) and would therefore in general require less of an insult to kidney function to progress to ESKD. Moreover, it is reasonable to assume an increased prevalence of hypertension in the older age groups (25), which would be expected to accelerate the progression of DN.

However, at longer durations of diabetes, those with younger onset were at a substantially higher risk for ESKD. This

Table 2—Incidence rate of treated ESKD at different diabetes duration intervals; stratified by age of onset of diabetes

Age of onset of diabetes	Duration of diabetes (years)							
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39
10–29 years	0.18 (0.10–0.33)	0.31 (0.21–0.48)	0.76 (0.58–1.01)	1.78 (1.40–2.27)	4.26 (3.18–5.70)	7.89 (5.41–11.50)	8.59 (5.54–13.31)	4.19 (2.00–8.79)
30–39 years	0.23 (0.17–0.31)	0.39 (0.32–0.49)	1.11 (0.96–1.28)	2.24 (1.95–2.57)	4.83 (4.07–5.74)	6.06 (4.71–7.81)	3.45 (2.17–5.48)	4.90 (2.90–8.27)
40–49 years	0.34 (0.29–0.40)	0.64 (0.57–0.73)	1.52 (1.39–1.66)	3.07 (2.82–3.34)	3.04 (2.64–3.49)	3.77 (3.00–4.75)	3.93 (2.77–5.59)	—
50–59 years	0.43 (0.39–0.48)	0.68 (0.62–0.74)	1.46 (1.35–1.57)	2.45 (2.26–2.66)	2.48 (2.16–2.84)	2.49 (1.85–3.35)	—	—
60–69 years	0.52 (0.47–0.57)	0.92 (0.84–0.99)	1.37 (1.26–1.49)	1.48 (1.31–1.67)	0.71 (0.49–1.03)	—	—	—
70–79 years	0.70 (0.63–0.78)	0.67 (0.59–0.76)	0.62 (0.50–0.75)	0.39 (0.23–0.66)	—	—	—	—

Rates are per 1,000 person-years (95% CI).

Table 3—Cumulative incidence of treated ESKD (%) at different diabetes durations, stratified by age of onset of diabetes and sex

Age of onset of diabetes	Duration of diabetes (years)											
	10			20			30			40		
	Males	Females	Overall	Males	Females	Overall	Males	Females	Overall	Males	Females	Overall
10–29 years	0.42 (0.23–0.65)	0.17 (0.10–0.26)	0.24 (0.16–0.32)	3.48 (2.68–4.37)	0.96 (0.75–1.21)	1.52 (1.27–1.78)	11.51 (9.24–14.11)	4.47 (2.94–6.25)	6.96 (5.59–8.39)	17.39 (13.75–20.71)	7.71 (5.26–10.53)	11.78 (9.50–13.95)
30–39 years	0.49 (0.39–0.61)	0.18 (0.13–0.23)	0.31 (0.25–0.36)	3.31 (2.94–3.65)	1.19 (0.99–1.36)	1.98 (1.79–2.17)	8.60 (7.63–9.77)	5.02 (4.01–6.15)	6.70 (5.94–7.43)	11.45 (10.04–13.10)	7.08 (5.55–8.78)	9.28 (8.10–10.46)
40–49 years	0.52 (0.46–0.58)	0.43 (0.36–0.51)	0.49 (0.43–0.54)	2.81 (2.62–3.01)	2.27 (2.07–2.48)	2.58 (2.44–2.73)	5.27 (4.80–5.82)	4.56 (4.01–5.18)	4.98 (4.58–5.34)	—	—	—
50–59 years	0.60 (0.55–0.65)	0.44 (0.39–0.50)	0.54 (0.50–0.57)	2.45 (2.31–2.59)	1.76 (1.61–1.90)	2.15 (2.05–2.25)	3.67 (3.38–3.97)	3.11 (2.76–3.48)	3.44 (3.21–3.67)	—	—	—
60–69 years	0.75 (0.69–0.81)	0.54 (0.49–0.60)	0.66 (0.62–0.70)	1.83 (1.71–1.94)	1.24 (1.14–1.34)	1.56 (1.48–1.65)	—	—	—	—	—	—
70–79 years	0.76 (0.69–0.84)	0.36 (0.31–0.41)	0.57 (0.52–0.61)	0.99 (0.90–1.08)	0.48 (0.42–0.55)	0.74 (0.68–0.80)	—	—	—	—	—	—

Data are presented as cumulative incidence (95% CI).

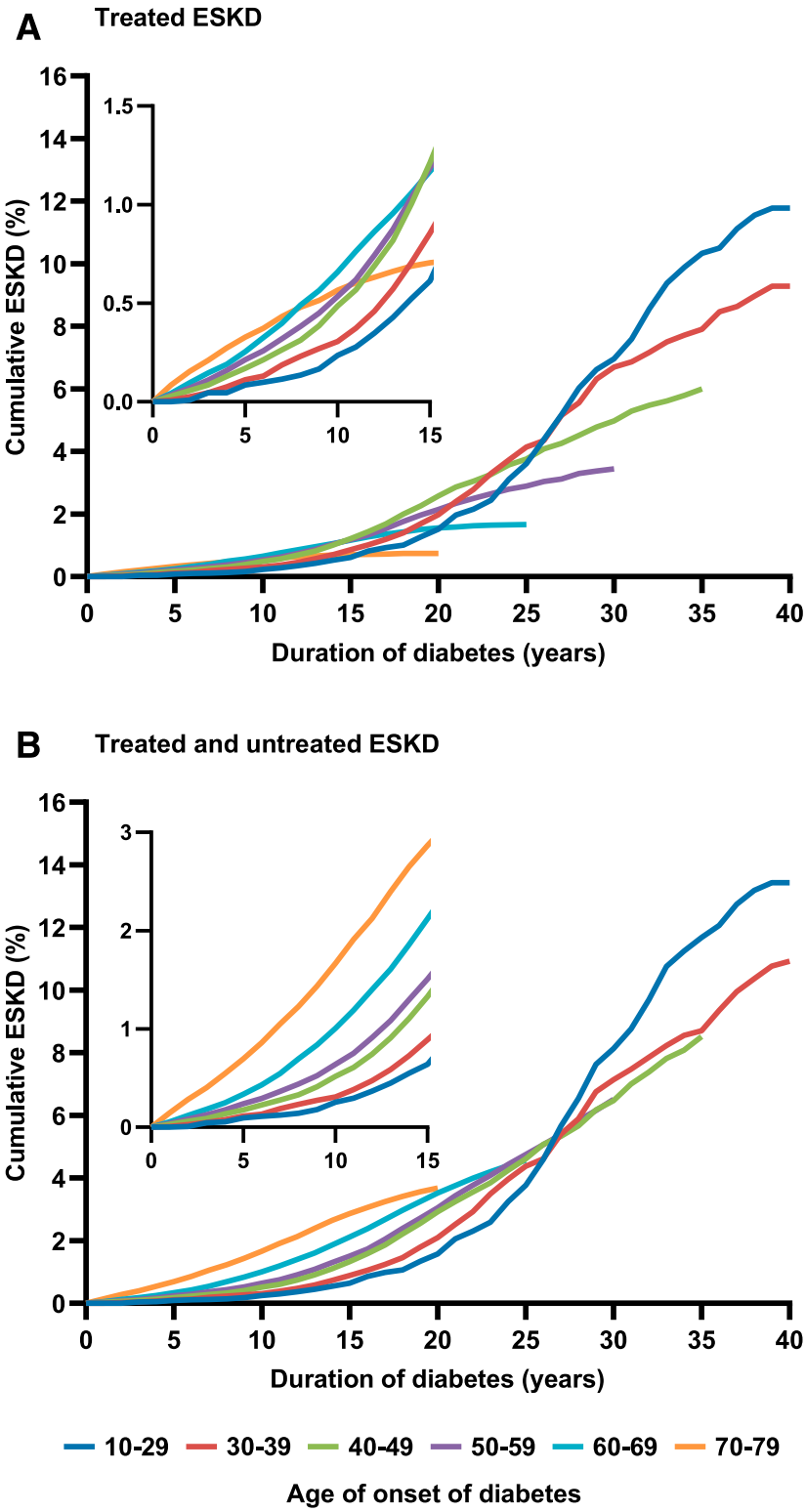

Figure 1—Cumulative incidence of ESKD by duration of type 2 diabetes stratified by age of onset of diabetes. Insets show the first 15 years of diabetes. *A*: Treated ESKD only. *B*: Treated and untreated ESKD.

observation is principally due to differences in attained age, because by definition, those with a later onset of diabetes are older at any given duration. There are two important consequences of higher attained age. First, the propensity to initiate RRT decreases dramatically with increasing age (8); thus, the incidence of ESKD as measured by initiation of RRT decreases. Indeed, when untreated ESKD is included, there was no clear excess risk among those with younger-onset diabetes, even at longer durations. Second, the competing risk of death with ESKD will be much greater with older onset of diabetes at any given duration (9). Thus, when duration of diabetes is adequately controlled for, younger-onset of diabetes carries less of a risk for ESKD during the initial years following onset, possibly because of better renal function at onset of diabetes. Nevertheless, those diagnosed with diabetes later in life are more likely to die before the onset of ESKD than those diagnosed earlier in life, and are therefore less likely to attain longer durations of diabetes. This is in large part responsible for the observation that the long-term risk of ESKD is higher in younger-onset diabetes, and we have found no evidence to suggest younger onset of diabetes leads to a greater risk of ESKD beyond the effect of attaining longer diabetes durations.

Notably, sex played an important role in risk for ESKD in younger-onset diabetes: risk of ESKD was markedly higher among males compared with females with diabetes onset before 40, whereas sex was less important for older-onset diabetes, consistent with earlier studies (3,5,15). The excess risk in males is unlikely to be explained by differences in classic risk factors for progression of DN, as evidence suggests that males with diabetes are more likely to achieve risk factor targets (26), although results are inconsistent across studies (27). As the protective effect in females is lost with increasing age of onset of diabetes, our results are compatible with a hypothesized protective effect of estrogens (28).

This nationwide, population-based study is the largest to have estimated the incidence of ESKD from onset of diabetes and is the first to estimate the risk of ESKD in a non-Indigenous population with type 2 diabetes beyond 25 years of diabetes duration. However, several important limitations of this analysis deserve consideration. While the NDSS is estimated to capture 80–90% of people with diagnosed type 2 diabetes in Australia (11), this may be biased toward those who require the services the NDSS provides, and in particular, may underrepresent those who manage diabetes with diet and exercise alone. Additionally, because this study uses administrative data, we do

not have detailed information on comorbidities associated with progression of DN and therefore could not investigate the contribution of these comorbidities to the observed association between age of onset of diabetes and ESKD risk, nor their effect on ESKD risk in general. Importantly, we do not have information on baseline kidney function and so cannot comment on the rate of decline in kidney function and whether this differs by age of onset.

While we have attempted to be as thorough in our definition of diabetes type as is practical, there will be a degree of misclassification with any definition of diabetes based on administrative data. We believe the degree of misclassification is small, because our population characteristics are similar to other known populations of type 1 and type 2 diabetes. Furthermore, we are lacking data on incident ESKD before 2002, and because incidence is likely to have fallen between NDSS inception and 2002, our results may overestimate the effect of duration on the risk of ESKD in diabetes relative to an inception cohort study. Finally, although ANZDATA and the NDI are virtually 100% complete, estimates of the true incidence of ESKD using either treated ESKD or both treated and untreated ESKD will involve some uncertainty. The incidence of treated ESKD should be extremely accurate at younger ages but will become a poorer marker of ESKD as age increases (8). This is theoretically overcome with the combination of treated and untreated ESKD; however, misclassification will still occur, because inaccuracies in the listed cause of death are not uncommon (29), although this should apply similarly across all ages.

In conclusion, this large, population-based nationwide linkage study indicates that the long-term risk of ESKD in type 2 diabetes is high, which disproportionately affects those with younger-onset type 2 diabetes because they are more likely to survive to longer diabetes durations. Our data did not, however, clearly support the hypothesis that younger-onset type 2 diabetes increases the risk of ESKD beyond its effects mediated by attainment of longer diabetes durations. This study supports the notion that delaying the onset of type 2 diabetes would be an effective method for reducing the risk of ESKD, and also adds to the body of evidence (4,30–32) highlighting the urgent requirement for development and implementation of effective interventions that attenuate the progression of DN in type 2 diabetes.

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Author Contributions. J.I.M. contributed to the design of the study and interpretation of data, performed the statistical analysis and literature search, and wrote and revised the manuscript. D.L. contributed to the design of the study, analysis and interpretation of data, and revision of the manuscript. S.P.M. contributed to acquisition and interpretation of data and revision of the manuscript. J.E.S. and D.J.M. are principal investigators and made substantial contributions to the design of the study, acquisition and interpretation of the data, and revision of the manuscript and contributed to the literature search. J.I.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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