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Editor's Choice

Estimated morbidity and mortality in adolescents and young adults diagnosed with Type 2 diabetes mellitus

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Abstract

Aims To estimate remaining life expectancy (RLE), quality-adjusted life expectancy (QALE), causes of death and lifetime cumulative incidence of microvascular/macrovascular complications of diabetes for youths diagnosed with Type 2 diabetes.

Methods A Markov-like computer model simulated the life course for a hypothetical cohort of adolescents/young adults in the USA, aged 15–24 years, newly diagnosed with Type 2 diabetes following either conventional or intensive treatment based on the UK Prospective Diabetes Study. Outcomes included RLE, discounted QALE in quality-adjusted life years (QALYs), cumulative incidence of microvascular/macrovascular complications and causes of death.

Results Compared with a mean RLE of 58.6 years for a 20-year-old in the USA without diabetes, conventional treatment produced an average RLE of 43.09 years and 22.44 discounted QALYs. Intensive treatment afforded an incremental 0.98 years and 0.44 discounted QALYs. Intensive treatment led to lower lifetime cumulative incidence of all microvascular complications and lower mortality from microvascular complications (e.g. end-stage renal disease (ESRD) death 19.4% vs. 25.2%). Approximately 5% with both treatments had ESRD within 25 years. Lifetime cumulative incidence of coronary heart disease (CHD) increased with longer RLE and greater severity of CHD risk factors. Incorporating disutility (loss in health-related quality of life) of intensive treatment resulted in net loss of QALYs.

Conclusions Adolescents/young adults with Type 2 diabetes lose approximately 15 years from average RLE and may experience severe, chronic complications of Type 2 diabetes by their 40s. The net clinical benefit of intensive treatment may be sensitive to preferences for treatment. A comprehensive management plan that includes early and aggressive control of cardiovascular risk factors is likely needed to reduce lifetime risk of CHD.

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Keywords adolescence, microvascular disease, modelling, mortality, Type 2 diabetes

Abbreviations QALY- Quality-adjusted life year; QALE- Quality-adjusted life expectancy

Introduction

Type 2 diabetes in youth has drawn increasing attention as the increase in childhood obesity contributes to its rising incidence and prevalence [1–5]. Longitudinal data from Pima Indians suggest that longer duration of diabetes among those with youth-onset diabetes contributes to higher incidence of end-stage renal disease (ESRD) and morbidity and mortality in middle age [6]. However, there are little data regarding the natural history of Type 2 diabetes diagnosed among youth in the general US population.

Understanding the natural history of Type 2 diabetes in youth has implications for clinical management, research and policy. Epidemiological studies suggest that youths with Type 2 diabetes are at risk for microvascular and macrovascular

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complications [7]. However, it may take decades to understand these risks. Several models (e.g. [8–11]) have projected outcomes for diabetes in adults, but these projections cannot be applied to adolescents/young adults, whose risks for diabetes complications and preferences for health states and treatment may differ. Narayan *et al.* [12] have previously modelled the lifetime risk of diabetes for individuals born in 2000, and life years and quality-adjusted life years (QALYs) lost because of diabetes by age at diagnosis. However, this model does not address the individual contributions of microvascular or macrovascular complications to these outcomes. We have, therefore, adapted an adult model of Type 2 diabetes progression, the CDC-RTI Diabetes Cost-Effectiveness Model [10,13] ('RTI Model'), for an adolescent/young adult US cohort ('Youth Model') to describe the morbidity, mortality, and health-related quality of life experienced by youths diagnosed with Type 2 diabetes following either 'conventional' or 'intensive' glycaemic control introduced at diagnosis.

Methods

Markov models, or state-transition models, can address complex diseases such as diabetes because they can capture the course of benefits and risks of treatment over time. These models represent mutually exclusive health states, and a cohort of people are initially distributed among these health states mirroring their prevalence in similar real-world populations [14]. With each cycle, people have a probability of remaining in their current state or transitioning to a different one [14]. Our variant of this modelling incorporates interdependencies among diabetes complications and time-varying transition probabilities to examine the natural history of Type 2 diabetes in youth.

Model structure

The RTI Model is a Markov-like model that includes cohorts in 10-year age groups, between 25 and 94 years [10,13]. In our Youth Model, we adapted the RTI Model to include an adolescent/young adult cohort, aged 15–24 years, at diabetes diagnosis. The RTI Model includes transition probabilities and intervention effects based on the outcomes of Type 2 diabetes patients in the UK Prospective Diabetes Study (UKPDS) [15]. In brief, the UKPDS was a randomized, controlled trial for newly diagnosed Type 2 diabetes patients between 25 and 65 years of age with a fasting glucose > 6 mmol/l (108 mg/dl) recruited in the UK between 1977 and 1991 [15]. The UKPDS trial compared 'intensive' treatment with either insulin or a sulphonylurea with 'conventional' treatment with diet. Details of the RTI Model and its use of UKPDS data have been previously described [10,13]. Technical Report S1 (see Supporting Information) provides additional information about the Youth Model adaptation of the RTI Model.

In the Youth Model simulation, patients diagnosed with diabetes progress simultaneously through disease paths representing nephropathy, neuropathy, retinopathy, coronary heart disease (CHD) and stroke. Health-state transitions may vary according to clinical and demographic characteristics: time since diagnosis, time between onset and diagnosis, age, sex, race/ethnicity, glycaemic control, smoking, hypertension and hypercholesterolemia. Patients can die from lower extremity amputation, ESRD, CHD, stroke, or non-diabetes related causes. Mortality rates from ESRD and other causes are a function of age, sex, and race/ethnicity.

Sources for adolescent/young adult-specific estimates

To create the Youth Model with a 15- to 24-year-old cohort, all RTI Model parameters were reviewed and replaced with age-specific estimates, when appropriate and available. Key updated assumptions included hazard rates for health-state transitions, initial prevalence of complications at diagnosis, glycaemic control parameters, and utilities (Table 1).

To inform parameters for the Youth Model, a systematic literature review was conducted in March 2007 to identify studies examining glycaemic control and microvascular and macrovascular outcomes in adolescents/young adults with Type 2 diabetes diagnosed before age 25 years. A total of 817 relevant studies were identified of which 110 articles and dissertations/theses and 12 abstracts were reviewed. Targeted searches of the published literature through December 2009 were performed to identify relevant new information. Data from the SEARCH for Diabetes in Youth study was used extensively for the assumptions in the Youth Model [1–5,16–20]. An expert panel convened in March 2008 informed key estimates in the Youth Model for which there remained ongoing uncertainty and limited or no available data.

Cohort description and health-state transitions

Based on the structure of the RTI Model, the 15- to 24-year-old newly diagnosed Type 2 diabetes cohort had to be subdivided by sex, race/ethnicity, hypertension, cholesterol and smoking status. These groupings were based upon the 2006 US Census [21] and published data [1–5,19,20] (see Supporting Information, Technical Report S1, eTable 30). Incidence of Type 2 diabetes was based on the SEARCH study [1–5]. The cohort based on these data included approximately 3500 adolescents/young adults with newly diagnosed Type 2 diabetes. Available data suggest that the pace of β-cell failure in youths with Type 2 diabetes is faster than that observed in adults [22]. For the Youth Model, we assumed onset of diabetes was less than 1 year from diagnosis, and therefore, at diagnosis for the purpose of modelling. Very low rates of screening-detected diabetes in youths [23,24] support this assumption. Weiss *et al.* [25] also showed that 24.2% of obese youths with impaired glucose tolerance screened with an oral glucose tolerance test at 18- to 24-month intervals progressed to Type 2 diabetes over an average follow up of 20.4 ± 10.3 months. Therefore, 0–2 years from onset to diagnosis was used as the range for

Table 1 Youth model parameters and ranges for sensitivity analyses

Parameter	Intensive glycaemic control	Conventional glycaemic control	Beta exponent [10]	Ranges for sensitivity analysis
Glycaemic control[a]				
Initial HbA_{1c} at onset, % [37]	7.4 (57 mmol/mol)	7.4 (57 mmol/mol)	N/A	6.8 [10]–10.9 [43] (51–96 mmol/mol)
Annual rate of HbA_{1c} change before treatment, % [18]	0.24	0.24	N/A	N/A
Years between onset and diagnosis*	0	0	N/A	0–2 [25]
One-time initial treatment effect, HbA_{1c} % [10]	−2.9	−2.0	N/A	N/A
Annual rate of HbA_{1c} change after treatment, % [18]	0.24	0.24	N/A	0.18–0.72 [18] 0.20 [10] Intensive
Minimum HbA_{1c} with/without treatment, % [10]	6.0 (42 mmol/mol)	6.0 (42 mmol/mol)	N/A	N/A
Maximum HbA_{1c} with treatment, % [10]	9.0 (75 mmol/mol)	11.0 (97 mmol/mol)	N/A	Conventional 13† (119 mmol/mol)
Prevalence of complications at diagnosis[b], % of cohort				
Microalbuminuria [16]§	16	16	N/A	0–40§
Retinopathy [10]§	0	0	N/A	0–10§
Peripheral neuropathy [10]§	0	0	N/A	0–10§
Coronary heart disease [10]	0	0	N/A	N/A
Stroke [10]	0	0	N/A	N/A
Adolescent utilities [27]‖[c]				
End-stage renal disease	0.511	0.511	N/A	0.005–0.999 [27] Adult 0.61 [10], 0.35 [34]
Lower extremity amputation	0.557	0.557	N/A	0.001–0.99 [27] Adult 0.8 [10], 0.55 [34]
Blindness	0.547	0.547	N/A	0.02–1.0 [27] Adult 0.69 [10], 0.38 [34]
Angina/coronary heart disease	0.587	0.587	N/A	0.03–0.995 [27] Adult angina 0.947 [10], 0.64 [34] Adult coronary heart disease 0.88 [10]
Stroke	0.587	0.587	N/A	0.03–0.995 [27] Adult 0.5 [10], 0.31 [34]
Intensive glycaemic control (mean difference vs. diet)¶	−0.063	N/A	N/A	Adult −0.21 [34]
Hazard rates (HR)[d]				
Normal to microalbuminuria	Calculated#	0.1455	4.28	Faster nephropathy progression, HR = 0.42; slower progression to microalbuminuria, HR = 0.042
Normal to retinopathy requiring photocoagulation	Calculated#	0.006	2.74	Faster retinopathy progression, HR = 0.04; slower progression to retinopathy, HR = 0.001
Normal to peripheral neuropathy	Calculated#	0.0085	3.07	Faster neuropathy progression, HR = 0.4702; slower progression to neuropathy, HR = 0.0019

Numbers in square brackets are references. Superscript letters refer to Tables from Technical Report S1 in the Supporting Information : [a]eTables 21a,b; [b]eTables 1a–5a; [c]eTable 32; [d]eTables 6a–8a for base case HR; eTable 22 for beta exponent; and eTable 33 for sensitivity analyses. *Assumption supported by [23–25]. †Assumption supported by [18]. §Discussed and approved by Expert Panel. ‖Based on $N = 66$ valid respondents. ¶Disutility compared with conventional treatment (i.e. the decrease in utility of intensive treatment with insulin vs. conventional treatment with diet therapy). #Hazard rate for intensive treatment is derived in the model by the impact of the beta exponent on the conventional treatment HR. NA, not applicable.

sensitivity analysis. Based on input from our expert panel and research suggesting that the UKPDS risk engine may be preferable to the Framingham risk equation in younger adult populations with Type 2 diabetes [26], we chose to use the UKPDS risk engine to calculate risk of CHD for the base case analysis.

Hazard rates for health-state transitions for microvascular complications among adolescents/young adults with Type 2

diabetes (Table 1) were calculated from the weighted average of hazard rates derived from relevant studies identified through the systematic review. A detailed description of these studies is included in Technical Report S1 (eTables 6a–8a).

Interventions

The Youth Model predicts outcomes for those receiving either conventional or intensive glycaemic control based on the outcomes of these treatments in the UKPDS [15]. Specifically, the Youth Model assumes that conventional glycaemic control achieves an average HbA_{1c} of 63 mmol/mol (7.9%) over a median of 10 years and that intensive glycaemic control reduces the average HbA_{1c} over a median of 10 years to 53 mmol/mol (7%). Glycaemic control affects transition probabilities and, therefore, the cumulative incidence of complications and deaths from complications (Table 1). Other interventions were retained from the RTI Model [10] (discussed in Technical Report S1 sections 2.2.–2.4.) and applied to all patients in the Youth Model as appropriate regardless of their treatment for diabetes. Specifically, patients with hypertension receive moderate hypertension control, which reduces CHD by 13% and stroke by 17%; patients with hypercholesterolaemia (total cholesterol ≥ 200 mg/dl) receive statin therapy, which reduces CHD by 31% and progression by 25%; and smokers receive brief counselling with a marginal quit rate of 1.86% and relapse rate of 45%. Quitters experience a reduction in CHD and stroke risk. One year after quitting, the risk is halved and then declines linearly until reaching the risk of a never-smoker at year 15. Adherence to treatments in the Youth Model is assumed to be comparable to that of adults.

Utilities

Utilities for diabetes complications and treatments in the Youth Model were based on adolescents with or at risk of Type 2 diabetes (Table 1). Utilities represent health-related quality of life associated with health states where 1.0 represents perfect health and 0 represents dead. We interviewed 70 overweight/obese, 12- to 18-year-old youths with, or at risk of Type 2 diabetes, in-person between April 2006 and February 2008 using the standard gamble to elicit preferences for seven hypothetical Type 2 diabetes health states and treatments [27]. For the base case, utility of intensive treatment was set at 1.0, reflecting no disutility (i.e. loss in health-related quality of life). To determine the disutility associated with intensive treatment in sensitivity analyses, we assumed that intensive treatment for youths with Type 2 diabetes included insulin and compared it with conventional treatment with diet (Table 1).

Primary analysis

For a hypothetical cohort of 15- to 24-year-olds with newly diagnosed Type 2 diabetes, primary outcomes were remaining life expectancy (RLE), quality-adjusted life expectancy (QALE), causes of death and cumulative incidence of microvascular and macrovascular complications. Remaining life expectancy was defined as remaining life years, undiscounted, from diagnosis. QALE, defined in QALYs, was discounted using a 3% annual discount rate in the base case and included adolescent utilities.

Sensitivity analyses

One-way sensitivity analyses, changing assumptions about one parameter, were performed for conventional glycaemic control (QALYs) and the incremental benefit of intensive compared with conventional glycaemic control (difference in QALYs), presented as percent change from the base case. Parameters evaluated included: prevalence of complications at diagnosis; rates of microvascular disease progression; years from onset to diagnosis; HbA_{1c} at diagnosis and maximum HbA_{1c} under conventional treatment; rate of HbA_{1c} change; estimate for abnormal blood pressure; prevalence of hypertension; interventions such as intensive hypertension control; utilities; CHD risk; discount rate; intensive glycaemic control impact on CHD and variation of individual CHD risk parameters. The impact of microvascular and macrovascular disease progression on cumulative incidence of diabetes complications was also evaluated. Tornado diagrams were used to show those individual parameters that resulted in at least a ± 0.5% change in QALYs resulting from conventional glycaemic control and a ± 2.5% change in the incremental benefit of intensive compared with conventional glycaemic control (difference in QALYs).

In addition, a number of multi-way sensitivity analyses were performed to evaluate the impact of changes in combinations of key model parameters. Specifications for these analyses are detailed in eTable 34 in Technical Report S1.

Results

Remaining life expectancy and quality-adjusted life expectancy

Compared with an average 20-year-old without diabetes in the USA with RLE of 58.6 years [28], for the US population of newly diagnosed Type 2 diabetes patients between 15 and 24 years old, conventional treatment in the Youth Model produced a RLE of 43.09 years, QALE of 39.32 QALYs (undiscounted) and 22.44 QALYs (3% discounted). The QALY gains and losses can reflect changes in quality of life throughout the lifetime, not just related to an extension in life expectancy. Intensive treatment afforded an incremental 0.98 years, 1.32 QALYs (undiscounted), and 0.44 QALYs (discounted). However, when the disutility of intensive treatment, assumed to include insulin, relative to a conventional treatment with diet therapy was included in the Youth Model, those treated intensively lost 2.29 QALYs (undiscounted) and 1.35 QALYs

(discounted) and intensive treatment resulted in a net loss of QALYs compared to conventional treatment (Table 2).

Incidence of complications and death

Those treated intensively had lower lifetime cumulative incidence of all microvascular complications (Fig. 1). The divergence in cumulative incidence of microvascular complications occurred between intensively treated and conventionally treated patients after 20–30 years of diabetes. Figure 2 highlights this pattern for ESRD and blindness. The result was lower mortality from microvascular complications among those treated intensively (e.g. ESRD death 19.4% vs. 25.2%). Greater survival among those treated intensively for 30–40 years contributed to higher lifetime cumulative incidence of stroke (32.4% vs. 29.8%) and CHD (36.1% vs. 34.0%) and higher mortality from cardiovascular complications (e.g. death from CHD 25.1% vs. 23.1%) in this group (Fig. 1). Based on our youth cohort of approximately 3500 people with newly diagnosed Type 2 diabetes annually, the number of adolescents and young adults annually, who would experience each diabetes complications in their lifetime is presented in Table 2.

The model predicted that microalbuminuria would be present in nearly the whole cohort by the end of life regardless of treatment (Fig. 1). However, there was a higher lifetime cumulative incidence of ESRD in the conventional group (29.0% vs. 22.3%). After 25 years, at least 5% in both groups had ESRD and after 35 years, at least 10%. Lifetime cumulative incidence of blindness was 13.8% and 18.5% in the intensive and conventional groups, respectively. However, after 35 years, at least 10% in both groups experienced blindness. Lower extremity amputation occurred infrequently with lifetime cumulative incidence of 3.6% and 4.7% in intensive and conventional groups, respectively.

Sensitivity analyses

Changing the Youth Model assumptions had only modest impact on conventional treatment outcomes. The only change that produced more than a 10% change in QALYs was the discount rate, which resulted in 16.92 QALYs with a 5% discount rate and 39.32 QALYs with 0%. Increasing the rate of progression of microvascular complications, particularly retinopathy, reduced the benefit of conventional treatment (Fig. 3a). Change in the discount rate also had the most significant impact on the incremental benefit of intensive treatment. A 0% discount rate produced an incremental benefit of 1.32 QALYs (as above) vs. 0.23 QALYs with 5%. Intensive treatment was more favourable if HbA_{1c} at diagnosis was higher, if HbA1c increase per year was higher, if retinopathy progression was faster or if adolescent utilities for diabetes complications were lower (Fig. 3b). In our base case analysis, nephropathy was the only microvascular complication for which we assumed a faster initial rate of disease progression in US youths than in adults [10] (Table 1). Slowing the rate of progression to microalbuminuria increased the benefit of conventional treatment by less than 5% (Fig. 3a) and reduced the incremental benefit of intensive treatment by approximately 10% (Fig. 3b). In contrast, assuming a faster rate of progression of nephropathy for those with hypertension decreased the

Table 2 Youth model outcomes: remaining life years, quality adjusted life expectancy and complications

Outcome	Treatment		
	Conventional glycaemic control	Intensive glycaemic control	Incremental benefit of intensive treatment
Remaining life years (undiscounted)	43.09	44.07	0.98
QALYs (undiscounted) without loss in HRQOL for intensive treatment	39.32	40.64	1.32
QALYs (undiscounted) with loss in HRQOL for intensive treatment vs. conventional (diet therapy)	39.32	38.35	−0.96
QALYs (discounted 3%) without loss in HRQOL for intensive treatment	22.44	22.88	0.44
QALYs (discounted 3%) with loss in HRQOL for intensive treatment vs. conventional (diet therapy)	22.44	21.53	−0.91
Adolescents and young adults annually, who experience each diabetes complications in their lifetime*			
End-stage renal disease (*n*)	1015	781	234
Coronary heart disease (*n*)	1190	1264	–74
Blindness (*n*)	648	483	165
Lower extremity amputation (*n*)	165	126	39

*Based on a yearly cohort size of 3500 as described in the methods. HRQOL, health-related quality of life; QALY, quality-adjusted life year.

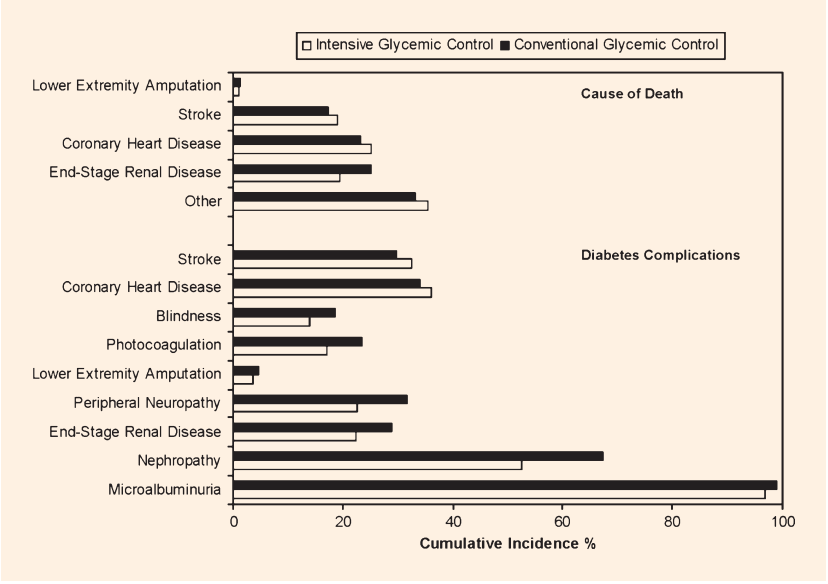

FIGURE 1 Lifetime cumulative incidence of diabetes complications and cause of death. All patients were newly diagnosed as having Type 2 diabetes between 15 and 24 years of age and received conventional or intensive glycaemic control. The upper set of bars represent causes of death, and the lower set represent diabetes complications. Open bars, intensive glycaemic control; closed bars, conventional glycaemic control.

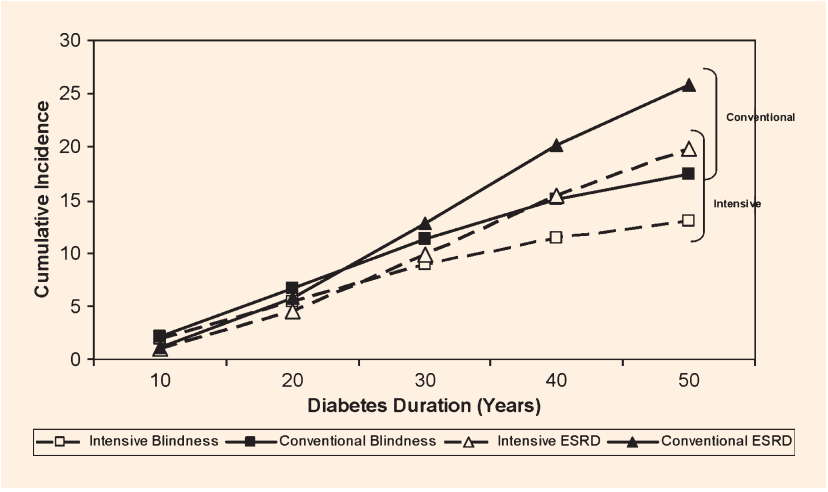

FIGURE 2 Progression of end-stage renal disease (ESRD) and blindness by diabetes duration. All patients were newly diagnosed as having Type 2 diabetes between 15 and 24 years of age and received conventional or intensive glycaemic control. Open squares, cumulative incidence of blindness with intensive treatment; closed squares, cumulative incidence of blindness with conventional treatment; open triangles, cumulative incidence of ESRD with intensive treatment; closed triangles, cumulative incidence of ESRD with conventional treatment.

benefit of conventional treatment by less than 5% (Fig. 3a) and increased the incremental benefit of intensive treatment by approximately 15% (Fig. 3b). When considering the disutility of treatment, intensive treatment would not be considered effective (i.e. fewer QALYs were produced compared with conventional treatment) if its utility was more than 0.02 lower than conventional treatment.

Compared with our base case, assuming a slower rate of progression to microalbuminuria (Table 1) led to a slightly lower lifetime cumulative incidence of microalbuminuria (conventional 87.4% vs. intensive 72.6%) and to lower rates of nephropathy and ESRD (20.9% vs. 14.2%). This was a difference of approximately 8% from our base case, but a delay of only 3 years (28 years diabetes duration) for at least 5% in both groups to have ESRD. Using the slower, adult rate of progression to microalbuminuria [10] for patients after 10 years of diabetes, lifetime cumulative incidence of microalbuminuria was also lower (conventional 92.3% vs. intensive 82.6%). In contrast to microalbuminuria, progression to retinopathy in youths was assumed to occur at a slower rate than

in adults (Table 1). Using the faster, adult rate of progression from normal to retinopathy [10] for patients after 10 years of diabetes, lifetime cumulative incidence of blindness increased (conventional 27.0% vs. intensive 20.1%). A higher cumulative incidence of blindness was also noted (conventional 38.8% vs. intensive 29.3%) if progression from normal to retinopathy for hypertensive patients with moderate control was assumed to be faster, as in adults [10]. If intensive hypertension control is applied for those with hypertension after 10 years of diabetes and it affects progression of retinopathy, lifetime cumulative incidence of blindness is somewhat attenuated (conventional 26.2% vs. intensive 19.6%). While the absolute reduction in incidence of blindness with intensive glycaemic control was greater in the adult scenarios, percentage reduction was similar to the base case. For peripheral neuropathy, cumulative incidence increased to 52.4% and 67.1% in the intensive and conventional treatment groups, respectively, if the faster adult rate of progression to peripheral neuropathy was applied after 10 years of diabetes compared with 22.6% and 31.7%, respectively, in the base case. This also led to a slightly higher cumulative incidence of lower extremity amputation (intensive 6.0% vs. conventional 7.8%). Finally, assuming a higher baseline estimate of abnormal blood pressure (145/90) for those with hypertension resulted in a higher lifetime cumulative incidence of CHD in conventional and intensive treatment groups (35.6% vs. 37.7%, respectively). If intensive glycaemic control was assumed to reduce the risk of CHD by 16.0%, as in the UKPDS [15], intensively-treated patients would have a lower cumulative incidence of CHD compared with the base case (intensive 32.3% vs. conventional 34.0%).

Results of multi-way sensitivity analyses are presented in the Supporting Information, Table S1 (on-line appendix). When significant microvascular disease was assumed to be present at diagnosis and all microvascular complications progressed more quickly than the base case, RLE was 39.77 years and QALE was 18.65 QALYs. When no microvascular disease was assumed to be present at diagnosis and all microvascular complications progressed more slowly than the base case, RLE was 45.76 years and QALE was 23.90 QALYs. With these scenarios, the lifetime cumulative incidence of mortality caused by ESRD differed from the base case by an increase or decrease of approximately 10–15%, respectively. In the multi-way sensitivity analyses, compared with the base case, lifetime cumulative incidence of CHD could be higher as a result of prolonged survival as well as poorer glycaemic control at diagnosis or a higher estimate of abnormal blood pressure for those with hypertension, both of which influenced the initial the risk of developing CHD in the model.

Discussion

The natural history of Type 2 diabetes in US youth remains uncertain. Previous research suggests that one in three males and two in five females born in the USA in 2000 will develop diabetes over their lifetime [12]. To our knowledge, this is the first study to use modelling to describe the clinical outcomes associated specifically with Type 2 diabetes diagnosed among US adolescents/young adults. While the absolute burden of Type 2 diabetes in youth remains small [1–5], our findings suggest that adolescents/young adults with Type 2 diabetes carry a high risk of microvascular and macrovascular complications that shorten life expectancy and reduce health-related quality of life. With projected RLE of 43 years, youths diagnosed with Type 2 diabetes between 15 and 24 years old only live into their 60s compared with the average 20-year-old in the USA with RLE of 58.6 years, living into his/her 70s [28]. Our findings are consistent with a previous Markov-modelling study demonstrating a loss in RLE of 17.9 years for females and 17.2 years for males diagnosed with diabetes at age 20 [12]. However, we also describe the diabetes-related complications contributing to these trends. Adult studies suggest that diabetes complications significantly increase medical costs [29], and our findings suggest diabetes diagnosed in youth, regardless of intensity of glycaemic control, may add to economic and societal costs by the introduction of complications in the 40s and 50s.

Our model results demonstrated that intensive glycaemic control introduced at diagnosis of Type 2 diabetes in adolescents and young adults produces only modest improvements in RLE and QALE. However, longer survival can lead to a slightly higher lifetime cumulative incidence of macrovascular complications and deaths owing to macrovascular complications. Our multi-way sensitivity analyses further demonstrated that a higher lifetime cumulative incidence of CHD could be the result of either a longer life expectancy or greater severity of risk factors that contribute to the development of CHD. Focusing on aggressive early control of cardiovascular risk factors, such as through weight management, glycaemic control and treatment of hypertension, beginning in adolescence and young adulthood may be needed to reduce the longer term risk of CHD [30–32]. Such a strategy would be supported by recent randomized controlled trials in adults, which have demonstrated that patients with Type 2 diabetes of shorter duration and without established cardiovascular disease are most likely to experience cardiovascular benefits from intensive glycaemic control [30,33].

Adolescents with, or at risk of Type 2 diabetes, assign greater loss in quality of life to intensive treatment, assumed here to include treatment with insulin, than to a conventional treatment with diet. When desirability of treatment was considered in this fashion, intensive treatment with insulin resulted in net loss of QALE. Our findings are conceptually consistent with Huang *et al.* [34,35], who demonstrated disutility for insulin treatment among adults with Type 2 diabetes and an impact on the cost-effectiveness of treatments for Type 2 diabetes based on the assumptions made about the patient preferences for diabetes treatment [35]. This pattern is not unique to diabetes. For primary prevention of cardiovascular disease in women, Pignone *et al.* [36] demonstrated that, if the utility of taking aspirin were < 0.9995, aspirin would be less effective than no treatment. However, as adolescent and young adult preferences may differ from those of older adults [27,34], future research is

FIGURE 3 Sensitivity analyses representing percentage change from base case. (a) Conventional treatment; (b) Incremental benefit of intensive glycaemic control. Faster progression refers to the following hazard rates (HR): normal to retinopathy (photocoagulation) 0.04; normal to microalbuminuria 0.42; normal to neuropathy 0.4702; all other HR represent a 20% increase from base case. Faster progression of nephropathy with hypertension refers to HR for nephropathy transitions that are 20% above base case for those with hypertension with moderate control. Hypertensives progressing faster leads to faster progression from normal to retinopathy at the adult HR = 0.0166. Intensive hypertension control leads to reduced risk of coronary heart disease (CHD) and stroke. When applicable, intensive hypertensive control reduces progression to retinopathy applying adult HR after 10 years of diabetes. Slower progression to microalbuminuria refers to HR = 0.042; Slower progression to retinopathy (photocoagulation) refers to HR = 0.001. Slower progression to neuropathy refers to HR = 0.0019. Base case in Fig. (a) = 22.44 quality-adjusted life years (QALYs); Base case in (b) = 0.44 QALYs. Rx, treatment; references for HR are included in the Supporting Information, Technical Report S1 (eTable 33).

needed that incorporates age-specific utilities for diabetes treatments to inform strategies that optimize QALE and cost-effectiveness. The RTI Model adapted for the Youth Model did not allow for changes in preferences over time.

Modelling, such as our Youth Model, provides information about long-term health outcomes without the time investment of an epidemiological study. However, our Youth Model relies on current data regarding Type 2 diabetes in adolescents/young adults, including some areas for which only limited data exist. Sensitivity analyses identified parameters with the most influence on the Youth Model outcomes, and about which additional research may be warranted to confirm our findings. We found that rates of progression of microvascular disease, particularly retinopathy, influenced outcomes of conventional

treatment. Many of the studies on early progression of microvascular disease in youth with Type 2 diabetes are retrospective and offer incomplete data, which may bias outcomes. Larger, prospective and complete assessments of retinopathy screening and follow-up in youth with Type 2 diabetes can inform future modelling. With regard to intensive treatment, we found that a higher HbA_{1c} at diagnosis and faster annual increase in HbA_{1c} would support greater benefit from intensive treatment. While data are available regarding the HbA_{1c} at presentation [37], little published data are available to inform HbA_{1c} progression beyond the first year after diagnosis in youths with Type 2 diabetes [18,38]. One study of 59 predominantly African-American youths from Philadelphia, PA, USA, has shown that glycaemic control improves in the first year of treatment but deteriorates in the second year with variable rates of change over time [38]. Future modelling, which accounts for greater complexity in the longitudinal changes in HbA_{1c} as well as for possible differences in outcomes by gender, race/ethnicity, hypertension status, and other characteristics at diagnosis may need to be explored. Owing to the limits of available data, we were unable to assess such differences in this study. As this analysis was an adaptation of an adult model (the RTI Model), certain parameters, such as the age range of our cohort (15–24 years), were also fixed. As heterogeneity may exist within this age range, additional analyses addressing the differences that may exist within these subgroups may also be needed. Finally, the adolescent utilities used in the Youth Model were derived from a sample that included both adolescents with Type 2 diabetes and those at risk [27]. While differences in preferences could exist across these groups, the utilities did not differ significantly by diagnosis in this population sample [27].

The results of the Youth Model are based on the glycaemic control achieved with intensive and conventional interventions used in the UKPDS, which was an average HbA_{1c} of 53 mmol/mol (7.0%) and 63 mmol/mol (7.9%), respectively [15]. Glycaemic control within this range has been documented for youths with Type 2 diabetes in the SEARCH for Diabetes in Youth Study [18] making the interventions used in the Youth Model relevant. However, some of the specific treatments used in the UKPDS, including sulphonylureas and diet therapy [15], are not the most common treatment approaches used for adolescents with Type 2 diabetes [39]. Metformin is the most common initial oral hypoglycaemic agent used in this population as it is the only oral medication for treatment of Type 2 diabetes approved for use in children in the USA [40]. Therefore, future models incorporating data from the metformin arm of the UKPDS [41] or large trials specifically evaluating treatments for Type 2 diabetes in youth, such as the TODAY (Treatment Options for Type 2 Diabetes in Adolescents & Youth) Study [42], may facilitate further study of interventions specific to youths. As the focus of this analysis was on the adolescent/young adult cohort, we did not address updates to the adult component of the RTI Model [10,13], which has undergone recent validation [13].

In summary, we found that adolescents/young adults diagnosed with Type 2 diabetes lose approximately 15 years from average RLE and experience severe complications of Type 2 diabetes by their 40s. Intensive glycaemic control has modest effects on life expectancy and the net clinical benefit of interventions to improve glycaemic control may be sensitive to preferences for diabetes treatments. Comprehensive treatment that includes early and aggressive control of multiple cardiovascular risk factors is likely needed to reduce the lifetime risk of CHD in adolescents and young adults diagnosed with Type 2 diabetes.

Competing interests

E.T.R. received salary support from an unrestricted, philanthropic grant from the New Balance Foundation and was formerly Chief Medical Officer for Pediatric Weight Management Centers, LLC's Great Moves! Program, a company privately owned and operated in collaboration with the physicians of Children's Hospital Boston. E.T.R. provided contracted clinical and administrative services for the company but neither had nor has equity or other economic interest in the business. E.T.R. has also disclosed that her spouse owns stock in Bristol Myers Squibb and Pfizer. L.M.L. is a consultant for Lilly, Bristol Myers Squibb, Menarini, Sanofi-Aventis, Johnson & Johnson and Astra Zeneca, and receives grant support from Bayer. The remaining authors have nothing to declare.

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Supporting Information

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

Technical Report S1 Technical report for youth model

Table S1 Multi-way deterministic sensitivity analyses

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