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Estimation of global insulin utilization for type 2 diabetes mellitus, 2018 to 2030: A microsimulation analysis

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Abstract

Background:

The amount of insulin needed to effectively treat T2DM effectively worldwide is unknown. It also remains unclear how alternative treatment algorithms would affect insulin use and T2DM complication rates, given insulin access.

Methods:

We developed a microsimulation of T2DM burden from 2018 to 2030 across 221 countries using data from the International Diabetes Federation (IDF) for prevalence projections and from fourteen cohort studies representing >60% of the global T2DM population for haemoglobin A1c (A1c), treatment, and weight data. We estimated the number of people with T2DM expected to use insulin, international units (IU) required, and disability adjusted life years (DALYs) gained per year under alternative treatment algorithms targeting A1c from 6.5% to 8%, lower microvascular risk, or higher A1c for those ≥75 years old.

Results:

The number of people with T2DM worldwide was estimated to increase from 405.6 million in 2018 to 510.8 million in 2030. Insulin use would increase from 516.1 million 1000IU vials (95% CI: 409.0, 658.6 million) to 633.7 million per year (95% CI: 500.5, 806.7 million) from 2018 to 2030. Without improved insulin access, 7.4% (95% CI: 5.8%, 9.4%) of people with T2DM in 2030 would use insulin, increasing to 15.5% (95% CI: 12.0% to 20.3%) if insulin were widely accessible and prescribed to achieve a A1c≤7% (53 mmol/mol). If A1c≤7% was universally achieved, insulin would avert 331,000 DALYs per year by 2030 (95% CI: 256,600, 437,100). DALYs averted would increase 14.9% with access to newer oral glycemic agents. DALYS averted would increase by 44.2% if targeting A1c of 8% (64 mmol/mol) among people ≥75 years old, due to less hypoglycaemia.

Discussion:

The insulin required to treat T2DM is expected to increase by over 20% from 2018 to 2030, and may avert more DALYs if A1c targets are higher for older adults.

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Introduction

The prevalence of diabetes worldwide has nearly quadrupled since 1980.[1] Adult diabetes prevalence (both type 1 and type 2) reached 425 million people in 2017 (~ 1 in 11 adults).[2] Around 12% of overall global healthcare expenditures are spent on diabetes treatment.[2]

Insulin is necessary for all people with type 1 diabetes mellitus (T1DM) and a subset of patients with T2DM to avoid morbidity and mortality from ketoacidosis or hyperosmolar hyperglycaemic states, and to reduce long-term microvascular complications. The use of insulin for T2DM is dependent on treatment algorithms, particularly the target level of haemoglobin A1c (A1c).[3] Finding an optimal target that maximizes disability-adjusted life years (DALYs) gained, while minimizing disutility from insulin therapy (e.g., from hypoglycaemia) remains an important goal.[4] Insulin treatment is relatively costly,[5] with most insulin produced by three major manufacturers.[2] Hence, a prospective estimation of global insulin requirements and the DALYs averted by improving access may help plan what resources are required to deliver insulin. Complicating such estimations are the increasing numbers of people with T2DM, increasing survival of people with T2DM (which may increase insulin requirements), and increasing availability of newer oral diabetes treatments.

Here, we sought to estimate global insulin utilization for T2DM by country and year, worldwide, from 2018 to 2030 and the potential impacts of altering insulin treatment algorithms on insulin use and diabetes-related burden of disease.

Methods

A microsimulation (**Figure 1**) was constructed to simulate the population of adults with T2DM within each of 221 countries and territories worldwide to estimate the number of adults utilizing insulin, and to estimate the international units (IU) of insulin used under alternative treatment algorithms. IDF estimates for T2DM prevalence were multiplied by IDF estimates of the proportion of people diagnosed and then by the number estimated to need insulin (**Appendix Table 1**). The proportion estimated to need insulin was calculated in two ways, detailed below: (i) an approach using current estimates of insulin treatment from cohort studies; and (ii) an approach based on theoretical comprehensive insulin access (**Table 1**). In both cases, we used weight-based dosing and varied the A1c treatment target, then used the RECODe equations[6,7] to estimate the DALYs averted from microvascular complications by insulin treatment, and a new risk equation to estimate the DALYs caused by hypoglycaemia events requiring medical attention (**Appendix Table 2**).

Type 2 diabetes prevalence estimation

Diabetes prevalence (both diagnosed and undiagnosed) among adults in each country and year in the simulation was taken from projections made by the International Diabetes Federation (IDF) for the period 2018-2030.[2] The IDF prevalence estimates were based on a regression model using data from a systematic review of literature for the individual country or nearest neighbourhood; the reviewed data were used by the IDF to generate smoothed sex- and age-specific prevalence estimates for adults 20–79 years old, which were projected by the IDF into the future using UN population projections and assuming that the age- and sex-specific prevalence of diabetes would increase linearly with urbanization.[8] This conservative assumption produces a lower-bound estimate of future diabetes prevalence. Confidence intervals were constructed by the IDF by bootstrapping across study prevalence estimates in the systematic review, for which one study was removed from the data pool at a time. The prevalence estimates were for overall diabetes; based on a recent systematic review and projections, we estimated that 96.5% of total diabetes among adults could be attributed to T2DM[9] (varied in uncertainty

analyses to the range 92% to 99%). The estimate was based on a modelling exercise with extrapolation of ratios of incidence of T1DM in children to adults from available data applied to country-specific childhood T1DM incidence estimates.[9]

Insulin needs estimate

We undertook two parallel approaches to estimating the number of people utilizing insulin within each simulated country: (i) an approach accounting for demographic change but unchanged insulin access, which applied estimated proportions of people with T2DM currently treated with insulin to the estimated numbers of people with diagnosed T2DM in the future, and (ii) an approach accounting for demographic change and comprehensive insulin access, which estimated how many more people would be treated if all those estimated to need treatment with insulin under different treatment scenarios were provided with insulin, following appropriate oral glycaemic therapy, and conditional on a given treatment target for glycaemic control.

In the approach accounting for demographic change alone (with unchanged insulin treatment rates; **Figure 1A**), we multiplied the absolute number of people projected to have diagnosed T2DM in each year over the period 2018-2030 by the proportion of those people who are anticipated to be treated with insulin given current estimates of the proportion of people with T2DM who receive insulin treatment in each country.[2,10] The number of units of insulin required among those treated with insulin followed current guidelines based on weight, using the distribution of body weight among those diagnosed with T2DM and treated with insulin from regional surveys (**Table 1**). The estimates of body weight-based dosing assumed that 75% of those treated with insulin require only basal insulin at a dosage of 0.4 IU/kg/day, while the remaining individuals would require multiple dose injection therapy totalling 0.6 IU/kg/day.[11,12] In a sensitivity analysis, we tested alternative assumptions, using 70% and 80% for proportions of people treated with insulin who require only basal insulin.

In the approach accounting for both demographic change and improved insulin access (**Figure 1B**), we estimated the additional insulin required for the population not currently having access. First, we estimated the proportion of people with T2DM not currently receiving insulin from the geographically-closest regional diabetes survey for

each simulated country population, concatenating multiple surveys by taking an average if more than one was available (after accounting for survey sample weights from each) for a given country and bootstrapping across all available estimates when a close regional survey was unavailable. Details of each survey are provided in the **Table 1**, with comprehensive citations in the Appendix. Missing data—specifically, missing A1c values, body weight values, and indicators of whether or not a person was treated with insulin—were imputed with chained equations assuming data were missing at random,[13] followed by repeated Monte Carlo sampling from uncertainty distributions from each input parameter performed to estimate uncertainty.

Among those not yet on insulin, we estimated whether or not insulin would be necessary after maximum treatment with oral glycaemic agents to achieve a given target A1c level (detailed below). Following current World Health Organization (WHO) guidelines and the WHO Essential Medicines List,[14,15] titration was simulated up from 500 mg daily of metformin to 1000 mg twice daily of metformin, then if needed, further addition of 80 mg daily of gliclazide (a sulfonylurea), which could be titrated up to 160 mg twice daily. We Monte Carlo sampled from the distributions of typical A1c reductions for the full dose of each drug (uniform distributions) from a prior meta-analysis,[16] with proportionate linear values for doses below the maximum, taking into account existing dosage levels among those already on oral agents. Those people still above the target A1c after maximum titration of oral agents were assumed to achieve the target A1c only by starting insulin (after discontinuing the sulfonylurea) and setting their insulin use based on their weight (sampling from the weight estimates from the closest regional survey), estimating that 75% of those treated with insulin require only basal insulin at a dosage of 0.4 IU/kg/day (varied from 70% to 80% in sensitivity analyses), while the remaining individuals would require multiple dose injection therapy totalling 0.6 IU/kg/day.[11,12]Among the population already receiving insulin, we estimated total daily insulin needed using these same estimates of total units per kilogram required per day.

Finally, we conducted a sensitivity analysis to estimate how much less insulin may be required if newer agents were more widely available (e.g., GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors) and combined with metformin instead of combining

a sulfonylurea with metformin; we used the A1c reductions estimated in a recent meta-analysis to estimate the A1c effects of these newer agents.[17]

Treatment targets

For the scenario accounting for both demographic change and improved insulin access, we simulated five different treatment targets. Recognizing that some facilities lack A1c testing, we converted to the nearest average fasting plasma glucose (AFPG) target level.[16] We used the 2018 American Diabetes Association treatment guidelines as a primary clinical reference.[18]

First, we set the target A1c to 7.0% (53 mmol/mol) for all diagnosed and treated persons (AFPG = 8.0 mmol/L).

Second, we reduced the target A1c to a low of 6.5% (48 mmol/mol; AFPG = 7.5 mmol/L).

Third, we increased the target A1c to a high of 8.0% (64 mmol/mol; AFPG = 9.2 mmol/L).

Fourth, we simulated an age-based target, with persons <75 years old given an A1c target of 7% and those ≥75 years old given a target A1c of 8%.[19,20]

Fifth, we simulated a risk-based target, with persons having ≥5% risk over 10 years of composite microvascular complications (renal failure/end-stage renal disease, severe vision loss <20/200 on a Snellen chart, or loss of pressure sensation by monofilament testing) estimated from the RECODe equations[6,7] treated with insulin to an A1c of 7% or the A1c level that achieved an estimated risk ≤5% (whichever A1c was higher). The threshold was based on prior experiments for risk-based therapy.[21]

Outcome

The primary outcome metric we estimated was the number of people with T2DM estimated to use insulin for each year in each country and each world region (using United Nations categorizations of countries into regions).

The secondary outcome metric was the number of 10mL vials of U100 insulin (i.e., 1,000IU) used per year in the total population of each country and each world region for each year from 2018 to 2030.

For the scenario accounting for both demographic change and improved insulin access, the additional outcome metric was the DALYs averted by achieving the insulin treatment levels simulated. We computed the DALYs averted from each of three microvascular complications (renal failure/end-stage renal disease, severe vision loss <20/200 on a Snellen chart, or loss of pressure sensation by monofilament testing) using the RECODe equations for baseline risk for each complication re-calibrated to global DALY estimates from the Global Burden of Disease Project,[6,7,22] the relative risk reduction conditional on A1c reduction for each complication from a prior systematic review,[23] and the disability weights provided by a prior international survey (**Appendix Table 3**).[24] We also computed the increase in DALYs due to: (i) the disutility of daily finger stick glucose monitoring; (ii) disutility from injection therapy, and (iii) disutility due to hypoglycaemia requiring hospitalization, emergency care, or other external medical assistance due to severe cognitive impairment, based on a risk equation to estimate the frequency of hypoglycaemia (**Appendix Table 3**). The hypoglycaemia risk equation was based on individual participant data from the ACCORD trial, and was a multivariable equation incorporating demographics, insulin units used, and related treatment covariates (**Appendix Table 2**). DALYs were computed at a standard 3% annual discount rate, integrated over the full life-course of all simulated individuals.

Outcomes were computed up to the year 2030, and additionally for the midpoint year of analysis (2024) for comparison.

All estimates were performed in *R* (v. 3.4, R Foundation for Statistical Computing, Vienna), using the code deposited at https://github.com/sanjaybasu/insulinestimates for reproducibility.

Results

First, we simulated the approach accounting for demographic change alone (with unchanged insulin access. The number of people projected to have T2DM over the period 2018-2030 based on IDF estimates[2] were 405.6 million in 2018 (95% CI: 315.3, 533.7 million) and 510.8 million in 2030 (95% CI: 395.9, 674.3 million). The estimated number of people with T2DM in each country was typically proportional to population size, with the largest absolute number in 2018 residing in China (111.9 million; 95% CI: 97.1, 146.3 million; 7.9% prevalence) and India (72.5 million; 95% CI: 52.8, 91.9 million; 5.4% prevalence), followed by the United States, which had a higher prevalence (29.3 million; 95% CI: 26.7, 31.7 million; 9.0% prevalence). Projections for the year 2030 by the IDF[2] were proportional to anticipated population growth, aging, and urbanization in less developed countries, with the largest absolute numbers of people with T2DM projected to be in China (130.2 million; 95% CI: 113.4, 163.3 million; 9.0% prevalence), India (98.0 million; 95% CI: 73.7, 122.9 million; 6.5% prevalence), then the United States (31.8 million; 95% CI: 28.7, 34.5 million; 9.0% prevalence). When we combined data on the number of people with T2DM with the proportions diagnosed and treated with insulin,[2,10] we estimated that insulin utilization would increase from 516.1 million 1000-unit vials (95% CI: 409.0, 658.6 million) to 633.7 million vials per year (95% CI: 500.5, 806.7 million) between 2018 and 2030. The number of vials utilized decreased or increased by 2% if the proportion of people treated with basal insulin only decreased from 75% to 70% or increased to 80%. The absolute number of people estimated to use insulin and the number of U100 insulin vials required would be lowest in the Oceanic region (4.2 million vials in 2030) and highest in Asia (321.6 million vials in 2030) due to population size (**Table 2**). In relative terms, the proportion of people with diagnosed T2DM utilizing insulin would be lowest in the African region due to low medication access and low prevalence of T2DM (1.8% of people with T2DM treated with insulin in 2030) and highest in the Americas region in the context of greater insulin use and higher T2DM prevalence (13.6% of people with T2DM treated with insulin in 2030).

Second, we simulated both demographic change and improved insulin access. We estimated the proportion of people diagnosed with T2DM who could receive insulin after maximum oral therapy, if insulin were widely available and if providers aimed to achieve

a target A1c of 7% (**Appendix Figure 1**). The distribution of A1c among those with diagnosed T2DM (**Table 1**) had a global mean of 9.1% and 95% centiles extending from 5.1% to 15.1%. The proportion of people with T2DM who we anticipated to use insulin increased from 7.4% (95% CI: 5.8%, 9.4%) to 15.5% (95% CI: 12.0% to 20.3%), on average, when changing from the scenario assuming persistence of current insulin access levels, to the scenario assuming comprehensive insulin access (**Table 2**). The greatest relative increase in number of people anticipated to use insulin between the two scenarios would be in the African region (7.1-fold increase from 718,800 if insulin access were at current levels to 5,119,900 under universal access), while the greatest absolute increase would be in the Asian region (+26.5 million people utilizing insulin from 21.1 million if insulin access were at current levels to 47.6 million under universal access). The ratio of actual utilization (given current insulin access levels) to estimated utilization (given comprehensive insulin access) varied from 0.14 in Africa to 0.71 in the Americas and was 0.48 worldwide.

We next estimated the net number of DALYs averted as a composite measure, accounting for the DALYs averted with comprehensive insulin access by preventing microvascular complications and subtracting the DALYs caused by insulin-related hypoglycemia and treatment-related inconvenience. When aiming for a treatment target of A1c of 7%, we estimated that comprehensive access to insulin would avert 263,000 DALYs in the year 2018, increasing to 331,000 in the year 2030, with 65% of the DALYs averted in Asia alone (**Table 2**). On average, individuals reduced their composite lifetime risk of microvascular complications (renal failure, severe vision loss, and pressure sensation loss) from 17.4% to 15.9%, but increased their average lifetime risk of hypoglycaemia requiring medical attention from 11.9% to 20.0%. Nevertheless, due to the greater disutility of microvascular complications than of hypoglycaemia, overall net DALYs were averted through insulin treatment over the life-course, after accounting for the delayed onset of microvascular disease and a 3% annual discount rate on disutility over time.

Changing the target A1c produced a proportional change in the number of people estimated to use insulin, and in the absolute amount of insulin estimated to be required, though with overlapping confidence intervals based on Monte Carlo sampling (**Figure 2**).

A strict glycaemic control target of A1c = 6.5% increased the global number of people required to be on insulin, and the amount of insulin required, by 38.9% as compared to targeting A1c = 7%; conversely, a more liberal target of A1c = 8% reduced the global number of people required to be on insulin, and the amount of insulin required, by 45.0%.

The overall net DALYs averted was related in a complex way to treatment targets (**Figure 2C**). In particular, targets of A1c = 6.5% or 7% had lower numbers of net DALYs averted than a target of 8%, as the lower levels of targeting increased DALYs caused by hypoglycaemia (see **Figure 2D**). The highest net DALYs averted was when targeting A1c = 7% for people <75 years old and 8% for people ≥75 years old, because this target helped avoid hypoglycaemic events that were concentrated primarily among older adults (**Figure 2C**). This age-stratified cut-off had 44.2% higher net DALYs averted than the universal target of 7%. Additional analyses in which the target A1c was risk-based (target of ≤5% for composite microvascular risk) was similar to the target A1c = 8% scenario (**Figure 2C**). Net DALYS averted for the midpoint year of 2024 were lower (by ~10%) than for the final year 2030, because of lower rates of diagnosis and lower total numbers of people with T2DM in 2024 than in 2030 (**Appendix Figure 2**).

Finally, we conducted sensitivity analyses to estimate how much less insulin may be used if three types of newer agents were more widely available (GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors) and combined with metformin instead of combining a sulfonylurea with metformin. The absolute number of people requiring insulin, and the units of insulin, did not change meaningfully given the non-significant difference from sulfonylurea in A1c reduction.[17] However, the rate of hypoglycaemia was reduced due to avoidance of sulfonylurea treatment, and this increased the absolute net DALYs averted by 14.9%. The relative amount of net DALYs averted through each treatment target were not affected.

Discussion

We estimated global insulin utilization for T2DM by country and year, worldwide, from 2018 to 2030. We observed several major findings in the course of our estimation. First, we observed that current levels of insulin access are not only inadequate relative to projected need, but are disproportionately inadequate in the African, Asian, and Oceanic regions. The regions projected to increase insulin utilization most if access were improved were the African region in relative terms, and the Asian region in absolute terms. The finding that Africa has the largest relative unmet insulin need also highlights the importance of availability and affordability improvements to the insulin market. Asia would similarly be expected to use the most insulin whether or not insulin access improved. Second, we observed that the DALYs averted through insulin therapy would be highest if targeting A1c levels of 7% for younger adults (<75 years old) and 8% for those of older age, to balance the risk of hypoglycaemia against the benefit of longer-term reduced microvascular disease (though with overlapping confidence intervals between the alternative approaches simulated). The incremental reduction in microvascular risk by further lowering the A1c target was not outweighed by the increase in serious hypoglycaemia risk. We found that—for the overall population as a whole—using more liberal target A1c of 8% used half as much insulin with only a 20% decline in DALYs saved. In comparison, intensive treatment to a goal A1c of 6.5% dramatically increased insulin use while increasing diabetes-related harms. Finally, we found that such insulin needs would be unlikely to be affected by expanded access to newer oral diabetes drugs, as such medicines are generally not more potent than existing drugs in reducing A1c;[17] however, such drugs may substantially lower the risk of hypoglycaemia and thereby improve DALYs averted through therapy, though their cost may preclude their use in many situations.

Several key assumptions should be noted. First, the projections of T2DM prevalence from the IDF are based on population projections and the existing relationships between age, sex, urbanization and diabetes prevalence. As dietary and physical activity environments can change in both obesogenic and disease-reducing ways, the IDF projections may be either optimistic or pessimistic in unpredictable directions. Second, the RECODE equations we used were previously derived and

validated from U.S. samples, though we recalibrated the baseline hazard rates of events here to match Global Burden of Disease estimates.[6,7,22] The use of these equations assumes that the relationship between underlying demographics (age, sex), biomarkers (blood pressure, A1c) and complications is consistent across countries, which may neglect some ethnic variations. Third, our estimates of hypoglycaemia risk are based on a logistic regression (incorporating risk factors such as age and insulin dosage) internally cross-validated in the ACCORD study sample, but not externally validated in another study sample. Fourth, we used the distributions of body weight, A1c and insulin utilization from available cohort studies in the absence of comprehensive longitudinal data of high quality across all countries. Additionally, we lacked sufficient data to estimate the degree to which different oral antidiabetic agents have different durability in maintaining A1c reductions over time.[25–27]

Future research into the issues raised here should consider how key barriers to availability and accessibility of diagnosis and therapy in the African region in particular may be overcome,[28] and how Ministries of Health can best prepare for the anticipated large increase in insulin utilization needs in the coming years.

Prior to such research, our study reveals that insulin utilization is likely to rise particularly in Asia, and that targeting a moderate threshold for control—potentially based in part on age as a proxy for life expectancy and co-morbidities—may help balance the risks of insulin therapy with longer-term microvascular benefit.

Putting research in context

Evidence before this study

We conducted a PubMed search for articles with the keywords “insulin utilization” and “type 2 diabetes” from 2008 through August 2018. We found seven prior papers on the topic. Three papers reviewed the insulin dosing needs and effectiveness of insulin for people with T2DM when using basal insulin with or without other antidiabetic medications. Two articles examined the budgetary and cost impact of basal insulin utilization in the United States population. The remaining two papers estimated the low rates of access to insulin and challenges to access in East and South Asia.

Added value of this study

By comparison to the existing literature, our current study offers a direct estimate of the anticipated global use of insulin among persons with T2DM, using data from large representative cohort studies, and directly compares the implications of alternative treatment targets for reducing the burden of T2DM complications.

Implications of all the available evidence

The overall evidence suggests that the number of people requiring insulin and the amount of insulin required to treat T2DM is expected to increase and require substantial improvements to access in low- and middle-income countries.

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Contributors

SB, JSY and DB contributed to the study design, data collection, data analysis, and writing. SK, JD, SHW, KP, and JBS contributed to the literature search, study design, data interpretation and writing.

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Tables and Figures

Table 1: Input cohort data for estimating reduction in haemoglobin A1c necessary to achieve treatment targets, and baseline proportion of people with T2DM treated with insulin, among those diagnosed with T2DM. References for each cohort dataset are provided in the Appendix.

Dataset	N with diabetes by prior diagnosis or labs	Years	A1c, mean (95% centiles), %	% treated with insulin, among those diagnosed	Weight, mean (95% centiles), kg.
U.S. National Health and Nutrition Examination Survey	1,441	2009-2014	7.4 (5.2, 12.2)	22.2	89.5 (53.7, 148.2)
U.S. National Institutes of Health Global Health Centers of Excellence surveys from South Africa	1,842	2012	9.1 (5.4, 14.6)	-	83.0 (51.0, 125.0)
U.S. National Institutes of Health Global Health Centers of Excellence surveys from India	1,605	2015	8.7 (5.5, 13.4)	-	67.9 (43.0, 98.2)
South Africa National Health and Nutrition Examination Survey	747	2012	7.7 (5.4, 12.8)	4.4	78.0 (44.0, 116.6)
U.K. National Health Service National Diabetes Audit	16,585	2016-2017	7.3 (5.1, 12.1)	12.5	80.3 (48.1, 133.0)
Indian Jaipur Diabetes Registry	8,699	2014	9.0 (6.3, 14.8)	9.1	60.4 (30.6, 101.2)
Swedish National Diabetes Register	17,827	2016	8.4 (6.1, 10.1)	11.7	75.6 (48.5, 102.7)
Danish Adult Diabetes Registry	11,205	2014-2015	7.7 (5.4, 12.7)	15.8	70.9 (33.9, 123.5)
Turkish Nationwide survey of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus	4,672	2017	7.5 (5.3, 12.4)	9.6	84.7 (52.2, 117.2)
China Health and Nutrition Study	1,422	1999-2015	7.8 (5.2, 12.7)	18.3	65.5 (45.2, 90.0)
DiabCare study of the Philippines	770	2008	8.0 (5.6, 13.2)	25.0	58.5 (36.2, 85.9)
Japan National Health and Nutrition Survey	1,434	2016	7.2 (5.0, 11.8)	7.0	59.5 (32.2, 90.4)
Korea National Health and Nutrition Examination Survey	1,341	2010-2012	8.2 (5.7, 13.5)	3.0	66.0 (38.5, 93.7)
Joint Asia Diabetes Evaluation	28,111	2007-	7.7 (5.4,	21.0	76.8 (58.4,

Registry		2012	12.7)		90.0)

Table 2:

Outcome measures by world region, when the treatment target was set to haemoglobin A1c equal to 7%. T2DM: type 2 diabetes mellitus; CI: confidence interval.

Metric	**Region**	**Demographic change only**		**Demographic change and comprehensive access to insulin**	
		Outcome, 2018 (95% CI)	Outcome, 2030 (95% CI)	Outcome, 2018 (95% CI)	Outcome, 2030 (95% CI)
People with T2DM utilizing insulin, No. (95% CI), *% of people with T2DM*	Africa	502,647 (288,690, 798,943), *1.8%*	718,802 (421,154, 1,226,177), *1.8%*	3,580,238 (2,056,273, 5,690,693), *12.7%*	5,119,862 (2,999,782, 8,733,785), *12.5%*
	Americas	9,695,648 (7,665,389, 11,537,007), *13.7%*	12,235,005 (9,630,417, 14,632,677), *13.6%*	13,687,550 (10,821,390, 16,287,035), *19.3%*	17,272,413 (13,595,462, 20,657,257), *19.2%*
	Asia	16,684,889 (13,361,708, 21,796,053), *6.4%*	21,093,158 (16,923,703, 27,319,674), *6.4%*	37,619,272 (30,126,523, 49,143,366), *14.4%*	47,558,556 (38,157,723, 61,597,425), *14.3%*
	Europe	3,162,812 (2,385,353, 4,469,907), *7.5%*	3,372,393 (2,469,168, 4,761,120), *7.5%*	7,993,805 (6,028,827, 11,297,404), *19.0%*	8,523,506 (6,240,663, 12,033,426), *18.9%*
	Oceania	183,439 (123,104, 240,038), *7.8%*	218,324 (155,957, 282,674), *7.7%*	435,532 (292,280, 569,911), *18.5%*	518,356 (370,282, 671,140), *18.3%*
	Global Total	30,229,435 (23,824,244, 38,841,948), *7.5%*	37,637,682 (29,600,399, 48,222,322), *7.4%*	63,316,397 (49,325,293, 82,988,409), *15.6%*	78,992,693 (61,363,912, 103,693,033), *15.5%*
U100 insulin vials (1000 units each) used per year, No. (95% CI)	Africa	8,624,782 (4,912,881, 13,373,521)	12,305,853 (7,090,162, 20,337,229)	61,432,374 (34,993,342, 95,256,567)	87,651,814 (50,501,623, 144,857,489)
	Americas	185,734,884 (148,644,626, 218,458,562)	229,389,030 (182,349,618, 271,640,903)	262,205,836 (209,844,740, 308,402,539)	323,833,311 (257,426,785, 383,481,167)
	Asia	255,959,077 (206,143,552, 334,166,375)	321,604,383 (259,506,395, 415,709,828)	577,108,650 (464,790,030, 753,441,950)	725,118,538 (585,106,758, 937,297,246)
	Europe	62,218,758 (46,900,997, 88,025,335)	66,228,854 (48,525,714, 93,594,458)	157,253,927 (118,539,269, 222,478,398)	167,389,188 (122,645,636, 236,554,000)
	Oceania	3,517,167 (2,388,704, 4,588,735)	4,170,065 (2,989,682, 5,383,238)	8,350,661 (5,671,400, 10,894,840)	9,900,809 (7,098,276, 12,781,196)

	Global Total	516,054,668 (408,990,760, 658,612,528)	633,698,185 (500,461,571, 806,665,656)	1,066,351,448 (833,838,781, 1,390,474,294)	1,313,893,660 (1,022,779,078, 1,714,971,098)
DALYs averted by insulin treatment, No. (95% CI)	Africa	-	-	18,321 (10,517, 29,451)	26,585 (15,532, 45,613)
	Americas	-	-	46,019 (36,477, 54,594)	58,216 (45,933, 69,554)
	Asia	-	-	169,807 (135,827, 221,226)	215,179 (172,646, 277,939)
	Europe	-	-	27,208 (20,524, 38,645)	29,282 (21,192, 41,539)
	Oceania	-	-	1,529 (999, 2,026)	1,839 (1,298, 2,408)
	Global Total			262,884 (204,344, 345,942)	331,101 (256,601, 437,053)

Figure 1: Study flow diagram. Each cell describes a key input data (with source parenthetically) or outcome estimate (with estimation approach parenthetically). Two approaches were used to estimate the outcomes: (i) an approach incorporating demographic change only (left side of dashed line) and (ii) an approach incorporating both demographic change and improved insulin access (right side of dashed line). Legend: T2DM: type 2 diabetes mellitus. IDF: International Diabetes Federation.

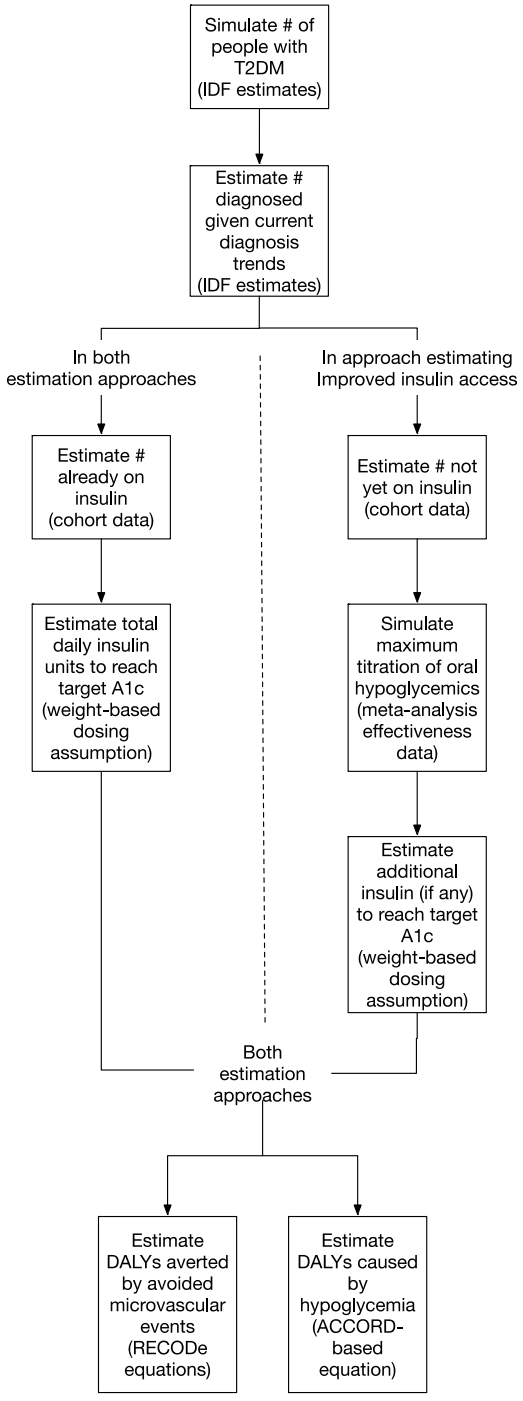
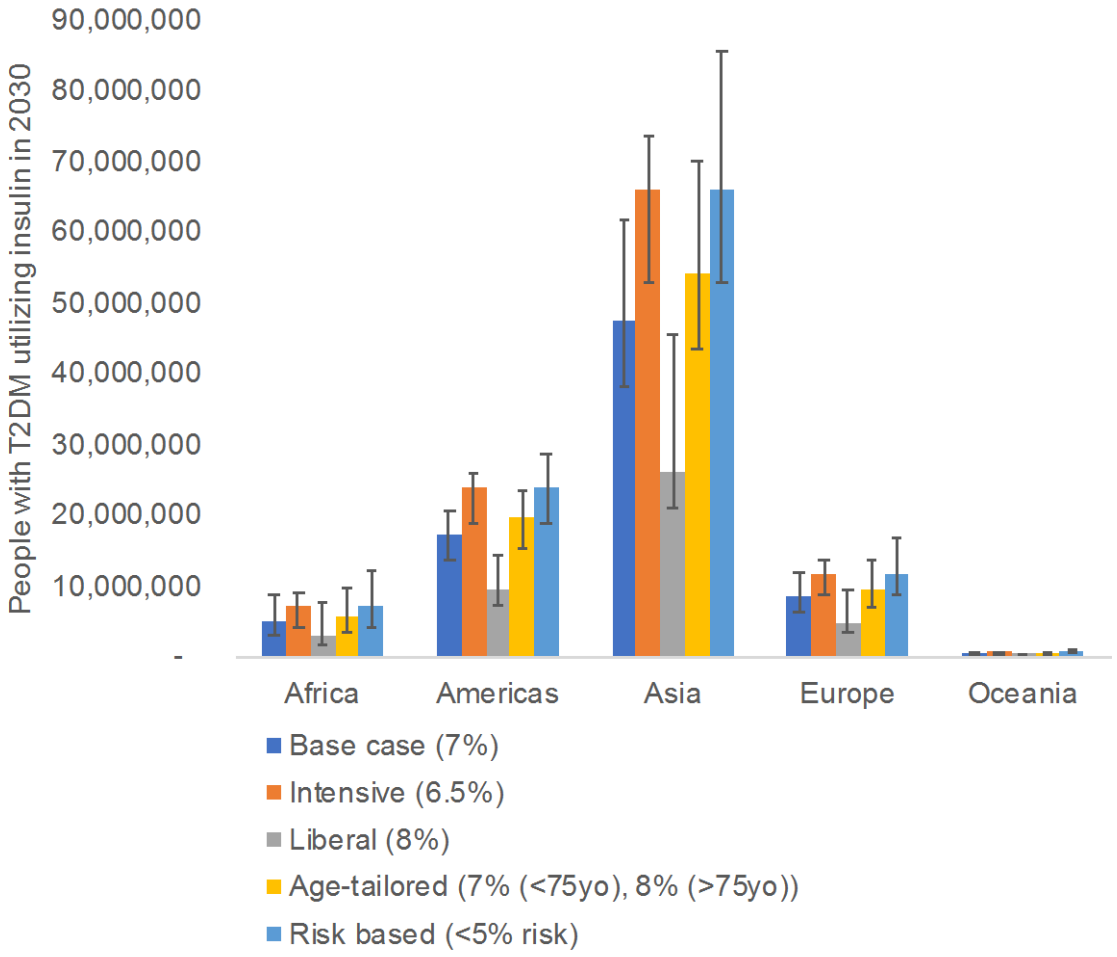
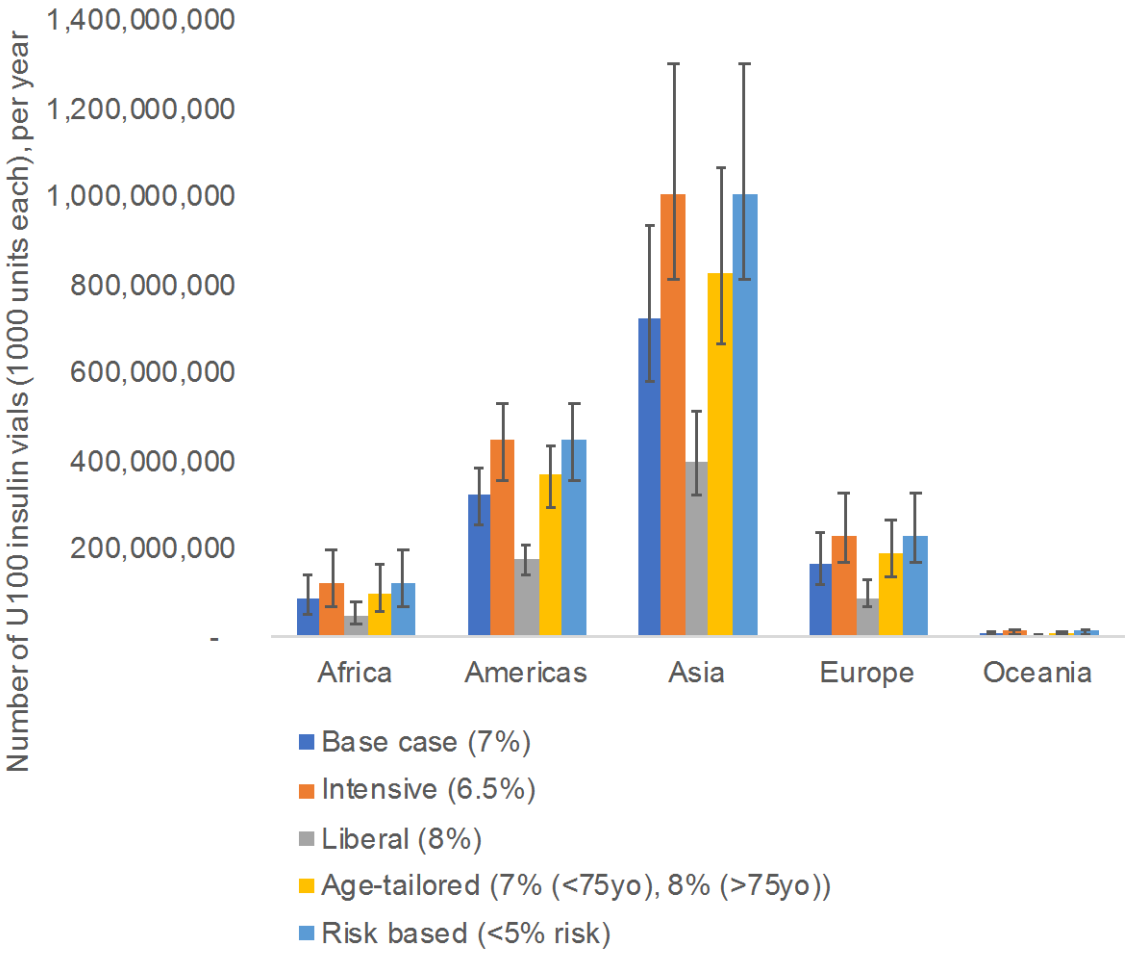


Figure 2: Variations in insulin treatment and DALYs averted under alternative treatment targets in the year 2030. All estimates are made with the approach defined in the Methods section that accounted for both demographic change and increased insulin access. The height of the bars reflects the mean, and error bars reflect 95% confidence intervals. Legend: Base case: target A1c of 7.0% (53 mmol/mol) for all diagnosed and treated persons (AFPG = 8.0 mmol/L); intensive: target A1c of 6.5% (48 mmol/mol; AFPG = 7.5 mmol/L); liberal: target A1c of 8.0% (64 mmol/mol; AFPG = 9.2 mmol/L); age-tailored: with persons <75 years old target A1c of 7% and for those ≥75 years old target A1c of 8%;[19,20] risk-based: with persons having ≥5% risk over 10 years of composite microvascular complications (renal failure/end-stage renal disease, severe vision loss <20/200 on a Snellen chart, or loss of pressure sensation by monofilament testing) estimated from the RECODe equations[6,7] target A1c of 7% or the A1c level that achieved an estimated risk ≤5% (whichever A1c was higher).[21] Numerical values corresponding to these figures are provided in Appendix Table 4.

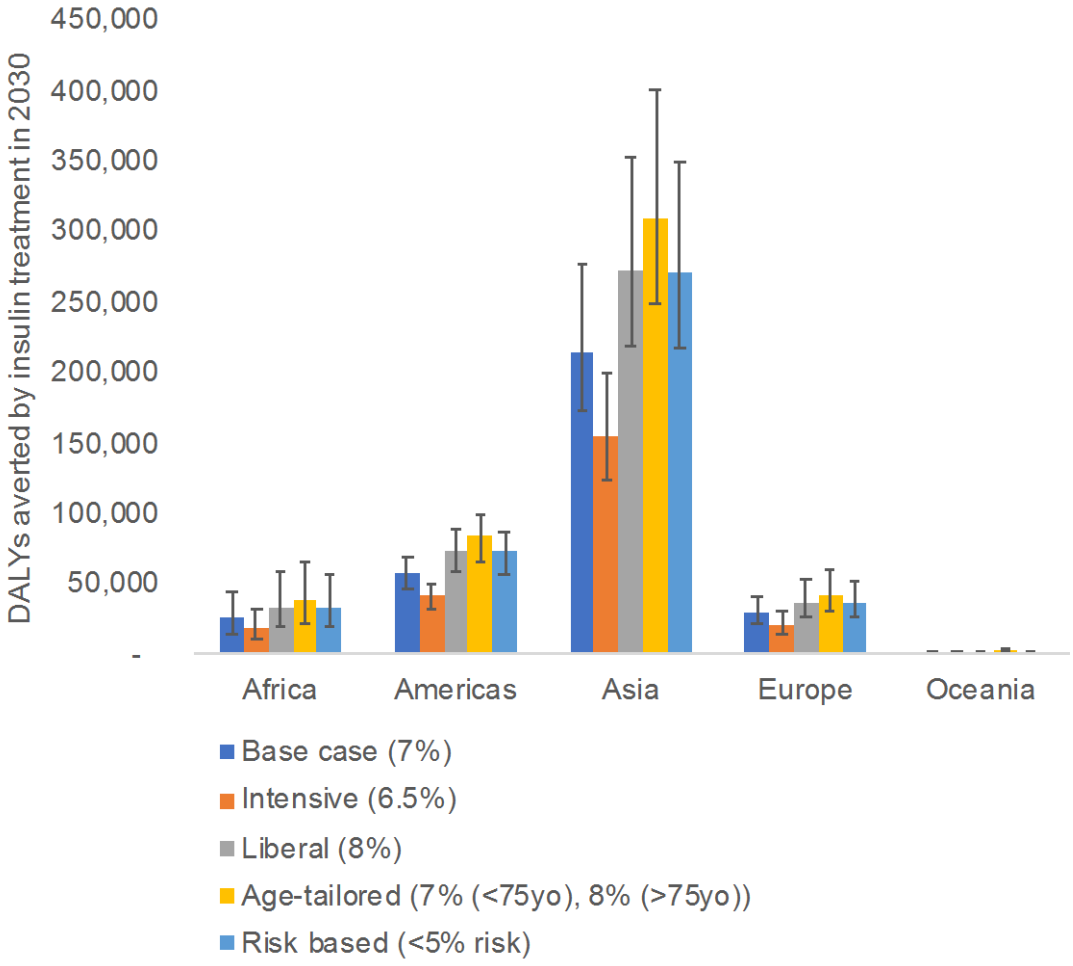
(A) People with type 2 diabetes mellitus estimated to use insulin



(B) Number of U100 insulin vials (1000 units each) used per year



(C) Net DALYs averted by insulin treatment



(D) Ratio of DALYS averted by prevention of microvascular events with insulin treatment, versus from DALYs induced by insulin treatment (including hypoglycaemia requiring medication attention, daily finger sticks, and injections), worldwide.