Projecting the Incidence of Type 2 Diabetes–Related End-Stage Kidney Disease Until 2040: A Comparison Between the Effects of Diabetes Prevention and the Effects of Diabetes Treatment

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OBJECTIVE

This study sought to examine the effects of two diabetes prevention approaches and of widespread use of sodium–glucose cotransporter 2 inhibitors (SGLT2is) among people with diabetes on the future incidence of diabetes-related end-stage kidney disease (ESKD-D).

RESEARCH DESIGN AND METHODS

We developed a life table model to project the incidence of ESKD-D for type 2 diabetes in Australia until 2040. We projected incident ESKD-D under three separate scenarios: a large-scale lifestyle modification program for diabetes prevention; a population-wide sugar-sweetened beverage tax for diabetes prevention; and widespread use of SGLT2is among people with diabetes.

RESULTS

Assuming current trends, we projected that the annual incidence of ESKD-D will increase from 3.7 per 100,000 of the general population in 2014 to 5.7 by 2040. Incorporating the diabetes prevention approaches, we projected that the annual incidence of ESKD-D will be between 5.2 and 5.5 per 100,000 by 2040. When we modeled scenarios in which 50% and 70% of eligible people with diabetes were prescribed an SGLT2i, the annual incidence of ESKD-D by 2040 was projected to be 4.7 and 4.3 per 100,000, respectively. SGLT2is were projected to reduce the total number of incident ESKD-D cases between 2020 and 2040 by 12–21% compared with current trends, whereas diabetes prevention reduced cases by 1–3%.

CONCLUSIONS

It is likely that the number of people developing ESKD-D will increase over the coming decades, although widespread SGLT2i use will be effective at limiting this increase. Diabetes prevention will be crucial to prevent an ever-increasing burden of diabetes complications.

Diabetes is now the leading cause of end-stage kidney disease (ESKD) worldwide (1) and is in large part responsible for the increased demand for renal replacement

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therapy (RRT) in high-income nations (1,2). More than one-half of the people initiating RRT in Australia and New Zealand have diabetes (3). Moreover, the incidence of ESKD has increased among people with type 2 diabetes in Australia (4). This may be due to improved survival of those with type 2 diabetes (5), as well as an increase in the prevalence of youth-onset type 2 diabetes (6), both of which allow a longer time for ESKD to develop (7).

Recent estimates for the U.S. project a continued increase in the incidence of RRT, as well as a larger increase in the prevalent population receiving RRT due to improved survival among those on dialysis (8). At the time of these projections, the effectiveness of sodium–glucose cotransporter 2 inhibitors (SGLT2is) on slowing the progression of diabetic kidney disease (DKD) had not been firmly established. It is now known that these are effective pharmacotherapies for DKD (9). Because a large proportion of ESKD can be attributed to diabetes, interventions that slow the progression of DKD have the potential to reduce the overall incidence of ESKD. It is therefore of great interest to project the incidence of diabetes-related end-stage kidney disease (ESKD-D) under scenarios of widespread SGLT2i use.

Similarly, interventions that delay the onset of diabetes also have the potential to reduce ESKD-D. Indeed, prevention of diabetes is becoming increasingly relevant as the prevalence of prediabetes has increased to more than one-third of adults in many populations (10–12), and approaches to reduce the incidence of diabetes are being considered and implemented globally (13,14). However, the degree to which diabetes prevention approaches compare with diabetes treatment to reduce diabetes complications at the population level has not been well quantified. Moreover, large-scale randomized trials of sufficient power to estimate the impact of diabetes prevention on rarer diabetes complications, such as ESKD, are unlikely to ever be performed. Thus, the assessment of benefits of diabetes prevention, and comparison with diabetes treatment, on the incidence of ESKD-D may be limited to modeling and observational studies. Therefore, we have modeled the future incidence of ESKD-D among people with type 2 diabetes in Australia and estimated the impact of both a targeted and population-wide diabetes prevention approach, as well as treatment of DKD with widespread uptake of SGLT2is, on the incidence of ESKD-D.

RESEARCH DESIGN AND METHODS

Models of ESKD

The lifetime risk of ESKD among people with type 2 diabetes was predicted using multistate life table modeling. These life tables simulated the progression of a cohort with type 2 diabetes initially free of ESKD, followed from diabetes onset and truncating at age 85 years, as very few people initiate RRT beyond this age (15). Another life table model was used to project the incidence of ESKD-D, a schematic of which is provided in Fig. 1. Detailed descriptions of both models are available in the Supplementary Material. The models are based on two transition probabilities: incidence of ESKD and all-cause mortality by attained age in single year intervals. Transition probabilities in both models were estimated with Poisson regressions as a function of sex, current age, and duration of diabetes (16) (Supplementary Material).

The simulation projecting the incidence of ESKD-D began with the Australian population aged ≥10 years with type 2 diabetes as of 1 January 2014 (Fig. 1). The cohort was followed until 31 December 2040, with addition of people with incident type 2 diabetes each year. The outcome events of interest were ESKD and all-cause mortality. The incidence of type 2 diabetes from 2015–2019 was ∼2.5 per 1,000 of the population, as measured by the number of new National Diabetes Services Scheme (NDSS) registrants with type 2 diabetes per year in Australia. In the primary model, we assumed that the incidence of diabetes remained constant at 2.5 per 1,000 from 2014 to 2040. The age and sex distribution of the incident population was also assumed to remain constant. The future Australian population size was estimated from the Australian Bureau of Statistics Australian Population Projections (series B) (17).

Data Sources

The data sources comprised: the NDSS, a national diabetes register including 80–90% of people with diagnosed diabetes in Australia, linked to the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) and the Australian National Death Index (NDI) for 2002–2013 (7); Australian population estimates and projections were drawn from the Australian Bureau of Statistics (17,18); and estimates of the effects of interventions were sourced from the published literature (described below). ANZDATA is a registry that collects data on all people who undergo kidney transplantation and/or dialysis, with complete coverage of all RRT units in Australia. ESKD was defined from ANZDATA as initiation of RRT. The NDI contains records of all registered deaths

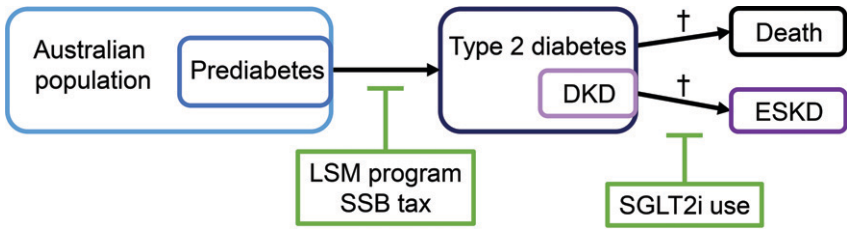

Figure 1—Schematic of the life table model used to estimate future ESKD-D. The model begins with the population with prevalent type 2 diabetes as of 1 January 2014 (middle box in the figure). The model then ages the population in yearly increments. Each year, two transition rates are applied: the incidence of ESKD and all-cause mortality in people without ESKD. Individuals developing ESKD are assumed to progress through DKD before progression to ESKD and are therefore candidates for SGLT2i use. Once ESKD or death occurs, the model no longer tracks these individuals. For individuals who do not develop ESKD or death, categorization remains prevalent type 2 diabetes. Each year, a population with incident type 2 diabetes is added to the model. Individuals developing type 2 diabetes are assumed to progress through prediabetes before progression to diabetes and are therefore candidates for an LSM program. Points at which the interventions act to reduce diabetes incidence (LSM program and SSB tax) or ESKD incidence (SGLT2i use) are indicated in green. Transitions are represented by black arrows. †Sex, age, and duration of diabetes-specific transition rates.

in Australia. We estimated ESKD incidence and all-cause mortality rates using data from those with type 2 diabetes registered on the NDSS as of 1 January 2002 and all new registrants from this date until 31 December 2013 from the NDSS-ANZDATA-NDI linkage. A table outlining the source for each model input is available in the Supplementary Material.

Interventions

Decision analysis was used to compare the impact on ESKD-D projections of three interventions versus the comparator situation (which assumed that current trends continued): a targeted lifestyle modification (LSM) program for diabetes prevention, a population-wide diabetes prevention approach via the implementation of a sugar-sweetened beverage (SSB) tax, and pharmacological treatment of DKD with SGLT2is (Table 1 and Fig. 1). We assumed that reductions in diabetes and ESKD incidence from the interventions were maintained throughout the period simulated. For each intervention strategy, we modeled the impact based on a set of likely effects as well as best-case effects.

Targeted Intervention Approach: LSM Program

A reduction in the incidence of diabetes following implementation of an LSM program is quickly apparent, sustained, and effective in real-world settings (19,20). A recent systematic review and meta-analysis of real-world diabetes prevention programs was identified as the best available evidence for estimation of the effect of a wide-scale LSM program on diabetes incidence in high-risk groups (people with prediabetes or diabetes risk factors) (19). The incidence of diabetes in controlled studies of these programs was reduced by 29% (relative risk 0.71 [95% CI 0.58–0.88]). Virtually all individuals who develop type 2 diabetes will first pass through prediabetes and thus be eligible for such a program; the incidence rate reduction was therefore applied to adults in the Australian population at the transition between prediabetes and type 2 diabetes (Fig. 1). The generalizability to adolescents with prediabetes is uncertain. We therefore applied this 29% incidence reduction to adults only (Table 1). We assumed an uptake of 35% into the program under the likely scenario; this assumes that 60% of high-risk individuals agree to be screened and 60% of those found to be at high risk agree to participate (21). Under the best-case scenario, uptake into the program was assumed to increase to 50%. We assumed that the LSM program was implemented in 2020 and became effective within 1 year.

Population-Wide Approach: SSB Tax

We selected the SSB tax as our population-wide diabetes prevention approach because there has been success in reducing SSB intake in countries that have already implemented such a tax (13) and because SSBs are linked to diabetes incidence (22) and are an entirely unnecessary part of a healthy diet. Direct evidence of the impact of an SSB tax on diabetes incidence is not available. The best available evidence for estimating the impact of an SSB tax on diabetes incidence was from a modeling study from the U.K. (23). This study was selected because SSB consumption is very similar in Australia and the U.K. (24). For the likely scenario, we modeled the diabetes incidence reductions when an SSB tax that results in a 9–20% increase in price of SSBs (depending on the sugar content of the SSB) is passed on to consumers from 2020 onward. Under the best-case scenario, we modeled diabetes incidence reductions when this tax is doubled. Increases in price are assumed to result in a diabetes incidence reduction through reduction in consumption of SSBs, which assumes that the relationship between SSB consumption and diabetes incidence is causal. To estimate the proportional reduction in diabetes incidence for each age-group, we compared the number of diabetes cases prevented in the modeling study with the actual incidence of diabetes in the U.K. used in that study (Supplementary Material). We estimated that in the likely scenario this leads to diabetes incidence reductions of 7.9%, 6.8%, and 2.7% in males age <18, 19–64, and 65–84 years, respectively. The corresponding incidence reductions for females were estimated to be 5.4%, 4.7%, and 2.5%. In the best-case scenario the corresponding incidence reductions were 16.8%, 14.4%, and 5.8% in males and 11.5%, 10.0%, and 5.4% in females, respectively (Table 1). The reductions are greater for younger individuals, as they consume a greater volume of SSBs.

Pharmacologic Treatment of DKD: SGLT2i Use

The effect of SGLT2is on the incidence of ESKD was estimated from a meta-

Table 1—Summary of modeled interventions

Intervention	Likely scenario	Best-case scenario
LSM program	A 29% reduction in diabetes incidence for 35% of high-risk adults from 2020	A 29% reduction in diabetes incidence for 50% of high-risk adults from 2020
SSB tax	An SSB tax introduced in 2020 leads to a reduction in diabetes incidence as follows: age <18 years, boys 7.9% and girls 5.4%; age 19–64 years, men 6.8% and women 4.7%; and ≥65 years, men 2.7% and women 2.5%	An SSB tax introduced in 2020 leads to a reduction in diabetes incidence as follows: age <18 years, boys 16.8% and girls 11.5%; age 19–64 years, men 14.4% and women 10.0%; age ≥65 years, men 5.8% and women 5.4%
SGLT2i use	A 35% reduction in ESKD among users of SGLT2is with DKD. Use increases to 50% among people with an eGFR >45 mL/min/1.73 m^2 by 2023	A 35% reduction in ESKD among users of SGLT2is with DKD. Use increases to 70% among people with an eGFR >30 mL/min/1.73 m^2 by 2024
Combination	Above three scenarios	Above three scenarios

Abbreviations: LSM — Lifestyle modification; SSB — Sugar Sweetened Beverage; SGLT2i — Sodium-glucose co-transporter 2 inhibitor.

analysis of phase III clinical trials (25); SGLT2is were found to reduce ESKD by 35% (relative risk 0.65; 95% CI 0.53–0.81). In Australia, SGLT2is are currently not recommended for individuals with an estimated glomerular filtration rate (eGFR) $<$45 mL/min/1.73 m^2. Therefore, under the likely scenario, we modeled SGLT2i uptake increasing to 50% among people with albuminuria or reduced eGFR (45–60 mL/min/1.73 m^2) by 2023 (Table 1). We modeled the increase in uptake as biphasic, with an acceleration following the publication of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) (9), published in 2019. This trial also demonstrated for the first time reduction in the incidence of ESKD with SGLT2i use in individuals with an eGFR 30–45 mL/min/1.73 m^2. Therefore, for the best-case scenario we modeled SGLT2i use increasing to 70% among people with an eGFR 30–60 mL/min/1.73 m^2 by 2024. We assumed that the vast majority of people with diabetes would pass through an earlier stage of chronic kidney disease (CKD) (albuminuria and/or reduced eGFR) before progressing to ESKD and therefore be candidates for SGLT2i use; thus, the incidence rate reduction was applied to the whole population at the transition between type 2 diabetes and ESKD (Fig. 1). Because SGLT2is were initially recommended for use in individuals with an eGFR $>$45 mL/min/1.73 m^2, and the majority of individuals who initiate RRT will have an eGFR $<$30 mL/min/1.73 m^2 in the year preceding RRT (26), there will be a delay between SGLT2i use and reduction in ESKD incidence. Therefore, a number of assumptions about eGFR trajectories prior to initiation of RRT were made, as well as assumptions about how SGLT2i use would increase over time (Supplementary Material). Because our estimation of ESKD incidence rates used data up until the end of 2013, and SGLT2is were not widely available in Australia until December 2013, there is not likely to be an effect of SGLT2 is on our baseline estimates of ESKD incidence.

Combination of Interventions

We also modeled a combined intervention approach, sequentially applying the LSM program, SSB tax, and SGLT2i use risk reductions. Likely and best-case scenarios were modeled together (Table 1).

Sensitivity Analyses

We conducted sensitivity analyses in which the incidence of type 2 diabetes was assumed to increase or decrease at 4% per year, starting at 2.5 per 1000 population, from 2020. Four percent was selected as maximal upper and lower bounds from a recent systematic review of diabetes incidence (27). Similarly, as mortality rates have continued to decline in diabetes, we performed a sensitivity analysis with mortality decreasing at 2.2% and 1.3% per year from 2014 for males and females, respectively (5).

We also undertook probabilistic sensitivity analyses using 1,000 Monte Carlo simulations based on the uncertainty in the model parameters. In each iteration, model parameters were drawn randomly from a specified distribution. Point estimates are the median value from these simulations, and uncertainty intervals (UIs) represent the 2.5th and 97.5th centiles. The sources of uncertainty in the baseline scenario included the incidence of type 2 diabetes, incidence of ESKD, all-cause mortality rate, and future population size (Supplementary Material). Uncertainty in the effectiveness of interventions was also simulated. The distributions reflecting uncertainty in these parameters were drawn from published estimates where available. Where the explicit distributions were not available from published data (SSB tax effect estimates by age, future population size, and incidence of diabetes), we assumed the error was normally distributed (Supplementary Material).

Analyses were performed with R software, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata, version 15.1 (College Station, TX).

This study was approved by the Alfred Hospital Ethics Committee (Melbourne, Australia; project no. 15/15) and the Australian Institute of Health and Welfare Ethics Committee (Canberra, Australia; EO 2015/1/148).

RESULTS

Lifetime Risk of ESKD

The characteristics of the population used for estimation of the lifetime risk of ESKD (the NDSS-ANZDATA-NDI linkage) are available in Supplementary Table 1. Between 2002 and 2013, there were 7,675 incident cases of ESKD among 1,174,563 people with type 2 diabetes during 8,071,623 person-years of follow-up. The remaining lifetime risk of ESKD from diagnosis with type 2 diabetes decreased sharply with increasing age of diagnosis of diabetes (Supplementary Table 2). The lifetime risk of ESKD was 29.5% (95% UI 23.1–37.9), 9.0% (8.0–10.2), and 2.5% (2.3–2.8) for men diagnosed with type 2 diabetes at 20, 40, and 60 years of age, respectively. Similarly, for women, the corresponding lifetime risk estimates were 17.7% (11.6–25.3), 8.4% (7.1–10.0), and 1.8% (1.6–2.1).

Interventions to Reduce the Future Incidence of Diabetes

Assuming the current trajectory of diabetes incidence, a total of 1,456,859 (95% UI 1,136,923–1,834,415) people were projected to develop type 2 diabetes between 2020 and 2040 (Supplementary Table 3), corresponding to an increase in the prevalence of diagnosed diabetes among people aged 10–84 years from 4.6 to 4.9% (Fig. 2). An LSM program was projected to reduce the number of incident diabetes cases by 143,927 (95% UI 55,395–232,234) (a 9.9% reduction in cases), compared with the current trajectory in the likely scenario, and by 205,803 (79,161–332,225) (a 14.1% reduction) in the best-case scenario. The corresponding reductions with an SSB tax were 68,882 (16,430–119,043) (4.7%) and 146,686 (33,393–251,947) (10.1%) in the likely and best-case scenarios, respectively. In combination, these interventions were projected to reduce the number of incident diabetes cases by 204,824 (106,004–312,035) (14.1%) and 328,911 (175,026–498,479) (22.6%) in the likely and best-case scenarios, corresponding to a diabetes prevalence among people aged 10–84 years in 2040 of 4.4% and 4.0%, respectively.

Reduction in ESKD

At currently observed ESKD and diabetes incidence rates, 33,495 people with type 2 diabetes (95% UI 28,481–39,743) were projected to develop ESKD between

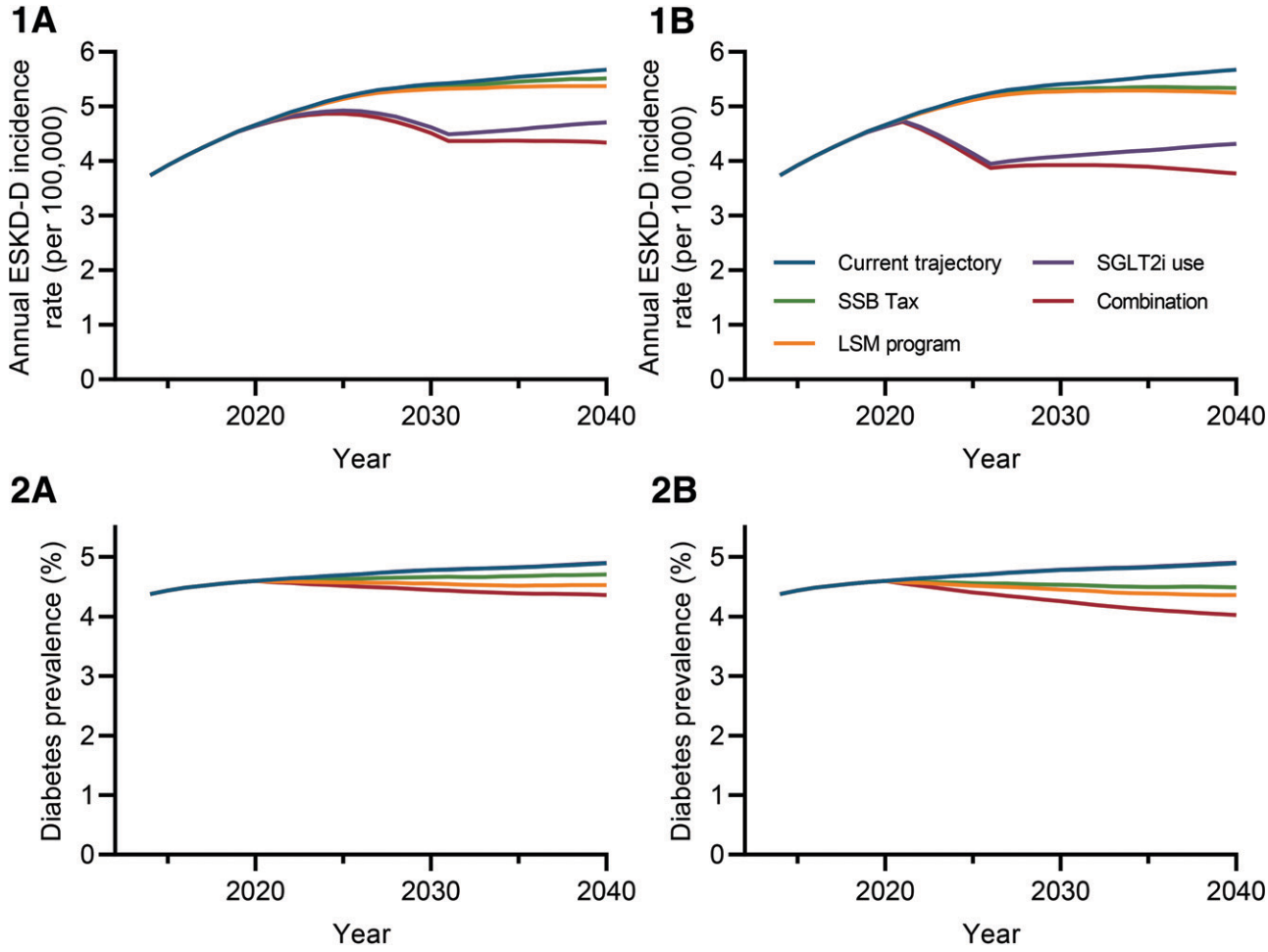

Figure 2—Incidence trends in ESKD-D per 100,000 of the general population (1) and diabetes prevalence among adults aged 10–84 years (2) in Australia by current trajectory and different interventions. *A*: Likely scenarios. *B*: Best-case scenarios.

2020 and 2040 (Table 2). This corresponded to 1,906 incident cases per year by 2040, up from 878 per year in 2014—a 117% increase (Supplementary Fig. 1). This exceeded expansion of the general population. The annual incidence of ESKD-D was projected to increase from 3.7 per 100,000 of the general population in 2014 to 5.7 per 100,000 in 2040 (Fig. 2). SGLT2i uptake reduced the number of people developing ESKD by 4,064 (95% UI 2,171–5,789) (a 12.1% reduction in cases) between 2020 and 2040 compared with the current trajectory in the likely scenario and by 6,913 (3,709–9,790) (20.6%) in the best-case scenario. Corresponding reductions for the LSM program were 741 (295–1,206) (2.2%) in the likely scenario and 1,059 (422–1,725) (3.2%) in the best-case scenario. An SSB tax was projected to reduce incident ESKD-D by 383 cases (98–661) (1.1%) in the likely scenario and 816 cases (194–1,400) (2.4%) in the best-case scenario.

The effects of SGLT2is on reduction of ESKD-D would be rapidly apparent following implementation, especially in the best-case scenario, whereas diabetes prevention approaches took longer before any meaningful reduction in ESKD-D was observed (Fig. 2). However, once SGLT2i uptake plateaued, increases in diabetes prevalence caused the incidence of ESKD-D to resume increasing (Fig. 2).

Both LSM and an SSB tax were projected to be increasingly effective for younger individuals at reducing ESKD-D, although the absolute reductions were still greatest for older individuals (Table 2). The effects of SGLT2is were consistent across age-groups. Both diabetes prevention approaches were relatively more effective in males and females, whereas effects of SGLT2is were similar by sex.

Sensitivity Analyses

The relative effectiveness of diabetes prevention was higher when diabetes incidence was assumed to increase and lower when diabetes incidence was assumed to decrease, but SGLT2is remained the most effective intervention (data not shown). When mortality rates were assumed to continue decreasing, the incidence of ESKD-D was projected to increase to 6.1 per 100,000 of the general population by 2040, with the increase relative to the primary analysis coming predominantly from older age-groups, but the relative effects of the interventions remained unchanged (data not shown).

CONCLUSIONS

We have found that the number of people with type 2 diabetes initiating RRT in Australia is expected to continue increasing, concomitant with expansion of

Table 2—Number of incident ESKD cases among people with type 2 diabetes expected and reduced by interventions between 2020 and 2040 in various modeled scenarios

	Number of cases expected, current trajectory	Number of cases reduced (%)							
		LSM program		SSB tax		SGLT2i use		Combination of all interventions	
		Likely	Best-case	Likely	Best-case	Likely	Best case	Likely	Best case
Men									
Age 18–39 years	189	8 (4.4)	12 (6.2)	6 (3.2)	13 (6.9)	23 (12.0)	39 (20.5)	34 (18.2)	56 (29.8)
Age 40–54 years	2,199	75 (3.4)	108 (4.9)	51 (2.3)	109 (5.0)	266 (12.1)	453 (20.6)	365 (16.6)	602 (27.4)
Age 55–69 years	8,498	214 (2.5)	306 (3.6)	140 (1.7)	299 (3.5)	1,029 (12.1)	1,751 (20.6)	1,307 (15.4)	2,172 (25.6)
Age 70–84 years	9,867	206 (2.1)	294 (3.0)	87 (0.9)	185 (1.9)	1,191 (12.1)	2,032 (20.6)	1,422 (14.4)	2,374 (24.1)
Total; 95% UI	20,754; 17,827–24,363	503 (2.4); 201–820	720 (3.5); 287–1,172	284 (1.4); 72–492	606 (2.9); 140–1,035	2,508 (12.1); 1,356–3,541	4,268 (20.6); 2,311–6,016	3,130 (15.1); 1,794–4,370	5,207 (25.1); 2,935–7,247
Women									
Age 18–39 years	68	4 (5.2)	5 (7.5)	2 (2.7)	4 (5.7)	8 (12.1)	14 (20.7)	13 (18.6)	21 (30.1)
Age 40–54 years	945	30 (3.1)	42 (4.5)	14 (1.5)	30 (3.2)	106 (11.2)	186 (19.7)	142 (15.0)	238 (25.2)
Age 55–69 years	5,615	110 (2.0)	157 (2.8)	50 (0.9)	107 (1.9)	671 (12.0)	1,156 (20.6)	804 (14.3)	1,348 (24.0)
Age 70–84 years	6,134	95 (1.6)	136 (2.2)	32 (0.5)	68 (1.1)	774 (12.6)	1,289 (21.0)	877 (14.3)	1,441 (23.5)
Total; 95% UI	12,751; 10,643–15,666	238 (1.9); 93–390	340 (2.7); 133–557	98 (0.8); 25–172	209 (1.6); 53–364	1,559 (12.2); 824–2,256	2,647 (20.8); 1,403–3,828	1,834 (14.4); 1,015–2,608	3,045 (23.9); 1,701–4,315
Overall: total; 95% UI	33,495; 28,481–39,743	741 (2.2); 295–1,206	1059 (3.2); 422–1725	383 (1.1); 98–661	816 (2.4); 194–1,400	4,064 (12.1); 2,171–5,789	6,913 (20.6); 3,709–9,790	4,952 (14.8); 2,827–6,968	8,232 (24.6); 4,633–11,565

Data are presented as number of expected cases for current trajectory and number of cases reduced (%) for each scenario.

the Australian population and therefore representative of an absolute increase in the number of people with type 2 diabetes. However, the increase in ESKD-D exceeded the increase in type 2 diabetes: with a 59% increase in the number of people with type 2 diabetes from 2014–2040, the annual number of people with diabetes initiating ESKD each year is projected to increase 117% over the same time period. Indeed, the incidence of ESKD-D was projected to increase from 3.7 to 5.7 per 100,000 of the general population from 2014 to 2040. This is largely due to people with prevalent diabetes in 2014 surviving longer, exposing them to greater risk of ESKD (7). The fact that the majority of ESKD-D is attributable to people diagnosed with diabetes several years prior is largely why noticeable reductions in ESKD-D incidence with diabetes prevention approaches took several years to manifest, despite immediate impacts on diabetes incidence.

SGLT2i use was the most effective single intervention, especially in the short-term, reducing the number of incident cases of ESKD-D by 12–21% between 2020 and 2040, compared with 1–3% for diabetes prevention approaches. Nevertheless, even in the best-case scenario where SGLT2i use increases to 70%, the incidence of ESKD-D was still projected to be increasing past 4.3 per 100,000 of the general population by 2040. Indeed, if the prevalence of diabetes keeps increasing, this will offset progress in reducing ESKD-D incidence relative to the general population, despite reductions in ESKD incidence among those with type 2 diabetes. Conversely, diabetes prevention continues to reduce ESKD-D over time. Nevertheless, it is concerning that even if implemented now, it would take many years for diabetes prevention approaches to affect ESKD-D.

These results highlight the urgent requirement to address the epidemics of diabetes and associated CKD. Continued improvements to treatment of CKD, as well as increased effectiveness of diabetes prevention, will need to be achieved if there is any hope of preventing the ever-rising RRT demand. Moreover, the difference between diabetes prevention and treatment on the incidence of ESKD-D that we observed is likely generalizable to both other diabetes

treatments and complications, illustrating that unless the incidence of diabetes is reduced, reductions to the incidence of diabetes complications through advances in treatment will be offset by increasing diabetes prevalence.

Notably, a reduction in ESKD-D has been achieved in some high-risk populations, coinciding with widespread implementation of a diabetes surveillance and management program (28). Whether similar benefits could be achieved in lower-risk populations is unknown, but improvements are certainly possible (29), and opportunities to improve care for DKD in lower-risk populations exist (30,31).

Fortunately, there is already evidence to suggest prompt SGLT2i uptake (32), so ESKD incidence rates are unlikely to continue as they were prior to SGLT2i use, especially since use of SGLT2is is associated with a reduction in ESKD in real-world studies similar to that in clinical trials (33). Notably, when the eGFR threshold for initiation of SGLT2is was lowered from 45 to 30 mL/min/1.73 m^2, the reduction in ESKD-D was more rapid, providing support for broadening the indications for SGLT2is to people with more advanced DKD.

It is important to note the distinction between the impact of diabetes prevention on the population-level risk of ESKD and the impact to the individual who has, or is at risk for, type 2 diabetes. For example, if a man who was going to develop type 2 diabetes at age 20 years is able to delay the onset of type 2 diabetes through weight loss and lifestyle change by 10 years, he would reduce his remaining lifetime risk of ESKD from approximately one in three to one in five. Moreover, in highly motivated individuals it is conceivable that diabetes may never develop if LSM persists indefinitely, and thus lifetime ESKD risk is markedly reduced. Therefore, encouragement of weight loss and LSM is still highly warranted, regardless of availability of official LSM programs.

Our results should be interpreted in light of several limitations. Most importantly, these projections only show how the incidence of ESKD-D would change if the underlying assumptions of the model were maintained for the period projected. While we estimated uncertainty in projections, the greatest uncertainty is in regard to changes that we have not modeled. For example, glucagon-like peptide 1 receptor agonists not only have some renoprotective effects (34), they are also extremely effective at preventing new-onset type 2 diabetes in clinical trials (35). Additionally, diabetes care continues to improve (36), and new therapies for DKD are likely to be released by 2040 (37). Moreover, we have assumed no change in the propensity to offer RRT to people with ESKD and have not taken into account the rising prevalence of nonalbuminuric CKD (38), in which there is a reduced risk for ESKD (39). There could therefore be meaningful changes to the underlying incidence of diabetes, ESKD, and death that we have assumed in our model, which in the primary analysis were assumed to remain static. Importantly, a decrease in the underlying incidence of ESKD among people with diabetes would not modify the relative effectiveness of the interventions, and if mortality continues to decrease, the incidence of ESKD-D was projected to increase. Furthermore, while we drew estimates of the effects of an LSM program and SGLT2is from meta-analyses, the effects of an SSB tax were drawn from a single modeling study. We have also assumed that the effects of interventions persist long-term. While it is too early to determine whether effects of SGLT2is diminish over time, it is known that the magnitude of diabetes reduction from LSM programs does diminish over time (20), whereas reduction in consumption of SSBs following price increases may even accelerate over time (13). Our results should therefore be primarily interpreted as a comparison of the relative effectiveness of different interventions on ESKD-D and not as robust predictions of future ESKD-D.

As the NDSS is poorly representative of Indigenous Australians, we were unable to take into account the contribution of this group to ESKD incidence; similarly, we were missing the 10–20% of Australians with diagnosed diabetes who are not registered on the NDSS, as well as those who remain undiagnosed. We have also excluded type 1 diabetes, which currently comprises ~10% of incident ESKD-D (3), and although the cumulative incidence of ESKD has been decreasing in this population (40), as with type 2 diabetes, increased survival may increase the overall incidence of ESKD in type 1 diabetes. Thus, with these exclusions, we will have underestimated the true incidence of ESKD-D.

Notably, SGLT2is have recently been shown to have similar renoprotective effects in people with and without type 2 diabetes (41); thus, the impact of SGLT2is on overall ESKD incidence may be more substantial than projected. Furthermore, it is also possible that SGLT2is could prevent ESKD in people with type 1 diabetes. However, clinical trials addressing CKD in this population are lacking.

We did not specifically account for other diabetes complications. We also did not account for socioeconomic status, which may modulate the effect of interventions. For example, the SSB tax introduced in Mexico led to the largest fall in consumption among those of low socioeconomic status (13); thus, a greater reduction in diabetes incidence for these individuals would be expected. Similarly, while these results are likely generalizable to other high-income countries with similar diabetes and ESKD incidence rates, the generalizability to lower- and middle-income countries is uncertain. Indeed, the high cost of SGLT2is may be a barrier to widespread use in countries without universal health care.

Finally, beyond their effects on ESKD-D, there are several other important considerations for each intervention that we have not considered, for example, the cost-effectiveness, practicality, and limitations of the interventions. While SGLT2is and LSM programs may be cost-effective (42,43), an SSB tax would actually generate revenue, which could be used for other health-promoting activities. In terms of feasibility, the high prevalence of prediabetes in some populations and current screening inadequacies, as well as very low engagement and retention in real-world LSM programs, has led to criticism of reliance on these programs for large-scale diabetes prevention (14,44). Population-wide approaches for diabetes prevention are therefore often viewed as more viable strategies for curbing the diabetes epidemic. Nevertheless, SSB taxes can be regressive and will require political will to implement. It is also worth noting that SGLT2is are not without side

effects, some of which may limit widespread use.

In conclusion, our results suggest that it is likely the demand for RRT from people with type 2 diabetes will increase over the coming decades. Widespread SGLT2i use is likely to be the most effective single intervention for limiting this rise. However, in the longer term, implementation and improvement of interventions that prevent diabetes are likely to be necessary to prevent an ever-increasing demand for RRT.

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