

## Research: Health Economics

# Assessing the economic value of maintained improvements in Type 1 diabetes management, in terms of HbA<sub>1c</sub>, weight and hypoglycaemic event incidence

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### Abstract

**Aims** Insulin therapy is indicated for people with Type 1 diabetes mellitus; however, treatment-related weight gain and hypoglycaemia represent barriers to optimal glycaemic management. This study assessed the health economic value of maintained reductions in HbA<sub>1c</sub>, BMI and hypoglycaemia incidence among the UK Type 1 diabetes population.

**Methods** The Cardiff Type 1 Diabetes Model was used to estimate lifetime costs, life-years and quality-adjusted life-years (QALYs) for individuals with Type 1 diabetes at different baseline HbA<sub>1c</sub>, BMI and hypoglycaemic event rates. Results were discounted at 3.5%, and the net monetary benefit associated with improving Type 1 diabetes management was derived at £20 000/QALY gained. Per-person outputs were inflated to national levels using UK Type 1 diabetes prevalence estimates.

**Results** Modelled subjects with an HbA<sub>1c</sub> of 86 mmol/mol (10.0%) were associated with discounted lifetime per-person costs of £23 795; £12 649 of which may be avoided by maintaining an HbA<sub>1c</sub> of 42 mmol/mol (6.0%). Combined with estimated QALY gains of 2.80, an HbA<sub>1c</sub> of 42 mmol/mol (6.0%) vs. 86 mmol/mol (10.0%) was associated with a £68 621 per-person net monetary benefit. Over 1 year, unit reductions in BMI produced £120 per-person net monetary benefit, and up to £197 for the avoidance of one non-severe hypoglycaemic event.

**Conclusions** Maintained reductions in HbA<sub>1c</sub> significantly alleviate the burden associated with Type 1 diabetes in the UK. Given the influence of weight and hypoglycaemia on health economic outcomes, they must also be key considerations when assessing the value of Type 1 diabetes technologies in clinical practice.

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### Introduction

Type 1 diabetes mellitus is a chronic autoimmune disorder associated with significant morbidity and mortality, and an estimated loss in life expectancy of 11–13 years among young adults in the United Kingdom (UK) [1]. The management of the condition and its long-term complications impose significant direct costs on the National Health Service (NHS), and its societal burden is associated with additional indirect costs. While Type 1 diabetes affected 400 000 individuals in the UK during 2010–2011, recent projections

suggest that Type 1 diabetes prevalence will rise to 652 000 individuals by 2035–2036, and the economic burden of the condition will grow accordingly [2]. Between 2010–2011 and 2035–2036, the direct healthcare costs of Type 1 diabetes are predicted to rise from £1.0 billion to £1.8 billion, with indirect costs of Type 1 diabetes-related morbidity and mortality predicted to rise from £900 million to £2.4 billion during the same period [2].

Micro- and macrovascular complications account for approximately 70% of NHS expenditure on Type 1 diabetes management [2]. These include potentially avoidable complications that arise as a consequence of poor glycaemic control; thus, improved disease management may produce significant cost savings for the UK public healthcare system. Treatment regimens that mimic physiological insulin secretion serve to control HbA<sub>1c</sub> levels in people with Type 1

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**What's new?**

- This study demonstrated the burden of inadequate Type 1 diabetes management, and quantified the value of reducing HbA<sub>1c</sub>, weight and hypoglycaemia frequency among the UK Type 1 diabetes population.
- Significant cost savings, quality-adjusted life-year gains and net monetary benefit were predicted in those who achieve HbA<sub>1c</sub> targets recommended in national guidelines; nevertheless, any incremental improvement in glycaemic management substantially reduced the burden of Type 1 diabetes mellitus on individuals and healthcare systems.
- Given the influence of weight and hypoglycaemia on health economic outcomes, these factors should also be key considerations when assessing the value of Type 1 diabetes technologies.

diabetes, with a view to preventing the long-term health complications associated with the condition. However, exogenous insulin is often associated with weight gain and the incidence of hypoglycaemic events, which in turn are barriers to optimal glycaemic management [3,4]. Updated guidance from the National Institute for Health and Care Excellence (NICE) recommend insulin therapy in combination with diet and lifestyle changes for the management of Type 1 diabetes, which collectively aim to normalize HbA<sub>1c</sub> levels, control weight and minimize cardiovascular risk factors [5].

Although NICE guidance published in 2004 recommended that Type 1 diabetes therapy should aim to reduce HbA<sub>1c</sub> levels to < 59 mmol/mol (7.5%), the 2015–2016 National Diabetes Audit found that 71% of people with Type 1 diabetes in England and Wales failed to achieve and maintain this goal [6]. Since 2015, NICE guidelines now recommend that adults with Type 1 diabetes aim for a target HbA<sub>1c</sub> of 48 mmol/mol (6.5%) or below [5]; a level of glycaemic control that only 8% currently reach [6]. Despite the difficulty faced by individuals and their clinicians to achieve a stricter treatment target, health economic modelling has recently demonstrated the value of making modest, incremental improvements to glycaemic control in Type 1 diabetes. Based on current UK population data, it was estimated that an achievable HbA<sub>1c</sub> reduction of 4 mmol/mol (0.4%) could avoid 81 000 microvascular and 7000 macrovascular events over 25 years [7]. Fewer complications were subsequently associated with per-person cost savings between £2057 and £4136 over 25 years, which equated to a potential cost avoidance of £995 million for the total UK population [7]. Importantly, the economic impact of differing levels of glycaemic control, in addition to treatment effects, on individual outcomes and quality of life remain poorly characterized.

With this in mind, the aim of this study was to quantify the health economic burden of elevated HbA<sub>1c</sub>, BMI and frequency of hypoglycaemic events in people with Type 1 diabetes, expressed in terms of costs, life-years and quality-adjusted life-years (QALYs) at a per-person and national level. The cost savings and QALY gains associated with incremental, maintained reductions in HbA<sub>1c</sub>, BMI and hypoglycaemia incidence were subsequently estimated, and the net monetary benefit associated with improved Type 1 diabetes management was derived.

**Methods****The Cardiff Type 1 Diabetes Model**

The Cardiff Type 1 Diabetes Model has been described in detail previously [8]. In brief, it is a fixed-time-increment stochastic microsimulation model designed to evaluate the lifetime impact of therapeutic changes for individuals with Type 1 diabetes. Consistent with both established and recently published Type 1 diabetes models [9], risk equations implemented within the Cardiff Type 1 Diabetes Model were adapted to incorporate long-term epidemiological evidence derived from the Diabetes Control and Complications Trial (DCCT) [10] and follow-up study (Epidemiology of Diabetes Interventions and Complications; EDIC) [11], in addition to cardiovascular risk equations from the Swedish National Diabetes Registry [12]. A flow diagram of the Cardiff Type 1 Diabetes Model is shown in Fig. S1; approaches to simulate Type 1 diabetes-related complications within the model are summarized in Table S1. Further details regarding the development and validation of the Cardiff Type 1 Diabetes Model are provided in its original publication [8].

**Costs and utilities**

The direct costs of managing Type 1 diabetes and its complications were implemented within the Cardiff Type 1 Diabetes Model. The occurrence of diabetes-related events was associated with a reduction in quality of life; the utility decrements applied (additively) were consistent with the default values of the CORE Diabetes Model [13] and those applied in recent guidelines [5]. Further details regarding the costs and utilities applied in the model are provided in Tables S2–S4. The utility decrement associated with hypoglycaemia was modelled using regression equations that linked event frequency and severity to utility, via the fear of hypoglycaemia score [14].

**Baseline characteristics and time-dependent risk factors**

Two characteristic profiles were modelled, representing an average person with Type 1 diabetes in the UK ('average UK profile') and a more recently diagnosed individual ('younger

**Table 1** Type 1 diabetes characteristic profiles

Parameter	Average UK profile	Younger UK profile	Source
Baseline demographics and modifiable risk factors			
Mean age (years)	42.98	27.00	NICE NG17 [5], Nathan <i>et al.</i> [15]
Mean duration of diabetes (years)	16.92	9.10	NICE NG17 [5], NDA [16]
Proportion women	0.43	0.45	NICE NG17 [5], NDA [16]
Proportion smokers	0.22	0.26	NICE NG17 [5], NDA [16]
Mean total cholesterol (mg/dl)	176.50	176.50	NICE NG17 [5], Nathan <i>et al.</i> [15]
Mean HDL cholesterol (mg/dl)	50.25	50.25	NICE NG17 [5], Nathan <i>et al.</i> [15]
Mean SBP (mm Hg)	128.27	121.48	NICE NG17 [5], NDA [16]
Mean DBP (mm Hg)	73.55	73.55	Saunders <i>et al.</i> [17]
Mean BMI (kg/m <sup>2</sup> )*	27.09	24.90	NICE NG17 [5]
Clinical history and management (proportion)			
History of CVD	0.003	Assumed none	NICE NG17 [5], HSCIC [18]
History of microalbuminuria	0.181		NICE NG17 [5], NDA [16]
History of neuropathy	0.049		NICE NG17 [5], Nathan <i>et al.</i> [15]
Hypertension	0.880		NICE NG17 [5]
ACE inhibitor therapy	0.710		NICE NG17 [5]
Annual frequency of hypoglycaemia			
Non-severe events	28	35.5	UK Hypoglycaemia Study Group [19]
Severe events	0.46	0.22	

\*Weight initialized in the model based on an assumed height of 1.72m<sup>2</sup>.

ACE, angiotensin converting enzyme; CVD, cardiovascular disease; HSCIC, Health and Social Care Information Centre; NDA, National Diabetes Audit; NICE, National Institute for Health and Care Excellence.

UK profile'), consistent with those reported in NICE guideline NG17 [5] (Table 1). The likelihood of clinical events was influenced by several risk factors; while the model has the capability of allowing modifiable risk factors to change with respect to time, HbA<sub>1c</sub>, weight, blood pressure and lipid parameters remained constant for this study, in the absence of any specific intervention.

## Analyses

The model was used to evaluate the impact of stepwise reductions in HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 42 mmol/mol (6.0%), non-severe hypoglycaemic events from 100 to zero, severe hypoglycaemic events from five to zero, and BMI from 35 kg/m<sup>2</sup> to 25 kg/m<sup>2</sup>, on costs, life-years and/or QALYs. Modelled changes in HbA<sub>1c</sub> from baseline were applied over the first 6 months and maintained over a lifetime (up to 80 years). Changes in hypoglycaemia incidence and BMI were modelled over 1 year; outputs were then scaled to estimate lifetime benefits in an average UK person with Type 1 diabetes. Outputs were discounted at 3.5% annually and reported on a per-person basis. Using predicted cost savings and QALY gains, net monetary benefit (NMB) was additionally derived, based on a conventional threshold for cost-effectiveness in the UK. Model analyses were treatment-independent and did not consider pharmacological management costs; therefore, NMB represents both the burden associated with inadequate Type 1 diabetes management, and the amount that could be spent to achieve a given reduction in HbA<sub>1c</sub>, BMI and hypoglycaemia frequency, and associated QALY gains, whilst maintaining

cost-effectiveness at a willingness-to-pay threshold of £20 000 per additional QALY gained.

To quantify the national level burden of HbA<sub>1c</sub> in people with Type 1 diabetes, costs, life-years and QALYs were predicted for a person in each of four HbA<sub>1c</sub> categories [ $< 48$  mmol/mol ( $< 6.5\%$ ); 48–58 mmol/mol (6.5%–7.5%); 58–86 mmol/mol (7.5%–10.0%);  $\geq 86$  mmol/mol ( $\geq 10.0\%$ )], using modelled HbA<sub>1c</sub> levels of 6.0%, 7.0%, 8.75% and 10.0%, respectively. Health economic outcomes associated with HbA<sub>1c</sub> were then estimated at a national level, by scaling per-person outputs to the UK Type 1 diabetes population. The total diabetes population (comprising people with Type 1 and Type 2 diabetes) was estimated using 2015 diabetes prevalence data for England [20], Wales [21], Scotland [22] and Northern Ireland [23]. The Type 1 diabetes population (approximately 10% of all people with diabetes [20,22]) was stratified into the four HbA<sub>1c</sub> categories, according to distributions reported by the National Diabetes Audit 2014–2015 [24].

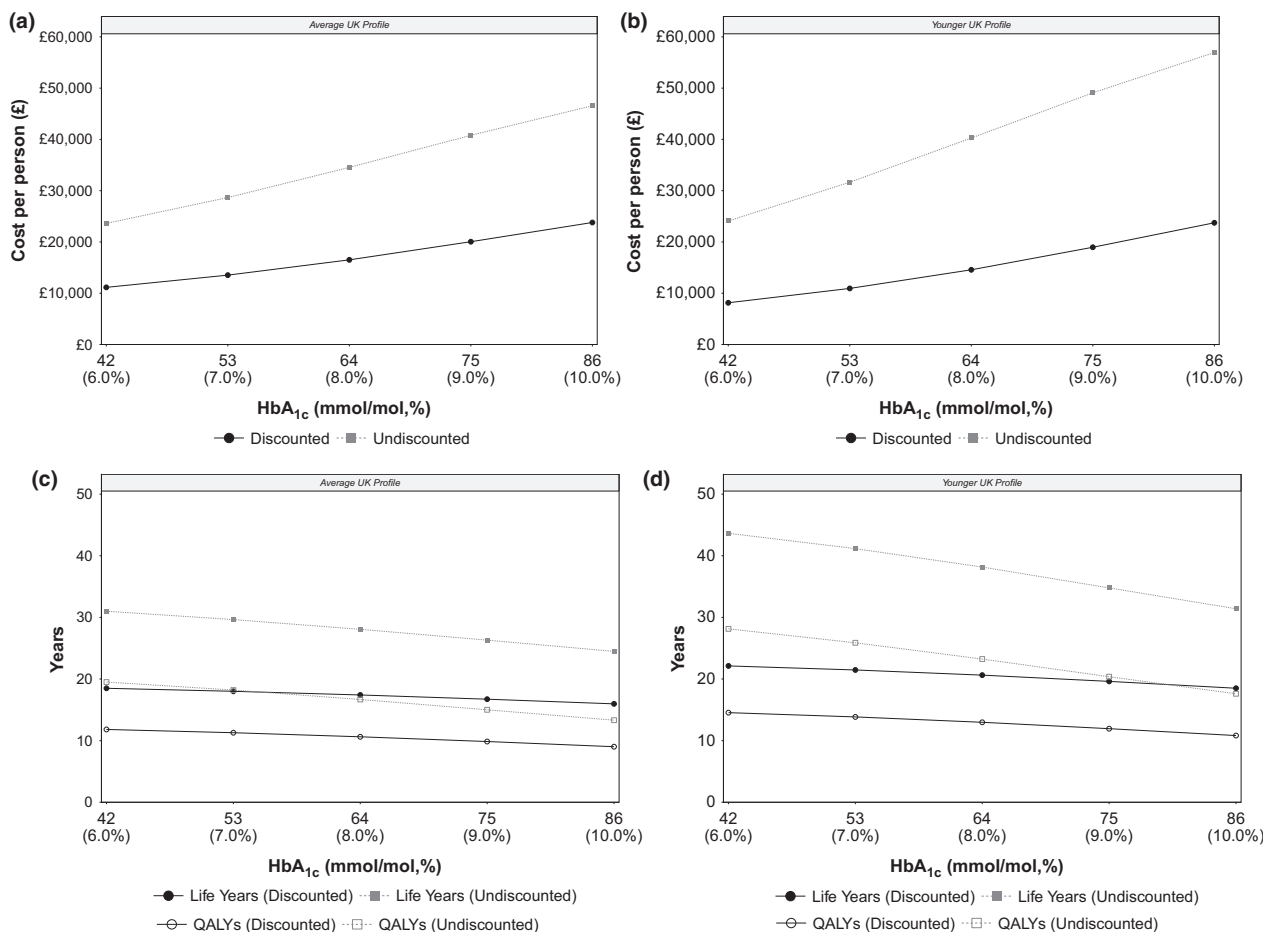
## Results

### Value of improved glycaemic control

Figure 1 demonstrates the impact of reducing HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 42 mmol/mol (6.0%) on per-person costs, life-years and QALYs. An average UK person with Type 1 diabetes and an HbA<sub>1c</sub> of 86 mmol/mol (10.0%) was expected to cost a discounted total of £23 795 over a lifetime. Lowering HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 42 mmol/mol (6.0%) in 11 mmol/mol (1.0%) increments

was associated with gross cost savings of £3746, £3538, £2983 and £2382 (totalling £12 649). Predicted cost savings were attributed to the avoidance of diabetes-related complications; a breakdown of discounted per-person costs are provided in Fig. S2. For a unit reduction in HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 75 mmol/mol (9.0%), predicted cost savings were largely driven by reduced costs of neuropathy (−£2492; −66.5%), retinopathy (−£901; −24.1%) and nephropathy (−£503; −13.4%), while some additional costs were incurred for severe hypoglycaemia (+£121; +3.2%), cardiovascular disease (+£17; +0.4%) and ketoacidosis (+£13; +0.3%). Despite overall cost savings, monetized QALY gains were the major driver of NMB associated with improved glycaemic control. Lowering HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 42 mmol/mol (6.0%) in 11 mmol/mol (1.0%) units led to incremental QALY gains of 0.84, 0.77, 0.66 and 0.53 (totalling 2.80); and associated NMB of £20 518, £18 935, £16 175 and £12 993 (totalling £68 621), respectively.

Estimated costs increased for a more recently diagnosed individual. A person with a ‘younger UK profile’ and an HbA<sub>1c</sub> of 86 mmol/mol (10.0%) was estimated to incur a total discounted lifetime cost of £23 739. Gross cost savings when HbA<sub>1c</sub> was reduced from 86 mmol/mol (10.0%) to 42 mmol/mol (6.0%) in 11 mmol/mol (1.0%) increments were estimated to be £4772, £4394, £3634 and £2800 (totalling £15 601). Predicted cost savings were similarly attributed to the avoidance of adverse events; a breakdown of discounted per-person costs are provided in Fig. S3. For a unit reduction in HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 75 mmol/mol (9.0%), the majority of cost savings were related to the reduced costs of neuropathy (−£2871; −63.9%), nephropathy (−£1260; −28.1%) and retinopathy (−£855; −19.0%), while some additional costs were incurred for ketoacidosis (+£381; +8.5%) and cardiovascular disease (+£113; +2.5%). However, the predicted value of improved glycaemic control was largely driven by mon-



**FIGURE 1** Per-person costs, life-years and quality-adjusted life-years (QALYs) in people with Type 1 diabetes according to HbA<sub>1c</sub> level. Incremental improvements in HbA<sub>1c</sub> were associated with reduced lifetime costs for people with an average UK profile (a) and a younger UK profile (b). Reducing HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 42 mmol/mol (6.0%) was also associated with improvements in life-years and QALYs for people with an average UK profile (c) and a younger UK profile (d). Circles represent discounted costs, life-years and QALYs; squares represent undiscounted costs, life-years and QALYs.

etized utility gains; lowering HbA<sub>1c</sub> from 86 mmol/mol (10.0%) to 42 mmol/mol (6.0%) in 11 mmol/mol (1.0%) units was associated with incremental QALY gains of 1.12, 1.04, 0.87 and 0.69 (totalling 3.72), and NMB of £26 711, £24 753, £20 774 and £16 385 (totalling £88 624), respectively.

At a national level, 447 338 people were estimated to have Type 1 diabetes in the UK, comprising 38 706 people (8.7%) with HbA<sub>1c</sub> < 48 mmol/mol (< 6.5%), 95 035 (21.2%) with HbA<sub>1c</sub> 48–58 mmol/mol (6.5%–7.5%), 242 971 (54.3%) with HbA<sub>1c</sub> 58–86 mmol/mol (7.5%–10.0%), and 70 625 (15.8%) with HbA<sub>1c</sub> ≥ 86 mmol/mol (≥ 10.0%). When modelled with an ‘average UK profile’, the Type 1 diabetes subpopulation with HbA<sub>1c</sub> ≥ 86 mmol/mol (≥ 10.0%; *N* = 70 625) was estimated to cost £1.7 billion in total; a maintained HbA<sub>1c</sub> reduction to 42 mmol/mol (6.0%) was associated with a gross cost saving of £0.9 billion. If an HbA<sub>1c</sub> level of 42 mmol/mol (6.0%) could be achieved and maintained among those with HbA<sub>1c</sub> ≥ 48 mmol/mol (≥ 6.5%; *N* = 408 632), the total costs associated with Type 1 diabetes-related complications could be reduced by more than half (gross cost saving of £3.0 billion). Table 2 provides national level costs, life-years and QALYs for each HbA<sub>1c</sub>

cohort, modelled with an ‘average UK profile’ and ‘younger UK profile’. Figures S4–S6 additionally illustrate per-person and national level costs, life-years and QALYs according to HbA<sub>1c</sub> category, respectively.

#### Value of reduced frequency of hypoglycaemia

In people experiencing no more than 10 non-severe hypoglycaemic events, one fewer event was associated with one-year QALY gains ranging between 0.001 (reduction from 10 to nine events) and 0.01 (reduction from one to zero events). As no costs were applied to the incidence of non-severe hypoglycaemia in this study, the predicted value of reduced event frequency was driven entirely by monetized QALY gains. Thus, at a willingness-to-pay threshold of £20 000 per QALY, one fewer non-severe event equated to incremental NMB ranging between £27 and £197 (Fig. 2). If modelled reductions in non-severe hypoglycaemia frequency were maintained in an average UK person with HbA<sub>1c</sub> of 75 mmol/mol (9.0%), this would translate to lifetime QALY gains of between 0.023 (reduction from 10 to nine events) and 0.164 (reduction from one to zero events), and associated incremental NMB of £452–£3289.

**Table 2** National level costs, life-years and quality-adjusted life-years for UK populations with Type 1 diabetes, stratified by HbA<sub>1c</sub> category

			HbA <sub>1c</sub>				
			< 48 mmol/mol (< 6.5%)	48–58 mmol/mol (6.5–7.5%)	58–86 mmol/mol (7.5–10.0%)	≥ 86 mmol/mol (≥ 10.0%)	Sum of all categories
Modelled HbA <sub>1c</sub> value (%)			6.00	7.00	8.75	10.00	NA
Population size			38 706	95 035	242 971	70 625	447 338
Costs							
Discounted	Average UK profile	Total	£431 439 676	£1 285 670 103	£4 645 594 362	£1 680 558 443	£8 043 262 583
		Incremental*	–	£226 349 970	£1 937 296 097	£893 326 834	£3 056 972 901
Undiscounted	Younger UK profile	Total	£314 993 860	£1 039 538 661	£4 330 124 053	£1 676 557 223	£7 361 213 797
		Incremental*	–	£266 129 639	£2 352 797 043	£1 101 799 876	£3 720 726 558
Discounted	Average UK profile	Total	£914 263 609	£2 724 199 930	£9 531 959 140	£3 288 530 807	£16 458 953 486
		Incremental*	–	£479 395 146	£3 792 805 591	£1 620 308 684	£5 892 509 422
Undiscounted	Younger UK profile	Total	£932 782 369	£3 007 575 099	£11 419 107 379	£4 021 985 457	£19 381 450 305
		Incremental*	–	£717 300 932	£5 563 705 071	£2 319 972 855	£8 600 978 858
Life-years							
Discounted	Average UK profile	Total	715 940	1 711 181	4 108 159	1 127 950	7 663 230
		Incremental*	–	1 253 294	3 650 271	670 063	5 573 628
Undiscounted	Younger UK profile	Total	856 353	2 040 321	4 832 873	1 306 883	9 036 429
		Incremental*	–	1 582 433	4 374 985	848 996	6 806 414
Discounted	Average UK profile	Total	1 199 905	2 817 259	6 503 596	1 729 530	12 250 291
		Incremental*	–	2 359 372	6 045 709	1 271 643	9 676 723
Undiscounted	Younger UK profile	Total	1 689 392	3 911 532	8 669 779	2 217 770	16 488 473
		Incremental*	–	3 453 645	8 211 892	1 759 882	13 425 419
QALYs							
Discounted	Average UK profile	Total	457 345	1 072 505	2 444 180	636 847	4 610 878
		Incremental*	–	615 160	1 986 836	179 502	2 781 499
Undiscounted	Younger UK profile	Total	562 836	1 316 273	2 968 217	764 552	5 611 877
		Incremental*	–	858 928	2 510 872	307 207	3 677 007
Discounted	Average UK profile	Total	755 029	1 730 417	3 750 648	940 775	7 176 869
		Incremental*	–	1 273 072	3 293 304	483 430	5 049 806
Undiscounted	Younger UK profile	Total	1 089 043	2 459 685	5 129 012	1 243 380	9 921 119
		Incremental*	–	2 002 340	4 671 667	786 035	7 460 042

\*Incremental costs, life-years and quality-adjusted life-years (QALYs) calculated with respect to the UK Type 1 diabetes population with HbA<sub>1c</sub> < 48 mmol/mol (< 6.5%).

In people experiencing 20–100 non-severe hypoglycaemia events, 10 fewer events resulted in one-year QALY gains ranging between 0.001 (reduction from 100 to 90 events) and 0.009 (reduction from 20 to 10 events), and associated incremental NMB of £30–£183 (Fig. 2). If modelled reductions in non-severe hypoglycaemia frequency were maintained in an average UK person with HbA<sub>1c</sub> of 75 mmol/mol (9.0%), this would translate to lifetime QALY gains of between 0.025 (reduction from 100 to 90 events) and 0.153 (reduction from 20 to 10 events), and associated incremental NMB of £495–£3068.

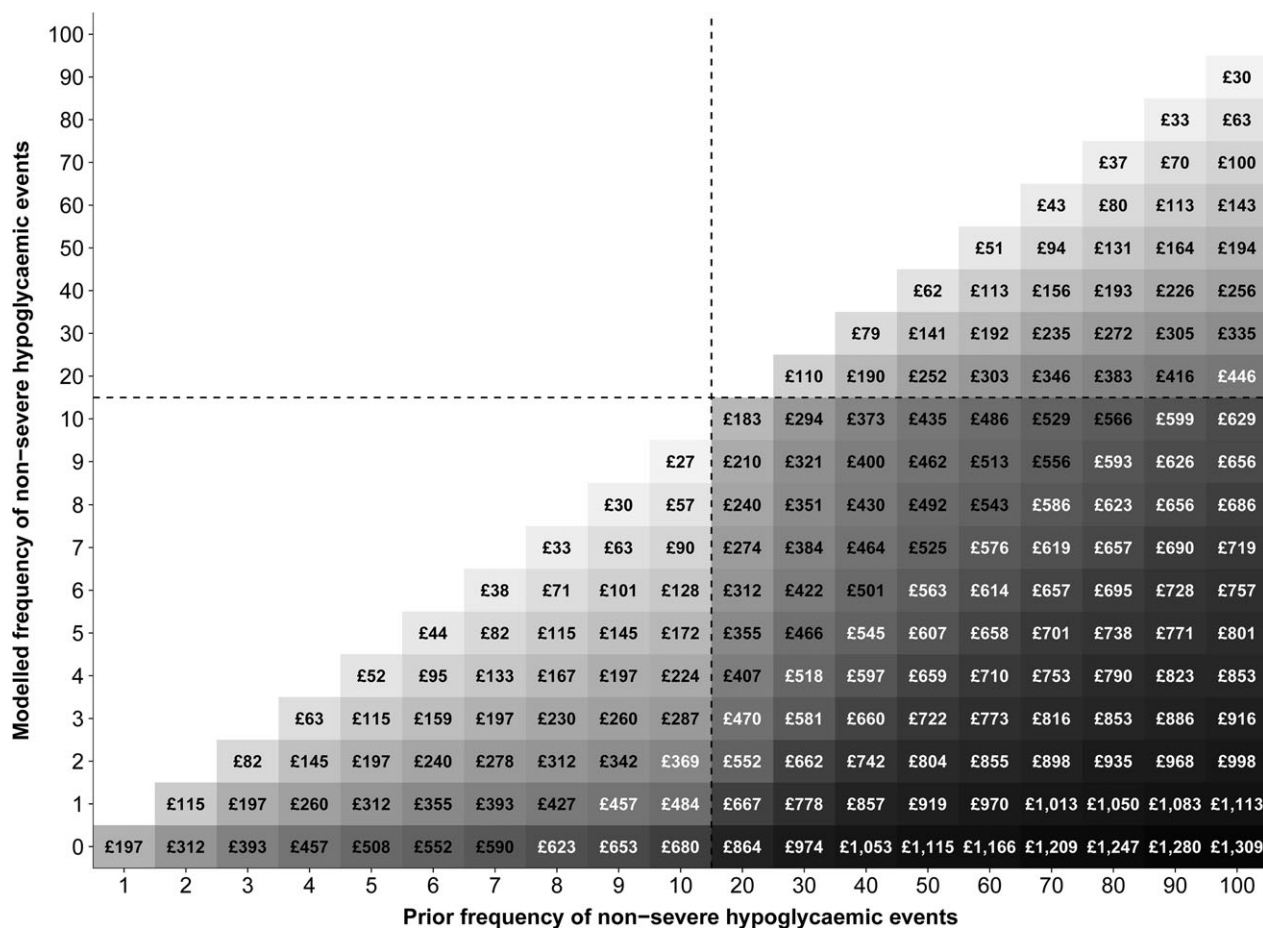
In people with no more than five severe hypoglycaemic events, the per-person cost saving was £344 for every severe hypoglycaemic event avoided. Complete avoidance of severe hypoglycaemia was associated with a 0.01 QALY gain over one year; thus, incremental NMB ranged between £544 (reduction from one to zero events) and £1921 (reduction from five to zero events) (Fig. S7). In an average UK person with HbA<sub>1c</sub> of 75 mmol/mol (9.0%), maintained avoidance of severe hypoglycaemia over a lifetime would translate to 0.167 QALYs gained, and incremental NMB between £9104 (reduction from one to zero events) and £32 136 (reduction from five to zero events).

### Value of reduced BMI

Costs associated with weight change were not applied in model analyses; thus, the predicted value of reduced BMI was driven entirely by monetized utility gains. Reducing BMI by 1 kg/m<sup>2</sup> was associated with a 0.006 QALY gain over one year, which corresponded to an incremental NMB of £120 for each unit reduction in BMI. Therefore, reducing BMI from 35 kg/m<sup>2</sup> to 25 kg/m<sup>2</sup> equated to an incremental NMB of £1200 per year, at a willingness-to-pay threshold of £20 000 per QALY. If modelled weight change was maintained in an average UK person with HbA<sub>1c</sub> of 75 mmol/mol (9.0%), each unit reduction in BMI would translate to a lifetime QALY gain of 0.100, and associated incremental NMB of £2007.

### Discussion

Recent studies have reported the health economic value of improved disease management in Type 2 diabetes [25], and estimated the potential costs avoided that a modest HbA<sub>1c</sub> reduction would achieve within the UK healthcare system [7]. In the present analysis, we quantified the health



**FIGURE 2** Discounted value of reduced non-severe hypoglycaemic event incidence in people with Type 1 diabetes (net monetary benefit at £20 000 per quality-adjusted life-year gained).

economic burden of inadequate Type 1 diabetes management in the UK, and estimated the value associated with incremental HbA<sub>1c</sub> improvements, fewer hypoglycaemic events and reduced BMI in people with Type 1 diabetes. Analyses using the Cardiff Type 1 Diabetes Model found that unit reductions in HbA<sub>1c</sub>, BMI and frequency of hypoglycaemia were independently associated with per-person cost savings, QALY gains and NMB. Monetized QALY gains were the major driver of NMB associated with improved Type 1 diabetes management, while predicted cost savings were attributed to the avoidance of long-term health complications that arise as a consequence of poor glycaemic control.

National guidelines recommend that adults with Type 1 diabetes aim to lower HbA<sub>1c</sub> to  $\leq 48$  mmol/mol ( $\leq 6.5\%$ ) [5], and the present study highlighted the considerable health economic benefits that could be achieved in those who successfully reach and maintain this 'ideal' HbA<sub>1c</sub> target. However, NICE additionally recognize that several factors, including comorbidities, risk of complications and history of hypoglycaemia, represent barriers to achieving optimal glycaemic control; and subsequently advocate the use of individualized HbA<sub>1c</sub> targets in these cases [5]. With this in mind, we demonstrated that unit reductions in HbA<sub>1c</sub> were associated with substantial per-person cost savings, and gains in life-years and QALYs, regardless of whether NICE treatment targets were met. The feasibility of realizing such benefits is highly individualized; nevertheless, the results of this study support the notion that incremental improvements in glycaemic control, in addition to BMI and hypoglycaemia incidence, can potentially alleviate the burden of Type 1 diabetes on individuals and healthcare systems. Analyses were conducted independent of pharmacological management and service delivery costs; and it is likely that strategies to improve glycaemic control, hypoglycaemia event rate and/or body weight will incur additional costs to the NHS. However, if this expenditure falls below the predictions of NMB generated in this study, such interventions would be deemed cost-effective at a willingness-to-pay threshold of £20 000 per additional QALY gained.

People with Type 1 diabetes who experience poor glucose control, high BMI and a high frequency of hypoglycaemia have the greatest risk of adverse clinical outcomes, health disutility and potential resource use. Indeed, previous estimates have indicated that a modest reduction in HbA<sub>1c</sub> (4 mmol/mol; 0.4%) among people with Type 1 diabetes and HbA<sub>1c</sub> exceeding 75 mmol/mol (9.0%) may save the NHS £447 million over 25 years [7]. Our results additionally illustrate that people with higher baseline HbA<sub>1c</sub> have the potential to achieve relatively greater QALY gains with improved glycaemic control, while reducing weight and avoiding hypoglycaemia in those with high BMI and hypoglycaemia event rates, respectively, was associated with increasing NMB. Improved population-based intervention strategies that target such 'high risk' individuals may therefore

provide the greatest clinical and financial benefits to the healthcare system. However, intervention-specific research is required to assess the feasibility of improving HbA<sub>1c</sub>, BMI and/or hypoglycaemia frequency in those with poorly managed Type 1 diabetes, and the resource and health system implications of realizing these targets in such a challenging population.

Injectable basal insulin therapies for Type 1 diabetes currently include intermediate-acting [neutral protamine Hagedorn (NPH) insulin], long-acting (glargine and detemir analogues) and ultra-long-acting (degludec analogue) agents. Based on evidence that multiple daily insulin injections using long-acting analogues are more efficacious than NPH insulin in Type 1 diabetes, current NICE guidelines recommend twice-daily insulin detemir as the optimal basal treatment regimen [5]. In those who fail to maintain HbA<sub>1c</sub> below 69 mmol/mol (8.5%) or experience disabling hypoglycaemia following multiple daily insulin injections, rapid-acting agents (aspart, glulisine and lispro analogues), delivered using continuous subcutaneous insulin infusion devices, are subsequently advocated [26]. Guideline recommendations are partly founded on cost-utility analyses; however, insulin therapy is highly individualized, and drawing direct comparisons between Type 1 diabetes technologies poses several methodological challenges. For example, insulin titration algorithms and levels of care are heterogeneous across studies and not reflective of routine clinical practice [27]; and the reporting of hypoglycaemic events in clinical trials is often confounded by ill-defined HbA<sub>1c</sub> thresholds and nocturnal periods [28]. Our study illustrates the value of reducing HbA<sub>1c</sub>, hypoglycaemia and body weight irrespective of treatment strategy; therefore, data describing these factors are useful to inform cost-effectiveness analyses for any therapeutic modality in Type 1 diabetes.

In light of this, the present study used an outcome-focused approach to quantify the health economic value of improving HbA<sub>1c</sub>, reducing the frequency of hypoglycaemic events and lowering BMI in people with Type 1 diabetes, regardless of the intervention used to achieve these responses. Our results do not support the adoption of any particular therapeutic strategy, but rather support the notion that modest improvements to Type 1 diabetes management can reduce the clinical and financial burdens associated with developing and managing its long-term health complications. This may be achieved through the use of insulin-based therapies; however, weight gain and hypoglycaemia are common adverse events and barriers to optimal glycaemic control [3 4]. In line with current NICE guidance, promoting lifestyle changes and educational tools, including the dose-adjustment for normal eating programme, will additionally assist in managing Type 1 diabetes and its complications [5]. Emerging adjunctive therapies, that serve to improve glycaemic control whilst reducing insulin-related side effects, are currently under investigation and may provide significant health economic value in the future [29].

Several computer simulation models have been developed to characterize Type 1 diabetes, including the CORE Diabetes Model [30], Sheffield Type 1 Diabetes Policy Model [31] and the Economic Assessment of Glycaemic Control and Long-Term Effects of Diabetes Model [32]. By simulating disease progression over a time horizon longer than that feasible in clinical trials, computer modelling represents an important tool to quantify the long-term health economic outcomes of Type 1 diabetes interventions, and support clinical and reimbursement decision-making [9]. In this study, the value of modest improvements in disease management was quantified using the Cardiff Type 1 Diabetes Model, implemented with risk equations partially derived from DCCT/EDIC study data [10]. Model validity is contingent on the data used to inform its development; therefore, caution is required when extrapolating model predictions beyond the scope of DCCT/EDIC observations. However, several baseline characteristics act as predictive risk factors within the Cardiff Type 1 Diabetes Model (including age, gender, age at diabetes onset, HbA<sub>1c</sub> and weight); and the accuracy and generalizability of its outputs have previously been validated against other new and established Type 1 diabetes models [8]. Subsequently, this model represents a plausible approach to assess the value of improving glycaemic control, hypoglycaemia incidence and body weight in populations not reflective of the DCCT/EDIC study cohort, such as those over 60 years of age, or with a long duration of Type 1 diabetes. Furthermore, the impact of weight, hypoglycaemia and HbA<sub>1c</sub> on predicted QALYs in this study are consistent with published analyses using the Cardiff Type 2 Diabetes Model [25]; and the structure and performance of both Cardiff models have undergone rigorous scrutiny at several Mount Hood Diabetes Challenge Meetings [33–35].

Our study demonstrated the individual impact of HbA<sub>1c</sub>, weight and hypoglycaemia on health economic outcomes in people with Type 1 diabetes, with all other parameters held constant. Clinically, there is a well-recognized relationship between glycaemic control, weight and hypoglycaemia in Type 1 diabetes, and the assessment of each factor in isolation subsequently represents one limitation of this analysis. However, the objective of this study was to demonstrate the independent benefits of reducing HbA<sub>1c</sub>, BMI and hypoglycaemia incidence, and as such, aims to provide clinicians and payers with evidence to quantify the health economic value of improving each factor, both individually and in combination. Although the value of lowering HbA<sub>1c</sub> was evaluated over a lifetime, BMI and frequency of hypoglycaemia were assessed in the short-term due to the duration over which such changes may be observed, and the relative delays in the observed impact of each factor on individual outcomes. Nevertheless, QALY gains, cost savings and/or NMB predicted over one year were

scaled to illustrate the benefits of managing BMI and hypoglycaemia over a lifetime, in an average UK person with Type 1 diabetes. Furthermore, the impact of BMI and hypoglycaemia on the risk of adverse events including falls and fractures, cardiovascular disease and all-cause mortality, and their correlation with other risk factors related to Type 1 diabetes, were not considered [36–38]. Although these modelling assumptions may collectively underestimate the true, long-term value of lowering BMI and hypoglycaemic event incidence in people with Type 1 diabetes, our study nevertheless demonstrates the impact of weight and hypoglycaemia on health-related quality of life, to which a monetary value has been derived.

Due to the UK payer perspective adopted in the study, societal costs were not quantified, and the strength of the national level estimates reported is contingent on the quality of prevalence data available in the UK. This study did not account for changes in population size since 2015, people with Type 1 diabetes below 17 years of age, nor adjust for Quality and Outcomes Framework disease register estimates in Wales. Cumulatively, these factors may underestimate the true size of the UK Type 1 diabetes population, and therefore the true value associated with improved disease management. The UK perspective of this study may limit the relevance of its economic results to other national settings; however, predicted health utility changes are generalizable, and may be used in conjunction with country-specific cost data to inform local decision-making.

In conclusion, this study highlighted the health economic benefits of incremental improvements to HbA<sub>1c</sub>, BMI and hypoglycaemic event frequency in the UK Type 1 diabetes population. Model analyses found that monetized QALY gains were the major driver of NMB associated with improved Type 1 diabetes management, while predicted cost savings were attributed to the avoidance of its long-term health complications. Given the influence of weight and hypoglycaemia on health economic outcomes in Type 1 diabetes, these factors must be key considerations when assessing the cost-effectiveness of health technologies and their efficacy in clinical practice.

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#### Competing interests

P. McEwan, H. Bennett, K. Bolin and M. Evans have served as consultants to and received research funding from AstraZeneca Pharmaceuticals in relation to this study. K. Bergenheim is an employee of AstraZeneca Pharmaceuticals.



### Author contributions

P. McEwan and H. Bennett were involved in the study design, analysis, interpretation of results and writing of the manuscript. K. Bolin and K. Bergenheim were involved in the design, interpretation of results and writing of the manuscript. M. Evans assisted with interpretation of results and editing the manuscript.

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## Supporting Information

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

**Figure S1.** Flow diagram of the Cardiff Type 1 Diabetes Model.

**Figure S2.** Breakdown of discounted per-person costs related to Type 1 diabetes (average UK profile) at different HbA<sub>1c</sub> levels.

**Figure S3.** Breakdown of discounted per-person costs related to Type 1 diabetes (younger UK profile) at different HbA<sub>1c</sub> levels.

**Figure S4.** Discounted per-person and national level costs related to Type 1 diabetes at different HbA<sub>1c</sub> levels.

**Figure S5.** Discounted per-person and national level life-years related to Type 1 diabetes at different HbA<sub>1c</sub> levels.

**Figure S6.** Discounted per-person and national level QALYs related to Type 1 diabetes at different HbA<sub>1c</sub> levels.

**Figure S7.** Discounted value associated with reduced severe hypoglycaemia event (SHE) incidence in people with Type 1 diabetes (net monetary benefit at £20 000 per QALY gained).

**Table S1.** Summary of approaches to model Type 1 diabetes related complications in the Cardiff Type 1 Diabetes Model.

**Table S2.** Costs applied within the Cardiff Type 1 Diabetes Model.

**Table S3.** Derivation of minor and major amputation costs.

**Table S4.** Utilities applied within the Cardiff Type 1 Diabetes Model.