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

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 Registry	28,111	2007-2012	7.7 (5.4, 12.7)	21.0	76.8 (58.4, 90.0)

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)
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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 Registry	28,111	2007-2012	7.7 (5.4, 12.7)	21.0	76.8 (58.4, 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.

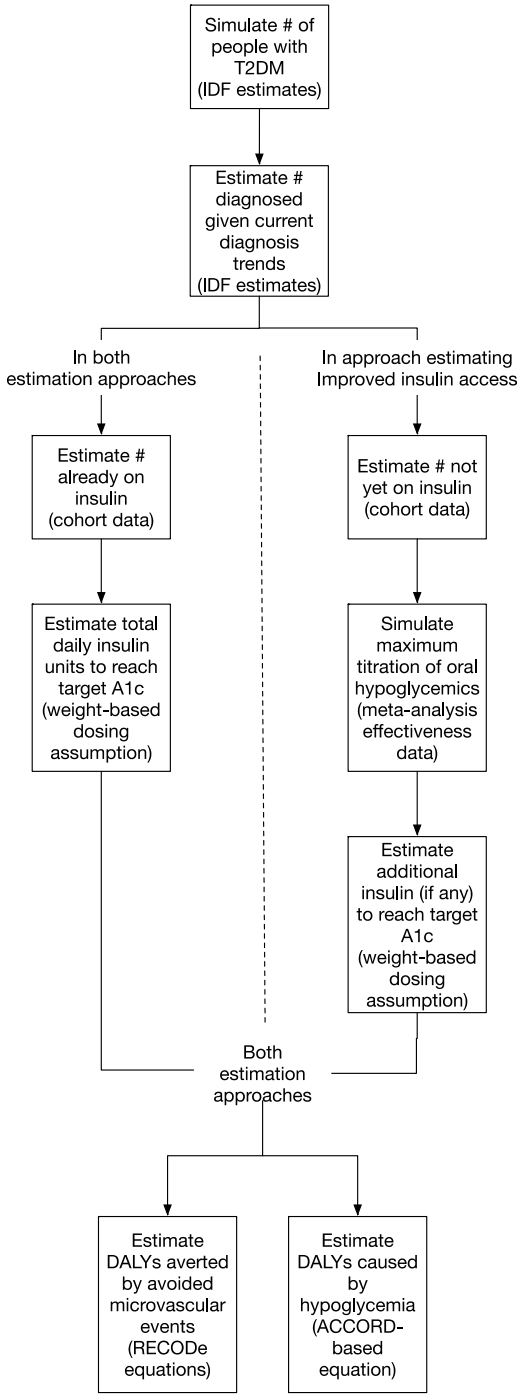
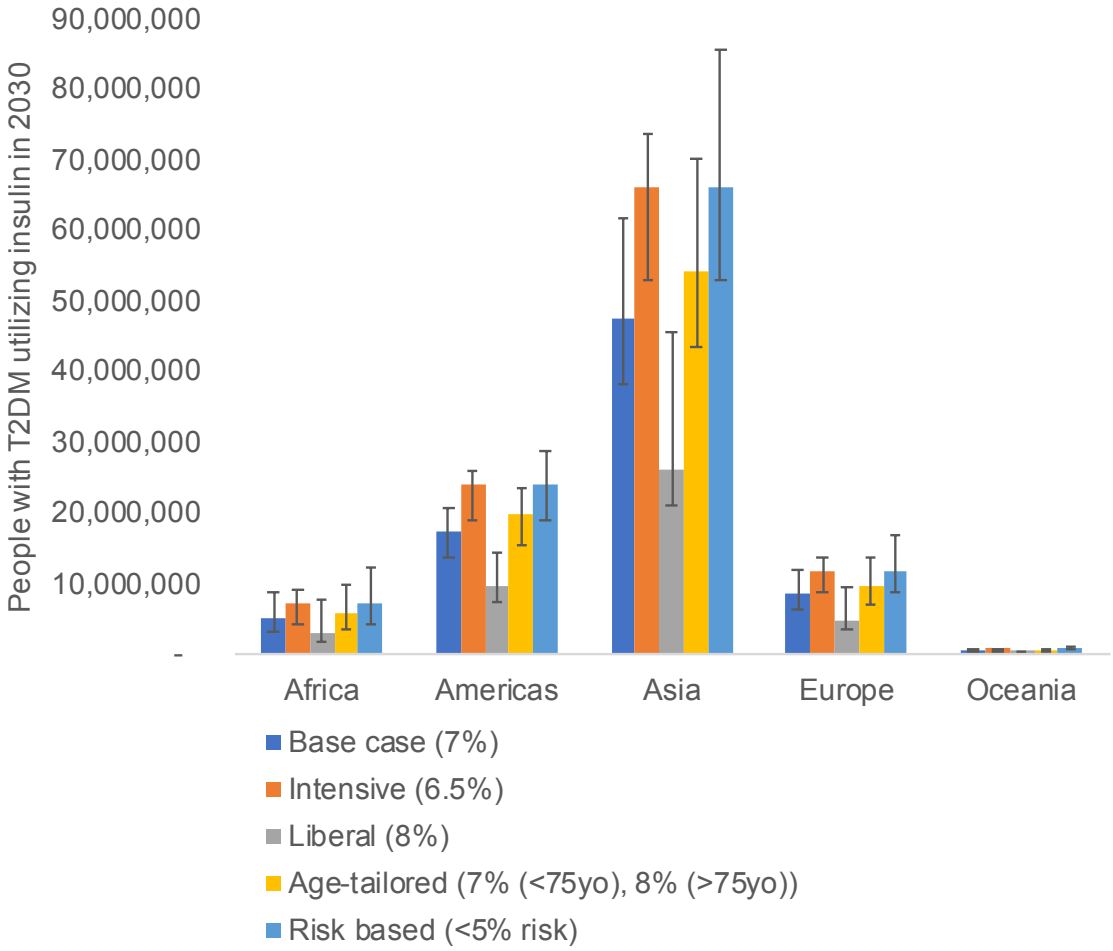
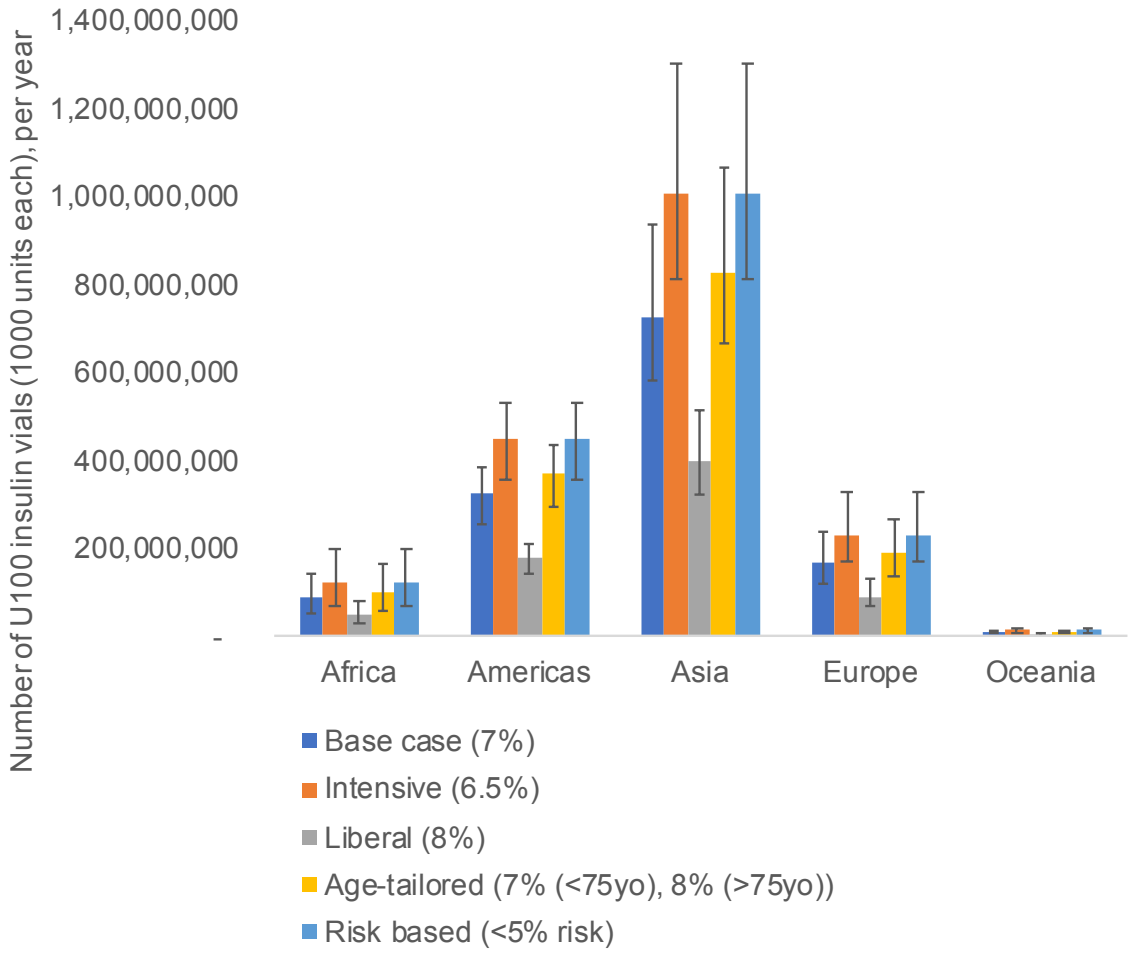


Figure 2: Variations in insulin treatment and DALYs averted under alternative treatment targets in the year 2030. All estimates are made with the approach defined in the Methods section that accounted for both demographic change and increased insulin access. The height of the bars reflects the mean, 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.

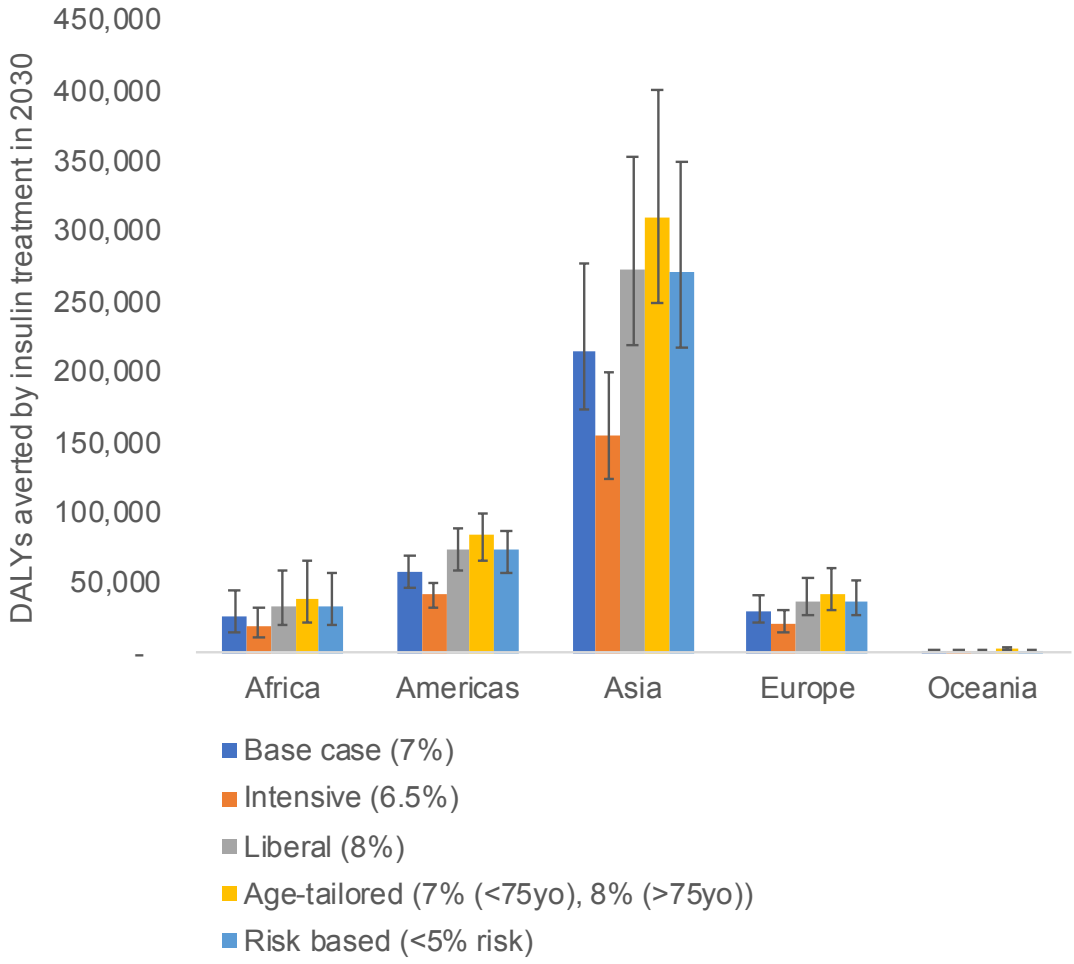
(A) People with type 2 diabetes mellitus estimated to use insulin



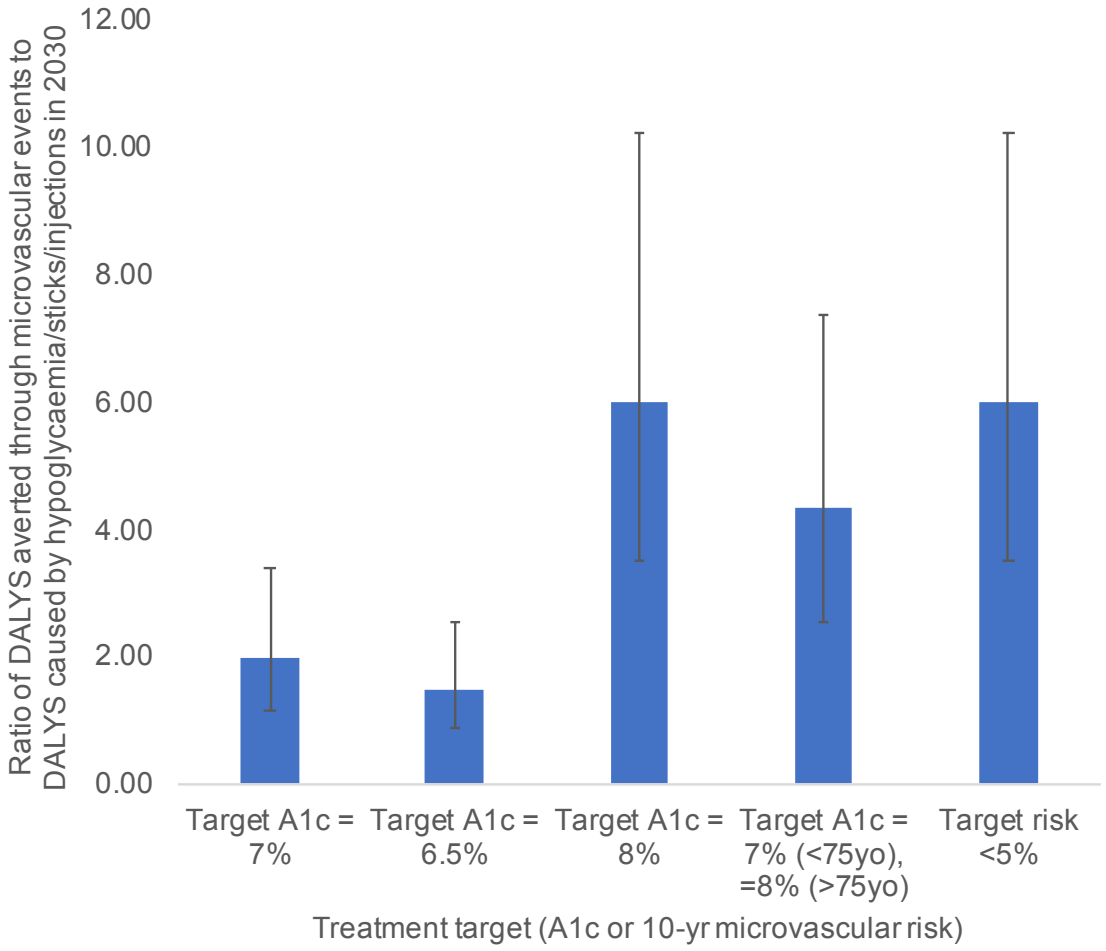
(B) Number of U100 insulin vials (1000 units each) used per year



(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.



Appendix

Details of input cohorts

Due to space limitations, detailed citations for referenced cohorts were not possible to list in the main text. Here, we reference the input cohort data, which were obtained from: the U.S. National Health and Nutrition Examination Survey (N = 1,441 with diabetes, 2009-2014);[1] the U.S. National Institutes of Health Global Health Centres of Excellence surveys from South Africa (N = 1,842 with diabetes, 2012) and India (N = 1,605 with diabetes, 2015);[2,3] the South Africa National Health and Nutrition Examination Survey (N = 747 with diabetes, 2012);[4] the U.K. National Health Service National Diabetes Audit (N = 16,585 with diabetes, 2016-2017);[5] the Indian Jaipur Diabetes Registry (N = 8,699 with diabetes, 2014);[6] the Swedish National Diabetes Register (N = 17,827 with diabetes, 2016);[7] the Danish Adult Diabetes Registry (N = 11,205 with diabetes, 2014-2015);[8] the Turkish Nationwide survey of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus (TEMD study; N = 4,672 with diabetes, 2017);[9] the China Health and Nutrition Study (N = 1,422 with diabetes, 1999-2015);[10] the DiabCare study of the Philippines (N = 770, 2008);[11] the Japan National Health and Nutrition Survey (N = 1434 with diabetes, 2016);[12] the Korea National Health and Nutrition Examination Survey (N =
1,341 with diabetes, 2010-2012);[13] and the Joint Asia Diabetes Evaluation Registry (N = 3,415 with diabetes from China, 15,196 from Hong Kong, 3,714 from India, 1,651 from Korea, 3,365 from Philippines, 692 from Vietnam, and 78 from Taiwan, 2007-2012).[14] See reference list at the end of this Appendix.

Appendix Table 1:

Estimates of absolute number of people aged 20-79 years old with T2DM for the years 2018 and 2030, by country, based on IDF estimates.[15] 95% confidence intervals are in parentheses. Monte Carlo sampling from the Gaussian distributions around these estimates was performed to incorporate the prevalence estimates into the outcome metrics. Classification of countries into regions is based on the International Standards Organization (ISO-3166) standard.

Country	Region	2018	2030
Afghanistan	Asia	1053371 (806706, 1519286)	1735972 (1315472, 2520914)
Albania	Europe	242142 (201328, 281372)	264658 (220480, 306960)
Algeria	Africa	1775544 (1182966, 2504770)	2443267 (1573364, 3432722)
Andorra	Europe	5899 (4841, 7776)	6629 (5412, 8665)
Angola	Africa	361802 (210879, 583250)	641394 (380636, 1059184)
Anguilla	Americas	1266 (980, 1558)	1523 (1148, 1842)

Antigua and Barbuda	Americas	8376 (7318, 9858)	10808 (9248, 12797)
Argentina	Americas	1728226 (1161169, 2535758)	2115204 (1471724, 3121943)
Armenia	Asia	163474 (106228, 270722)	175315 (111916, 314755)
Aruba	Americas	10905 (8659, 13926)	11379 (8904, 14484)
Australia	Oceania	1109756 (820101, 1367965)	1307034 (964216, 1612486)
Austria	Europe	578860 (482250, 746813)	670050 (544232, 812824)
Azerbaijan	Asia	475406 (308887, 771191)	568494 (364164, 1011771)
Bahamas	Americas	37195 (31945, 44455)	45120 (37604, 54011)
Bahrain	Asia	165463 (144834, 187189)	236962 (207196, 267498)
Bangladesh	Asia	6964460 (5381702, 10066385)	10331890 (7818844, 17844294)
Barbados	Americas	34519 (29181, 41139)	36271 (29824, 43810)
Belarus	Europe	465478 (379258, 995696)	463867 (379892, 936213)
Belgium	Europe	489465 (414227, 658096)	563199 (478336, 751277)
Belize	Americas	31641 (26298, 37442)	46333 (38600, 54549)
Benin	Africa	41138 (27585, 152265)	60019 (41092, 220249)
Bermuda	Americas	6403 (5210, 7700)	6226 (5028, 7442)
Bhutan	Asia	40351 (34021, 48669)	58819 (50240, 69588)
Bolivia (Plurinational State of)	Americas	391655 (306674, 620737)	563271 (442596, 891327)
Bosnia and Herzegovina	Europe	355029 (296772, 410643)	366553 (307572, 423014)
Botswana	Africa	53703 (30174, 89870)	89837 (44728, 146150)
Brazil	Americas	12483620 (10907665, 13871159)	17932750 (15509660, 20284592)
British Virgin Islands	Oceania	2793 (1942, 3784)	3428 (2288, 4636)
Brunei Darussalam	Asia	40591 (32689, 50660)	51980 (40652, 64931)
Bulgaria	Europe	408496 (312315, 553814)	397173 (302744, 554026)
Burkina Faso	Africa	154901 (103508, 341589)	249268 (175916, 592128)
Burundi	Africa	137536 (96068, 275190)	249218 (148748, 601528)
Cabo Verde	Africa	6301 (4754, 16445)	9075 (7380, 25133)
Cambodia	Asia	247640 (226498, 278527)	368324 (336600, 417771)
Cameroon	Africa	685681 (545318, 861466)	1034476 (825916, 1290784)
Canada	Americas	2536461 (2310079, 3605333)	2828931 (2576316, 3963758)
Cayman Islands	Americas	5370 (4579, 6436)	6705 (5544, 8109)
Central African Republic	Africa	122645 (97436, 154276)	202814 (162116, 252807)

Chad	Africa	245711 (195223, 308843)	469930 (374724, 586747)
Channel Islands	‘oceania	6840 (5834, 9097)	7741 (6516, 10507)
Chile	Americas	1194562 (968696, 1509074)	1635503 (1330040, 2052791)
China	Asia	111912900 (97135933, 146253900)	130175500 (113405864, 163337009)
China, Hong Kong SAR	Asia	620164 (521920, 742623)	697720 (587656, 836408)
China, Macao SAR	Asia	44487 (37526, 53735)	57699 (48672, 69515)
Colombia	Americas	2680858 (1832041, 3681089)	3915764 (3138500, 4758026)
Comoros	Africa	31660 (20932, 48879)	49815 (33100, 76002)
Congo	Africa	149839 (119415, 187887)	223649 (178028, 280019)
Cook Islands	Oceania	1526 (1043, 2442)	2589 (1528, 3594)
Costa Rica	Americas	314064 (261502, 374354)	387305 (314724, 463165)
Côte d'Ivoire	Africa	218019 (157070, 533761)	317909 (246028, 834944)
Croatia	Europe	210704 (152018, 447248)	202784 (147784, 443270)
Cuba	Americas	881872 (773338, 977614)	1070122 (920228, 1216624)
Curaçao	Americas	18196 (13672, 22260)	19535 (14896, 24104)
Cyprus	Asia	91566 (59824, 154812)	110522 (72808, 183985)
Czech Republic	Europe	746650 (528602, 992980)	815324 (597468, 1074245)
Dem. People's Republic of Korea	Asia	822711 (753318, 938325)	944538 (864208, 1093520)
Democratic Republic of the Congo	Africa	1765753 (1405219, 2216557)	3191200 (2542584, 3990432)
Denmark	Europe	375927 (310962, 435461)	408950 (336704, 472635)
Djibouti	Africa	39192 (28425, 59629)	52555 (34900, 83642)
Dominica	Americas	5902 (4660, 7566)	6893 (5380, 8785)
Dominican Republic	Americas	516104 (313894, 722264)	678949 (428264, 925164)
Ecuador	Americas	574084 (355057, 902437)	1042334 (739484, 1498838)
Egypt	Africa	8222605 (4172479, 9637605)	11675690 (5564772, 13742440)
El Salvador	Americas	327472 (271114, 433611)	404822 (312620, 552416)
Equatorial Guinea	Africa	31884 (25602, 39560)	46601 (37180, 58212)
Eritrea	Africa	86550 (61018, 157127)	157878 (98492, 321711)
Estonia	Europe	53495 (36112, 105893)	55529 (37240, 107587)

Ethiopia	Africa	2544054 (1064246, 3978151)	3336534 (1757664, 6626130)
Faroe Islands	Europe	2397 (1821, 2953)	2668 (2032, 3340)
Fiji	Oceania	79510 (57164, 164640)	87198 (59204, 152327)

Finland	Europe	357470 (237031, 445504)	358451 (245340, 447932)
France	Europe	3181527 (2521002, 3990908)	3418907 (2682628, 4305015)
French Guiana	Americas	13385 (11701, 14857)	22770 (19520, 25869)
French Polynesia	Oceania	44039 (35138, 52807)	46547 (36948, 56133)
Gabon	Africa	66183 (52579, 83306)	96563 (76992, 120703)
Gambia	Africa	14746 (13658, 46662)	24599 (22768, 75804)
Georgia	Asia	225317 (150554, 368704)	235271 (152488, 413941)
Germany	Europe	7190853 (5588558, 8179664)	6899742 (5678424, 7954977)
Ghana	Africa	501145 (141788, 847598)	511924 (292124, 1154934)
Greece	Europe	563015 (434274, 1279596)	622950 (483484, 1319760)
Greenland	Americas	849 (718, 2386)	849 (718, 2386)
Grenada	Americas	6435 (4836, 8815)	8505 (6564, 11243)
Guadeloupe	Americas	52018 (40238, 63217)	56121 (43180, 68749)
Guam	Oceania	25422 (20412, 31784)	28715 (21924, 36479)
Guatemala	Americas	763886 (473673, 1164502)	1214721 (719884, 1832447)
Guinea	Africa	123083 (85569, 282608)	185116 (134140, 450028)
Guinea Bissau	Africa	18484 (13696, 46298)	26982 (20728, 69537)
Guyana	Americas	51156 (41715, 70268)	58466 (46160, 78326)
Haiti	Americas	350988 (222919, 621926)	493518 (319668, 1233958)
Honduras	Americas	293829 (198434, 489075)	510330 (369760, 745513)
Hungary	Europe	681856 (496396, 1228223)	679389 (486028, 1212655)
Iceland	Europe	17607 (11734, 22278)	20689 (14316, 26110)
India	Asia	72515680 (52780422, 91884372)	97984690 (73723892, 122943283)
Indonesia	Asia	10163610 (8389611, 11282555)	13129440 (10981832, 14695560)
Iran (Islamic Republic of)	Asia	4985973 (3696940, 6758239)	7085210 (5164852, 9596423)
Iraq	Asia	1434580 (971431, 1962382)	2304600 (1542348, 3093410)
Ireland	Europe	141008 (105672, 199628)	194527 (147192, 261218)
Israel	Asia	412470 (315486, 707880)	547151 (418148, 929804)
Italy	Europe	3306987 (2859446, 3951471)	3591734 (3115728, 4275263)
Jamaica	Americas	205859 (158151, 266600)	252008 (189212, 318552)
Japan	Asia	6950767 (5638516, 9349323)	6587593 (5347852, 8802972)
Jordan	Asia	410733 (322997, 703945)	613262 (490512, 1039147)
Kazakhstan	Asia	799934 (524211, 1306241)	923920 (595472, 1664134)

Kenya	Africa	470785 (171369, 1779367)	806258 (422092, 3754071)
Kiribati	Oceania	12797 (6143, 17968)	15239 (9316, 20695)

Kuwait	Asia	444198 (370884, 535420)	668372 (520308, 923989)
Kyrgyzstan	Asia	218023 (146004, 341813)	276854 (184644, 518304)
Lao People's Democratic Republic	Asia	117111 (107077, 131677)	188192 (171968, 212187)
Latvia	Europe	98313 (75696, 126425)	97482 (74904, 124426)
Lebanon	Asia	570006 (442046, 717728)	631496 (493992, 791828)
Lesotho	Africa	30410 (17370, 52206)	44457 (26764, 74220)
Liberia	Africa	44374 (32937, 109938)	66648 (51052, 171580)
Libya	Africa	437317 (311660, 584694)	560971 (375812, 733194)
Liechtenstein	Europe	2747 (2224, 3049)	2828 (2416, 3168)
Lithuania	Europe	104959 (88282, 155223)	105609 (89256, 154040)
Luxembourg	Europe	24284 (15688, 43049)	30251 (19024, 52832)
Macedonia	Europe	183613 (152635, 213221)	200313 (167184, 231811)
Madagascar	Africa	383087 (242477, 632602)	662649 (397056, 1074326)
Malawi	Africa	204442 (123182, 363926)	390955 (233836, 655957)
Malaysia	Asia	3466658 (2959475, 4092486)	4621662 (3981568, 5390309)
Maldives	Asia	18534 (15510, 43272)	27637 (21904, 46345)
Mali	Africa	146026 (102960, 345065)	237180 (174864, 594194)
Malta	Europe	41073 (22387, 51804)	43882 (23976, 54975)
Marshall Islands	Oceania	10164 (6578, 13797)	9621 (6252, 12805)
Martinique	Americas	49261 (36674, 59706)	46920 (35388, 57433)
Mauritania	Africa	42990 (31600, 107666)	62440 (49240, 168657)
Mauritius	Africa	221730 (90222, 262526)	244800 (159088, 290294)
Mexico	Americas	11967890 (5741522, 14647724)	16274520 (8313900, 19977102)
Micronesia (Fed. States of)	Oceania	6123 (4406, 9030)	9310 (6720, 12960)
Moldova	Europe	187254 (148553, 264791)	234445 (191724, 321294)
Monaco	Europe	2131 (1716, 2609)	2337 (1884, 2914)
Mongolia	Asia	96291 (30782, 176701)	119723 (40588, 221205)
Montenegro	Europe	56089 (46628, 65102)	59024 (49196, 68310)
Montserrat	Americas	459 (402, 532)	524 (484, 620)
Morocco	Africa	1635004 (1231678, 2652294)	2241846 (1663352, 3484550)

Mozambique	Africa	300071 (192576, 541431)	511798 (303768, 935847)
Myanmar	Asia	1449515 (1038224, 2298843)	2643735 (1932512, 3837701)
Namibia	Africa	46147 (27030, 73564)	72560 (43600, 120216)
Nauru	Oceania	1460 (1051, 1889)	1611 (1080, 2101)
Nepal	Asia	657108 (435670, 1369372)	931796 (640284, 2063810)
Netherlands	Europe	943684 (676032, 1284715)	1037266 (736944, 1333805)
New Caledonia	Oceania	44820 (33930, 56061)	47902 (38908, 57450)
New Zealand	Oceania	316454 (232706, 402682)	338123 (259884, 420853)

Nicaragua	Americas	367569 (233135, 515416)	454314 (319444, 631990)
Niger	Africa	170693 (107704, 337352)	275763 (175816, 603702)
Nigeria	Africa	1710470 (1199146, 4040407)	2516065 (1904492, 6480549)
Niue	Oceania	239 (145, 316)	214 (116, 306)
Norway	Europe	291620 (200209, 365860)	340100 (240044, 426634)
Oman	Asia	369448 (249552, 462541)	544860 (375984, 675942)
Pakistan	Asia	7503461 (5068829, 11156193)	10995720 (7639344, 16080949)
Palau	Oceania	2346 (1602, 5051)	3172 (1732, 6022)
Panama	Americas	217090 (169298, 273477)	321697 (266440, 380268)
Papua New Guinea	Oceania	634321 (278875, 888434)	837167 (530976, 1160104)
Paraguay	Americas	299785 (259903, 338162)	446715 (380940, 510164)
Peru	Americas	1133160 (804665, 1719635)	1636648 (1114620, 2588600)
Philippines	Asia	3701124 (2817893, 4796906)	5014895 (3728880, 6581034)
Poland	Europe	2165593 (1523183, 6214533)	2262371 (1604812, 5844306)
Portugal	Europe	1031139 (725206, 1310302)	1071754 (766572, 1346624)
Puerto Rico	Americas	387705 (308179, 474341)	401566 (317424, 492305)
Qatar	Asia	260928 (229414, 296874)	390418 (342492, 441609)
Republic of Korea	Asia	3394361 (2460310, 4369531)	3996904 (2934152, 5126737)
Réunion	Africa	107165 (77290, 129096)	122928 (90884, 162954)
Romania	Europe	1710243 (1045290, 2195755)	1559033 (919592, 2107770)
Russian Federation	Europe	8323771 (6150186, 11169173)	10296650 (5987504, 14328933)
Rwanda	Africa	213430 (123970, 354544)	420148 (252812, 791552)
Saint Kitts and Nevis	Americas	4931 (3415, 6945)	6084 (4212, 8557)
Saint Lucia	Americas	13939 (11368, 19314)	17232 (13648, 22873)

Saint Vincent and the Grenadines	Americas	8281 (6636, 11016)	10028 (7884, 12999)
Samoa	Oceania	7268 (4966, 16412)	8672 (5820, 20312)
San Marino	Europe	2033 (1667, 2397)	2345 (1912, 2763)
Sao Tome and Principe	Africa	1762 (1317, 4560)	2643 (2104, 7365)
Saudi Arabia	Asia	3851964 (2954474, 4427450)	5469494 (4091752, 6280745)
Senegal	Africa	137876 (94233, 321353)	221791 (163420, 561438)
Serbia	Europe	828088 (690590, 958688)	819075 (684648, 946715)
Seychelles	Africa	7640 (5501, 10600)	12474 (7920, 16860)
Sierra Leone	Africa	60130 (42418, 139974)	87706 (64244, 213367)
Singapore	Asia	593076 (492114, 685353)	692618 (569140, 805408)
Sint Maarten (Dutch part)	Americas	3495 (2974, 4192)	4326 (3560, 5200)
Slovakia	Europe	396253 (236205, 475762)	451771 (261424, 537988)
Slovenia	Europe	156974 (100130, 207361)	169676 (104076, 222991)
Solomon Islands	Oceania	43077 (22953, 65124)	62058 (36076, 93538)
Somalia	Africa	222422 (158073, 374171)	386390 (244276, 708242)
South Africa	Africa	1829207 (1014950, 3729624)	2633569 (1367424, 5259500)
South Sudan	Africa	433982 (310884, 579605)	645568 (456804, 857835)
Spain	Europe	3497947 (2621566, 5015841)	3964455 (2929116, 5663136)
Sri Lanka	Asia	1168936 (791970, 1819035)	1322407 (882028, 2060194)
State of Palestine	Asia	172415 (104868, 364354)	286916 (158268, 610090)
Sudan	Africa	2218476 (1089710, 3758088)	2819352 (1451136, 5413432)
Suriname	Americas	44747 (29465, 89601)	52974 (38484, 82308)
Swaziland	Africa	17008 (9794, 29913)	23890 (14388, 40543)
Sweden	Europe	482449 (392324, 653875)	490056 (389996, 715770)
Switzerland	Europe	459769 (432382, 684840)	541227 (503700, 748367)
Syrian Arab Republic	Asia	726032 (547335, 996339)	1266416 (962324, 1724851)
Taiwan	Asia	1904876 (1362021, 2516152)	2090333 (1509376, 2722720)
Tajikistan	Asia	266955 (179299, 410837)	372998 (251064, 691050)
Thailand	Asia	4106930 (2998277, 4839127)	4654619 (3261984, 5423349)
Timor-Leste	Asia	32923 (27522, 38308)	47021 (40612, 53809)
Togo	Africa	172842 (49037, 278306)	253791 (78192, 408005)
Tokelau	Oceania	206 (110, 273)	252 (100, 340)

Tonga	Oceania	7129 (4649, 11318)	8609 (6228, 13838)
Trinidad and Tobago	Americas	115823 (91386, 157592)	145971 (121328, 181037)
Tunisia	Africa	751936 (563012, 1137407)	948897 (631676, 1366639)
Turkey	Asia	6625234 (5664827, 8081333)	8606189 (7377472, 10455463)
Turkmenistan	Asia	208272 (133923, 339282)	269369 (172880, 485995)
Tuvalu	Oceania	1697 (956, 2210)	1561 (836, 2354)
Uganda	Africa	297550 (165203, 674855)	867422 (494512, 2022548)
Ukraine	Europe	2729566 (1770750, 4692247)	2639892 (1687936, 4777706)
United Arab Emirates	Asia	1186784 (1005931, 1415700)	1699868 (1429464, 2034054)
United Kingdom	Europe	2682726 (2288142, 3600088)	3056956 (2574424, 4210151)
United Republic of Tanzania	Africa	939479 (578124, 2090382)	1826426 (1129524, 3882806)
United States of America	Americas	29338180 (26690902, 31679401)	31825320 (28715312, 34490266)
United States Virgin Islands	Oceania	11811 (9450, 14098)	11106 (8912, 13266)
Uruguay	Americas	149073 (118525, 196662)	168875 (125384, 261274)
Uzbekistan	Asia	1220580 (680900, 2050170)	1550373 (919460, 2841012)
Vanuatu	Oceania	16776 (12277, 25124)	30838 (22040, 42794)
Venezuela (Bolivarian Republic of)	Americas	1369611 (1021586, 1905704)	2618469 (2032188, 3329925)
Viet Nam	Asia	3520101 (2736766, 4858207)	4818023 (3490424, 7353720)
Western Sahara	Africa	9552 (8184, 25873)	12658 (10896, 36979)
Yemen	Asia	543920 (401731, 1001477)	927772 (694008, 1597533)
Zambia	Africa	230349 (132762, 377875)	423312 (252392, 703175)
Zimbabwe	Africa	114253 (70434, 467417)	334696 (202784, 668168)

Appendix Table 2:

(A) RECODe equations used to estimate rates of microvascular complications of T2DM. The 10-year risk of an outcome can be computed as 1- lambda^exp(sum(beta*x) – mean(sum(beta*x))), where beta are the equation coefficients and x are the values for each covariate for an individual patient within the cohort under study. Lambda values were 0.973 for renal failure/ESRD, 0.921 for vision loss, and 0.870 for loss of pressure sensation. After the equations' baseline hazard rates were recalibrated to match DALY estimates from the Global Burden of Disease project for each complication (see GBD website for cause-specific DALY estimates),[22] the mean(sum(beta*x)) values were 1.37 for renal failure, 130.9 for severe vision loss, and 4.99 for pressure sensation loss. To estimate the reduction in risk with treatment, we used estimates from a prior systematic review, in which the risks were first converted to rates (where initial rate = -ln(1-risk)/10, then calculated the new reduced rate of each treatment as (initial rate * (new A1c/initial A1c)^{b}), where b is 1.14 for renal failure, 1.29 for severe vision loss , and 1.19 for pressure sensation loss.[4] The new A1c was calculated from initial A1c as noted in the main text, by using values from a meta-analysis to estimate reduction with each treatment (typically 1-2% reduction with each oral medication, then reduction to target A1c level with insulin instead of sulfonylurea if necessary).[17] Blank cells indicate that the particular covariate is not included in the given equation (a beta coefficient of zero).

Covariate	Renal failure/end-stage renal disease	Severe vision loss	Pressure sensation loss
Age, years	–0.01938	0.02285	0.03022
Women	–0.01129	0.2264	–0.18680
Black	0.08812	–0.16770	–0.09448
Hispanic or Latino	0.2338	-	-
Tobacco smoking, current	0.1483	-	-
Systolic blood pressure, mm Hg	0.00303	0.00824	0.00456
	–0.02164	0.1127	0.26672
Cardiovascular disease history			

Blood pressure-lowering drugs	–0.07952	0.06393	0.18192
Oral diabetes drugs	–0.12560	–0.23490	–0.25747
Anticoagulants	0.03199		
HbA1c, %	0.1369	0.1449	0.18866
Total cholesterol, mg/dL	–0.00111	–0.00017	0.00219
HDL cholesterol, mg/dL	0.00629	0.00545	–0.00539
Serum creatinine, mg/dL	0.8609	0.6947	0.60442
Urine albumin:creatinine ratio, mg/g	0.00036	0.0002	-

(B) Hypoglycaemia risk equation. The risk equation was developed from the ACCORD study sample (N = 10,251),[16] using elastic net regularization[17] for parameter selection and refitting to avoid imprecise standard errors. The logistic regression equation estimates 5-year probability of hypoglycaemia requiring medical assistance. The risk equation was estimated through 5-fold crossvalidation using individual participant data from the ACCORD trial. The equation had a C-statistic of 0.76, and passed the Hosmer-Lemeshow test for calibration.[18] To calculate the probability of a hypoglycemic event requiring medical assistance, an individual's value for each covariate is multiplied by the coefficient then added to the intercept to derive a sum of terms, then the 5-year probability of a major hypoglycaemic event equals 1/(1+exp(-sum of terms)).

Covariate	Coefficient	Standard Error	Wald Z score	P value
Intercept	-8.8533	3.0621	-2.89	0.0038
Age, years	0.0136	0.0274	0.50	0.6190
Female	0.2835	0.3580	0.79	0.4284
Starting haemoglobin A1c value, %	0.6870	0.2184	3.15	0.0017
Change in haemoglobin A1c with therapy, %	0.1323	0.1593	0.83	0.4063

Systolic blood pressure, mmHg	-0.0026	0.0098	-0.26	0.7924
Alanine aminotransferase, mg/dL	-0.0472	0.0195	-2.42	0.0157
Loss of foot vibratory sensation	0.5126	0.4702	1.09	0.2757
Units of insulin per day	0.0005	0.0046	0.12	0.9080
On sulfonylurea	-0.3323	0.4269	-0.78	0.4363
Severe vision loss	0.0226	0.3919	0.06	0.9540
Serum creatinine, mg/dL	1.1783	0.7396	1.59	0.1112
Time since diabetes diagnosis, years	0.0391	0.0226	1.73	0.0844

Appendix Table 3:

Disability weights used for estimating DALYs averted through insulin treatment, based on a prior global survey and systematic review.[19]

Disease outcome	Utility value (95% CI)
Renal failure/end-stage renal disease	0.573 (0.397, 0.749)
Severe vision loss	0.191 (0.129, 0.269)
Pressure sensation loss	0.099 (0.066, 0.145)
Hypoglycaemia requiring medical attention	0.054 (0.033, 0.084)
Daily finger sticks and injections	0.009 (0.004, 0.018)

Appendix Table 4:

Numerical values corresponding to main text Figure 2. 95% confidence intervals are listed in parentheses.

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

	Base case (7%)	Intensive (6.5%)	Liberal (8%)	Age-tailored (7% (<75yo), 8% (>75yo))	Risk based (<5% risk)
Africa	5119862 (2999782, 8733785)	7112791 (4167460, 12133449)	2818170 (1651196, 4807412)	5838439 (3420804, 9959579)	7112791 (4167460, 12133449)
Americas	17272413 (13595462, 20657257)	23995776 (18887556, 28698186)	9507403 (7483467, 11370552)	19696612 (15503597, 23556522)	23995776 (18887556, 28698186)
Asia	47558556 (38157723, 61597425)	66070932 (53010784, 85574492)	26178065 (21003483, 33905600)	54233441 (43513193, 70242677)	66070932 (53010784, 85574492)
Europe	8523506 (6240663, 12033426)	11841319 (8669869, 16717489)	4691667 (3435102, 6623662)	9719788 (7116546, 13722328)	11841319 (8669869, 16717489)
Oceania	518356 (370282, 671140)	720129 (514416, 932385)	285323 (203818, 369422)	591108 (422252, 765336)	720129 (514416, 932385)

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

	Base case (7%)	Intensive (6.5%)	Liberal (8%)	Age-tailored (7% (<75yo), 8% (>75yo))	Risk based (<5% risk)
Africa	87651814 (50501623, 144857489)	121770667 (70159601, 201243902)	48246941 (27798042, 79735153)	99953823 (57589570, 165188365)	121770667 (70159601, 201243902)
Americas	323833311 (257426785, 383481167)	449886847 (357631290, 532752893)	178250353 (141697638, 211082835)	369283600 (293556860, 437303085)	449886847 (357631290, 532752893)
Asia	725118538 (585106758, 937297246)	1007374109 (812862130, 1302144310)	399133230 (322065343, 515924581)	826889561 (667227005, 1068847737)	1007374109 (812862130, 1302144310)
Europe	167389188 (122645636, 236554000)	232546164 (170385988, 328633682)	92137470 (67508892, 130208452)	190882407 (139859059, 269754561)	232546164 (170385988, 328633682)
Oceania	9900809 (7098276, 12781196)	13754743 (9861312, 17756333)	5449788 (3907165, 7035264)	11290397 (8094526, 14575048)	13754743 (9861312, 17756333)

(C) Net DALYs averted by insulin treatment

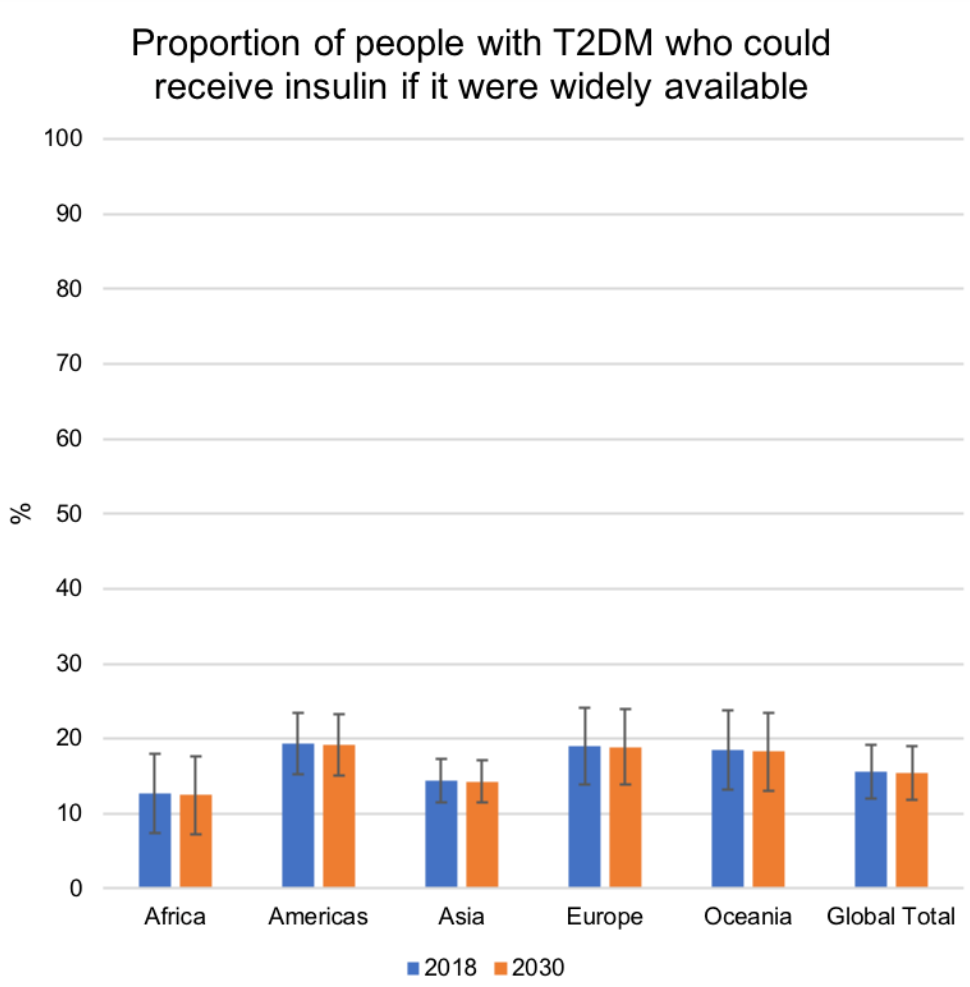
	Base case (7%)	Intensive (6.5%)	Liberal (8%)	Age-tailored (7% (<75yo), 8% (>75yo))	Risk based (<5% risk)
Africa	26585 (15532, 45613)	19091 (11154, 32755)	33817 (19757, 58020)	38336.45 (22397.44, 65774.21)	33471 (19555, 57426)
Americas	58216 (45933, 69554)	41806 (32985, 49948)	74051 (58428, 88474)	83947.72 (66236.61, 100298.18)	73293 (57830, 87569)
Asia	215179 (172646, 277939)	154524 (123981, 199593)	273711 (219609, 353543)	310291.43 (248958.82, 400792.63)	270909 (217360, 349923)
Europe	29282 (21192, 41539)	21028 (15218, 29830)	37247 (26956, 52839)	42224.94 (30558.64, 59900.63)	36865 (26680, 52298)
Oceania	1839 (1298, 2408)	1321 (932, 1729)	2339 (1652, 3063)	2651.63 (1872.66, 3472.36)	2315 (1635, 3031)

(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.

Target A1c = 7%	Target A1c = 6.5%	Target A1c = 8%	Target A1c = 7% (<75yo), =8% (≥75yo)	Target risk ≤5%
2.0 (1.4, 3.4)	1.5 (1.1, 2.6)	6.0 (4.2, 10.2)	4.3 (3.0, 7.4)	6.0 (4.2, 10.2)

Appendix Figure 1:

Proportion of people with T2DM who would receive insulin if targeting A1c of 7% after maximum oral therapy, if insulin were widely available.

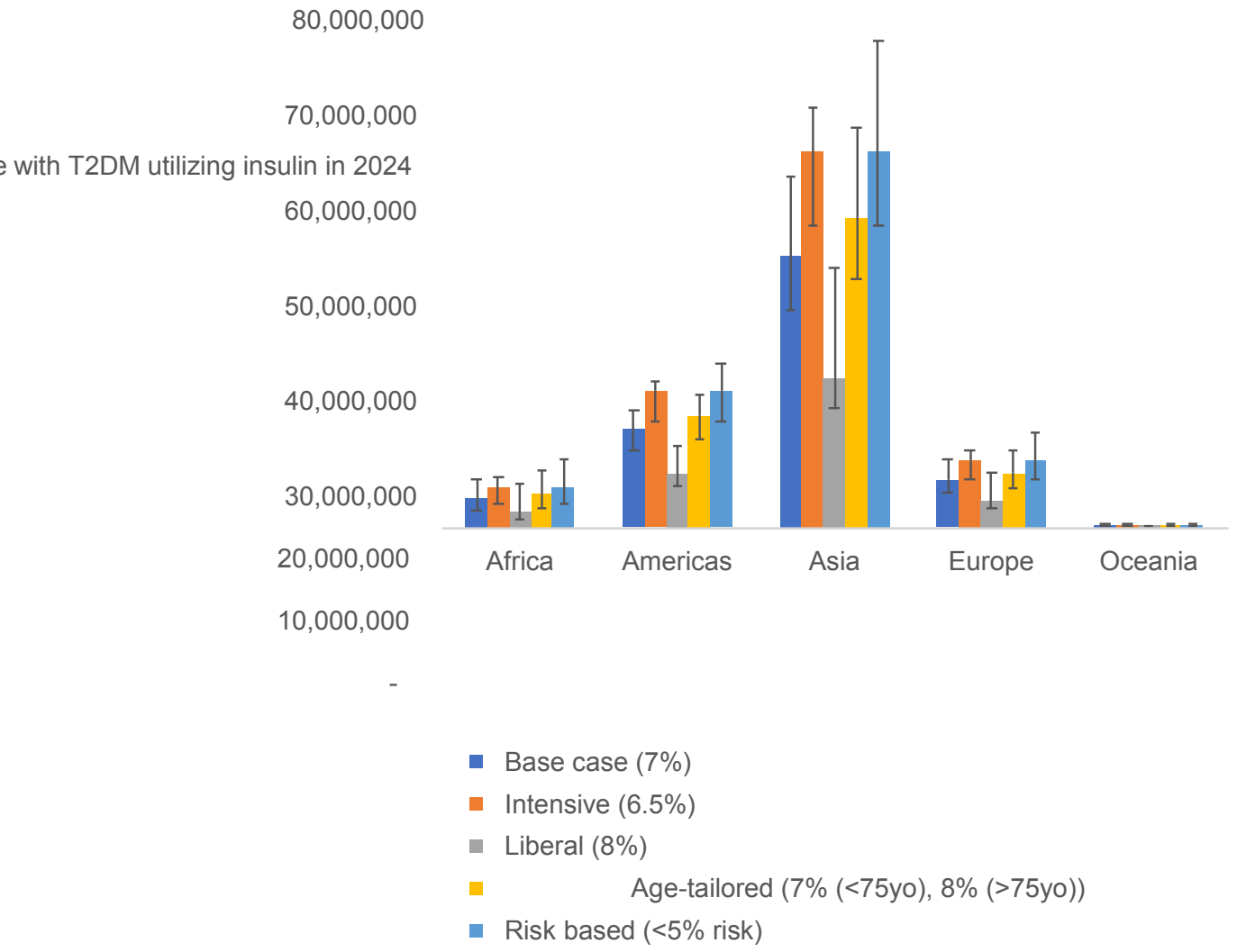


Appendix Figure 2:

Variations in insulin treatment and DALYs averted under alternative treatment targets in the year 2024. 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.

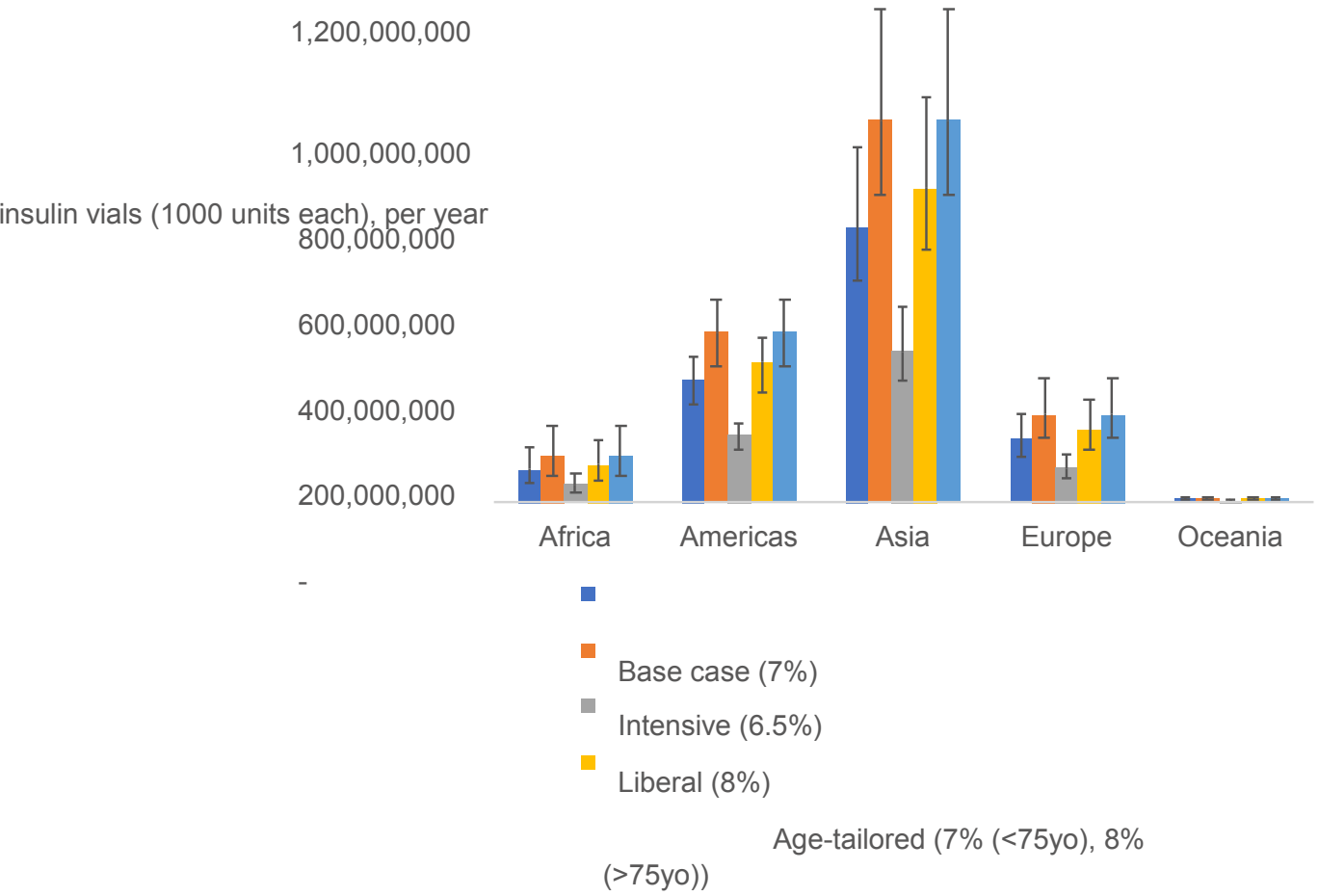
(A) People with type 2 diabetes mellitus estimated to use insulin

90,000,000



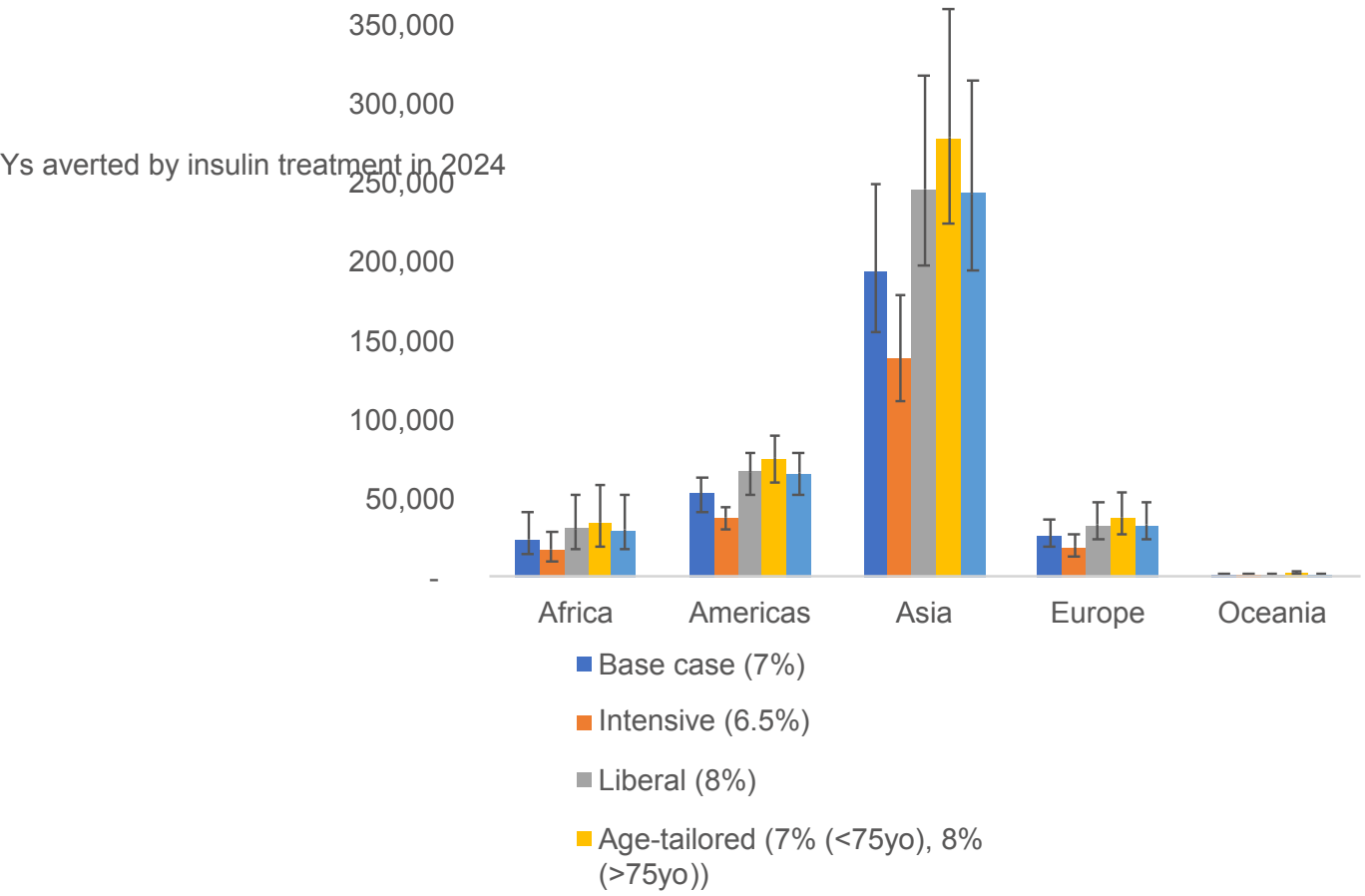
(B) Number of U100 insulin vials (1000 units each) used per year

1,400,000,000



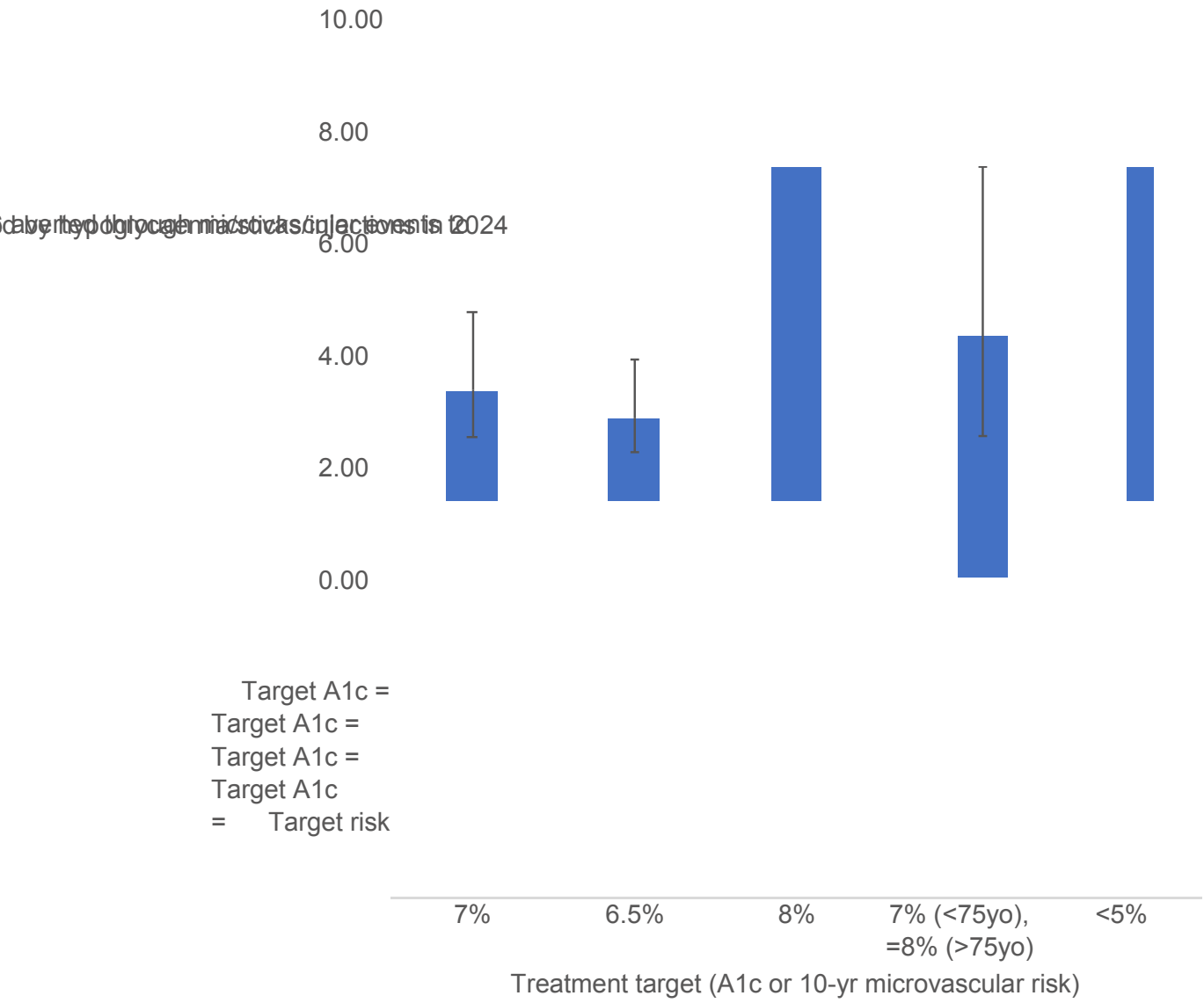
(C) Net DALYs averted by insulin treatment

400,000



(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.

12.00



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