Estimation of global insulin use for type 2 diabetes, 2018–30: a microsimulation analysis

Sanjay Basu, John S Yudkin, Sylvia Kehlenbrink, Justine I Davies, Sarah H Wild, Kasia J Lipska, Jeremy B Sussman, David Beran

Summary

Background The amount of insulin needed to effectively treat type 2 diabetes worldwide is unknown. It also remains unclear how alternative treatment algorithms would affect insulin use and disability-adjusted life-years (DALYs) averted by insulin use, given that current access to insulin (availability and affordability) in many areas is low. The aim of this study was to compare alternative projections for and consequences of insulin use worldwide under varying treatment algorithms and degrees of insulin access.

Methods We developed a microsimulation of type 2 diabetes burden from 2018 to 2030 across 221 countries using data from the International Diabetes Federation for prevalence projections and from 14 cohort studies representing more than 60% of the global type 2 diabetes population for HbA1c, treatment, and bodyweight data. We estimated the number of people with type 2 diabetes expected to use insulin, international units (IU) required, and DALYs averted per year under alternative treatment algorithms targeting HbA1c from 6·5% to 8%, lower microvascular risk, or higher HbA1c, for those aged 75 years and older.

Findings The number of people with type 2 diabetes worldwide was estimated to increase from 405·6 million (95% CI 315·3 million–533·7 million) in 2018 to 510·8 million (395·9 million–674·3 million) in 2030. On this basis, insulin use is estimated to increase from 516·1 million 1000 IU vials (95% CI 409·0 million–658·6 million) per year in 2018 to 633·7 million (500·5 million–806·7 million) per year in 2030. Without improved insulin access, 7·4% (95% CI 5·8–9·4) of people with type 2 diabetes in 2030 would use insulin, increasing to 15·5% (12·0–20·3) if insulin were widely accessible and prescribed to achieve an HbA1c of 7% (53 mmol/mol) or lower. If HbA1c of 7% or lower was universally achieved, insulin would aver 331 101 DALYs per year by 2030 (95% CI 256 601–437 053). DALYs averted would increase by 14·9% with access to newer oral antihyperglycaemic drugs. DALYs averted would increase by 44·2% if an HbA1c of 8% (64 mmol/mol) were used as a target among people aged 75 years and older because of reduced hypoglycaemia.

Interpretation The insulin required to treat type 2 diabetes is expected to increase by more than 20% from 2018 to 2030. More DALYs might be averted if HbA1c targets are higher for older adults.

Funding The Leona M and Harry B Helmsley Charitable Trust.

Copyright © 2018 Elsevier Ltd. All rights reserved.

Introduction

The prevalence of diabetes worldwide has nearly quadrupled since 1980.1 Adult diabetes prevalence (type 1 and type 2) reached 425 million people in 2017 (about one in 11 adults).2 Roughly 12% of overall global health-care expenditures are for diabetes treatment.2

Insulin is necessary for all people with type 1 diabetes and a subset of patients with type 2 diabetes to avoid morbidity and mortality from ketoacidosis or hyperosmolar hyperglycaemic states and to reduce long-term microvascular complications. The use of insulin for type 2 diabetes is dependent on treatment algorithms, particularly the target level of HbA1c.1 Finding an optimal target that maximises disability-adjusted life years (DALYs) averted, while minimising disutility from insulin therapy (eg, from hypoglycaemia), remains an important goal.1 In insulin treatment is costly,1 with most insulin produced by three major manufacturers.1 Hence, a prospective estimation of global insulin requirements and the DALYs averted by improving access might help in the planning of resources required to deliver insulin. Complicating such estimations are the increasing numbers of people with type 2 diabetes, increasing survival of people with type 2 diabetes (which might increase insulin requirements), and increasing availability of newer oral diabetes drugs.

Here, we sought to estimate global insulin use for type 2 diabetes by country and year, worldwide, from 2018 to 2030, and the potential effects of altering insulin treatment algorithms on insulin use and diabetes-related burden of disease.

Methods

Study design

We constructed a microsimulation (figure 1) to simulate the population of adults with type 2 diabetes within each of 221 countries and territories worldwide to estimate the number of adults using insulin and to estimate the...
Articles

Research in context

Evidence before this study

We searched PubMed using the keywords “insulin utilization” and “type 2 diabetes” for articles published from Jan 2, 2008, to Aug 31, 2018. We identified seven previous papers on the topic. Three papers reviewed the insulin dosing needs and effectiveness of insulin for people with type 2 diabetes when using basal insulin with or without other antidiabetes medications. Two articles examined the budgetary and cost effect of basal insulin use in the US 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

Our current study provides a direct estimate of the anticipated global use of insulin among people with type 2 diabetes, using data from large representative cohort studies, and directly compares the implications of alternative treatment targets for reducing the burden of type 2 diabetes complications.

Implications of all the available evidence

The number of people who require insulin and the amount of insulin required to treat type 2 diabetes worldwide are expected to increase. Substantial improvements in access to insulin in low-income and middle-income countries are needed in order to reduce inequalities in access and complications of diabetes compared with high-income countries. Having a higher threshold of HbA1c of 8% for older adults (age 75 years and older) and HbA1c of 7% for others might avert the greatest number of DALYs from insulin treatment, by balancing the risk of hypoglycaemia against the benefit of reducing microvascular complications.

Estimates of type 2 diabetes prevalence

Diabetes prevalence (both diagnosed and undiagnosed) among adults in each country and year in the simulation was taken from projections made by the IDF for the period 2018–30. The IDF prevalence estimates were based on a regression model that used data from a systematic review of the medical literature for the individual country or nearest neighbourhood; the reviewed data were used by the IDF to generate smoothed sex-specific and age-specific prevalence estimates for adults aged 20–79 years, which were projected by the IDF into the future using UN population projections and UN adult projections for the period 2018–30. The IDF prevalence estimates were for overall diabetes; based on a systematic review and projections, we estimated that 96·5% of total diabetes among adults could be attributed to type 2 diabetes (varied in uncertainty analyses to the range 92·0–99·0%). The estimate was based on a modeling exercise with extrapolation of ratios of incidence of type 1 diabetes in children to adults from available data applied to country-specific childhood type 1 diabetes incidence estimates.

Estimates of insulin needs

We had two parallel approaches to estimate the number of people using insulin within each simulated country: first, an approach accounting for demographic change but unchanged insulin access, which applied estimated proportions of people with type 2 diabetes currently treated with insulin to the estimated numbers of people with diagnosed type 2 diabetes in the future; second, 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, after appropriate oral antihyperglycaemic therapy, and conditional on a given treatment target for glycaemic control (HbA1c). In the approach accounting for demographic change alone (with unchanged insulin treatment rates), we multiplied the absolute number of people projected to have diagnosed type 2 diabetes in each year over the period 2018–30 by the proportion of people who are anticipated to be treated with insulin given current estimates of the proportion of people with type 2 diabetes who receive insulin treatment in each country. The number of units of insulin required among people given insulin followed current guidelines based on bodyweight, using the distribution of bodyweight among those diagnosed with type 2 diabetes and given insulin from regional surveys (table I). The estimates of bodyweight-based dosing assumed that 75% of patients given insulin...
require only basal insulin at a dose of 0·41 U/kg per day, while the remaining individuals would require multiple dose injection therapy totalling 0·6 U/kg per day.12,13 In a sensitivity analysis, we tested alternative assumptions using 70% and 80% for proportions of people given insulin who require only basal insulin.

In the approach accounting for both demographic change and improved insulin access, we estimated the additional insulin required for the population who do not currently have access. First, we estimated the proportion of people with type 2 diabetes not currently receiving insulin from the geographically closest regional diabetes survey (table 1; appendix) 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. The cohort survey data, after using survey weights, represented more than 60% of the global population with type 2 diabetes. Missing data—specifically, missing HbA1c values, body-weight values, and indicators of whether or not a person was on insulin—were imputed with chained equations assuming data were missing at random,28 followed by repeated Monte Carlo sampling from uncertainty distributions from each input parameter, done to estimate uncertainty.

Among people not yet on insulin, we estimated whether or not insulin would be necessary after maximum treatment with oral antihyperglycaemic drugs to achieve a given target HbA1c level (detailed below). Following current WHO guidelines and the WHO Essential Medicines List,15,16 titration was simulated up from 500 mg of metformin once per day to 1000 mg of metformin twice per day, then, if needed, further addition of 80 mg of glimepiride (a sulfonylurea) once per day, which could be titrated up to 160 mg twice per day. We Monte Carlo sampled from the distributions of typical HbA1c reductions for the full dose of each drug (uniform distributions) from a previous meta-analysis,5 with proportionate linear values for doses less than the maximum, taking into account existing dose levels among those already on oral drugs. Those people still above the target HbA1c after maximum titration of oral drugs were assumed to achieve the target HbA1c 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 given insulin require only basal insulin at a dose of 0·41 U/kg per day (varied from 70% to 80% in sensitivity analyses), while the remaining individuals would require multiple dose injection therapy totalling 0·6 U/kg per day.12,13 Among the population already receiving insulin, we estimated total daily insulin needed using these same estimates of total units per kg bodyweight required per day.

Finally, we did a sensitivity analysis to estimate how much less insulin might be required if newer drugs (glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors, and sodium-glucose co-transporter-2 [SGLT2] inhibitors) were more widely available and were combined with metformin instead of combining a sulfonylurea with metformin; we used the HbA1c reductions estimated in a meta-analysis27 to estimate the HbA1c-lowering effects of these newer drugs.

**Treatment targets**

For the scenario accounting for both demographic change and improved insulin access, we simulated five different treatment targets. Recognising that some facilities do not have HbA1c testing, we converted to the nearest average fasting plasma glucose (AFPG) target level.2 We used the 2018 American Diabetes Association treatment guidelines9 as a primary clinical reference.

First, we set the target HbA1c to 7·0% (53 mmol/mol) for all diagnosed and treated people (AFPG 8·0 mmol/L). Second, we reduced the target HbA1c to a low of 6·5% (48 mmol/mol; AFPG 7·5 mmol/L). Third, we increased...
the target HbA1c, to a high of 8·0% (64 mmol/mol; AFPG 9·2 mmol/L). Fourth, we simulated an age-based target, with people younger than 75 years given an HbA1c target of 7% and those aged 75 years and older given a target HbA1c of 8%. 20,21 Fifth, we simulated a risk-based target, with people having 5% or higher risk over 10 years of composite microvascular complications (renal failure or 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 equations7,8 given insulin to an HbA1c of 7%, or the HbA1c level that achieved an estimated risk 5% or less (which ever HbA1c was higher). The threshold was based on previous experiments for risk-based therapy.22

**Outcomes and statistical analysis**
The primary outcome metric we estimated was the number of people with type 2 diabetes estimated to use insulin for each year in each country and each world region (using UN categorisations of countries into regions). The secondary outcome metric was the number of 10 mL vials of U100 insulin (ie, 1000 IU) 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 or 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 recalibrated to global DALY estimates from the Global Burden of Disease Study,7,8,23 the relative risk reduction conditional on HbA1c reduction for each complication from a previous systematic review,24 and the disability weights provided by a previous international survey (appendix).25 We also computed the increase in DALYs due to the disutility of daily finger stick glucose monitoring, disutility from injection therapy, and disutility because of hypoglycaemia requiring hospitalisation, emergency care, or other external medical assistance due to severe cognitive impairment, based on a risk equation to estimate the frequency of hypoglycaemia (appendix).26 We computed DALYs at a standard 3% annual discount rate, integrated over the full life course of all simulated individuals.

<table>
<thead>
<tr>
<th>People with type 2 diabetes*</th>
<th>Mean HbA1c (95% centiles)</th>
<th>Percentage of people treated with insulin, among those diagnosed</th>
<th>Mean bodyweight, kg (95% centiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US National Health and Nutrition Examination Survey</td>
<td>1441</td>
<td>2009-14</td>
<td>7.4% (5.2–12.2)</td>
</tr>
<tr>
<td>US National Institutes of Health Global Health Centers of Excellence surveys from South Africa</td>
<td>1842</td>
<td>2012</td>
<td>9.1% (5.4–14.6)</td>
</tr>
<tr>
<td>US National Institutes of Health Global Health Centers of Excellence surveys from India</td>
<td>1605</td>
<td>2015</td>
<td>8.7% (5.5–13.4)</td>
</tr>
<tr>
<td>South Africa National Health and Nutrition Examination Survey</td>
<td>747</td>
<td>2012</td>
<td>7.7% (5.4–12.8)</td>
</tr>
<tr>
<td>UK National Health Service National Diabetes Audit</td>
<td>16 585</td>
<td>2016-17</td>
<td>7.3% (5.1–12.1)</td>
</tr>
<tr>
<td>Indian Jaipur Diabetes Registry</td>
<td>8699</td>
<td>2014</td>
<td>9.0% (6.3–14.8)</td>
</tr>
<tr>
<td>Swedish National Diabetes Register</td>
<td>17 827</td>
<td>2016</td>
<td>8.4% (6.1–10.1)</td>
</tr>
<tr>
<td>Danish Adult Diabetes Registry</td>
<td>11 205</td>
<td>2014-15</td>
<td>7.7% (5.4–12.7)</td>
</tr>
<tr>
<td>Turkish Nationwide survey of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus</td>
<td>46 72</td>
<td>2017</td>
<td>7.5% (5.3–12.4)</td>
</tr>
<tr>
<td>China Health and Nutrition Study</td>
<td>1422</td>
<td>1999-2015</td>
<td>7.8% (5.2–12.7)</td>
</tr>
<tr>
<td>DiabCare study of the Philippines</td>
<td>770</td>
<td>2008</td>
<td>8.0% (5.6–13.2)</td>
</tr>
<tr>
<td>Japan National Health and Nutrition Survey</td>
<td>1434</td>
<td>2016</td>
<td>7.2% (5.0–11.8)</td>
</tr>
<tr>
<td>Korea National Health and Nutrition Examination Survey</td>
<td>1341</td>
<td>2010-12</td>
<td>8.2% (5.7–13.5)</td>
</tr>
<tr>
<td>Joint Asia Diabetes Evaluation Registry</td>
<td>28 111</td>
<td>2007-12</td>
<td>7.7% (5.4–12.7)</td>
</tr>
</tbody>
</table>

References for each cohort dataset are provided in the appendix. NA=not available. *Previous diagnosis, treatment, or laboratory results.

**Table 1:** Input cohort data for estimating reduction in HbA1c necessary to achieve treatment targets, and baseline proportion of people with type 2 diabetes treated with insulin, among those diagnosed
Outcomes were computed up to the year 2030 and additionally for the midpoint year of analysis (2024) for comparison.

All estimates were generated in R (version 3·4). The R code has been shared for reproducibility.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
First, we simulated the approach accounting for demographic change alone (with unchanged insulin access). The numbers of people projected to have type 2 diabetes over the period 2018–30 based on IDF estimates2 were 405·6 million in 2018 (95% CI 315·3 million–533·7 million) and 510·8 million in 2030 (395·9 million–674·3 million). The estimated number of people with type 2 diabetes 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 million–146·3 million], 7·9% prevalence) and India (72·5 million [52·8 million–91·9 million], 5·4% prevalence), followed by the USA, which had a higher prevalence (29·3 million [26·7 million–31·7 million], 9·0% prevalence; appendix). Projections for the year 2030 by the IDF2 were proportional to anticipated population growth, aging, and urbanisation in less developed countries, with the largest absolute numbers of people with type 2 diabetes projected to be in China (130·2 million [113·4 million–163·3 million], 9·0% prevalence), India (98·0 million [73·7 million–122·9 million], 6·5% prevalence), then the USA (31·8 million [28·7 million–34·5 million], 9·0% prevalence). When we combined data on the number of people with type 2 diabetes with the proportions diagnosed and given insulin,13 we estimated that insulin use would increase from 516·1 million 1000-unit vials (95% CI 409·0 million–658·6 million) to 633·7 million vials (500·5 million–806·7 million) per year between 2018 and 2030. The number of vials used decreased or increased by 2% if the proportion of people given 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 Oceania (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 type 2 diabetes using insulin would be lowest in the African region due to lower medication access and low prevalence of type 2 diabetes (1·8% of people with type 2 diabetes given insulin in 2030) and highest in the Americas region in the context of greater insulin use and higher type 2 diabetes prevalence (13·6% of people with type 2 diabetes given insulin in 2030).

Second, we simulated both demographic change and improved insulin access. We estimated the proportion of people diagnosed with type 2 diabetes who could receive insulin after maximum oral therapy, if insulin were widely available and if providers aimed to achieve a target HbA1c of 7% (appendix). The distribution of HbA1c among people with diagnosed type 2 diabetes (table 1) had a global mean of 9·1% and 95% centiles extending from 5·1% to 14·8%. The proportion of people with type 2 diabetes who we anticipated to use insulin increased from 7·4% (95% CI 5·8–9·4) to 15·5% (12·0–20·3), 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 (an increase of 7·1 times from 718 802 if insulin access were at current levels to 5198 662 under universal access), while the greatest absolute increase would be in the Asian region (an increase of 26·5 million people using insulin from 21·1 million if insulin access were at current levels to 47·6 million under universal access). The ratio of actual use (given current insulin access levels) to estimated use (given comprehensive insulin access) varied from 0·14 in Africa to 0·71 in the Americas; the overall worldwide ratio was 0·48.

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 hypoglycaemia and treatment-related inconvenience. When aiming for a treatment target HbA1c of 7%, we estimated that comprehensive access to insulin would avert 262 884 DALYs in the year 2018, increasing to 331 101 in the year 2030, with 65% of the DALYs averted in Asia alone (table 2). Starting insulin reduced the composite mean lifetime risk of microvascular complications (renal failure, severe vision loss, and pressure sensation loss) from 17·4% to 15·9%, but increased mean 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 DALYs over time.

Changing the target HbA1c 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 CIs based on Monte Carlo sampling (figure 2). A strict glycaemic control target of 6·5% HbA1c increased the global number of people required to be on insulin, and the amount of insulin required, by 38·9% compared with targeting 7% HbA1c.
conversely, a more liberal target of 8% HbA1c 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 6·5% or 7% HbA1c had lower numbers of net DALYs averted than a target of 8% because the lower levels of targeting increased DALYs caused by hypoglycaemia (figure 2D). The highest net DALYs averted was when targeting an HbA1c of 7% for people younger than 75 years and 8% for people aged 75 years and older, because these targets helped to avoid hypoglycaemic events that were concentrated primarily among older adults (figure 2C).

Additional analyses in which the target HbA1c was risk-based (target of ≤5% for composite microvascular risk) was similar to the target of 8% HbA1c scenario (figure 2C). Net DALYs averted for the midpoint year of 2024 were lower (by about 10%) than for the final year 2030 because of lower rates of diagnosis and lower total numbers of people with type 2 diabetes in 2024 than in 2030 (appendix).
Finally, we did sensitivity analyses to estimate how much less insulin might be used if three types of newer drugs (GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors) were more widely available and were 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 HbA1c reduction. However, the rate of hypoglycaemia was reduced due to avoidance of sulfonylurea treatment, increasing the absolute net DALYs averted by 14·9%. The relative amount of net DALYs averted through each treatment target were not affected (appendix).

Discussion
We estimated global insulin use for type 2 diabetes by country and year, worldwide, from 2018 to 2030, identifying several important findings. First, 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 use 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 HbA1c 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 CIs between the alternative approaches simulated). The incremental reduction in microvascular risk by further lowering the HbA1c target from 8% to 7% among those aged 75 years or older was

---

Figure 2: Variations in insulin treatment and DALYs averted under alternative treatment targets in the year 2030

People with type 2 diabetes estimated to use insulin (A), number of U100 insulin vials (1000 units each) used per year (B), net DALYs averted by insulin treatment (C), and 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) (D), worldwide. All estimates accounted for both demographic change and increased insulin access. Error bars represent 95% CIs. Base case: target HbA1c of 7·0% (53 mmol/mol) for all diagnosed and treated people (AFPG 8·0 mmol/L); intensive: target HbA1c of 6·5% (48 mmol/mol; AFPG 7·5 mmol/L); liberal: target HbA1c of 8% (64 mmol/mol; AFPG 9·2 mmol/L); age-tailored: for people <75 years target HbA1c of 7% and for those ≥75 years target HbA1c of 8%; risk based: people having ≥5% risk over 10 years of composite microvascular complications (renal failure or end-stage renal disease, severe vision loss <20/200 on a Snellen chart, or loss of pressure sensation by monofilament testing) estimated from the Risk Equations for Complications of type 2 Diabetes equations target HbA1c of 7%, or the HbA1c level that achieved an estimated risk ≤5% ( whichever HbA1c was higher). Numerical values corresponding to these figures are provided in the appendix.

DALYs=disability-adjusted life years. AFPG=average fasting plasma glucose.
outweighed by the increase in serious hypoglycaemia risk. We found that—for the overall population as a whole—using a more liberal target HbA1c of 8% used half as much insulin with only a 20% decline in DALYs saved. By comparison, intensive treatment to a goal HbA1c of 6.5% dramatically increased insulin use while increasing hypoglycaemia-related harms. Finally, we found that such insulin needs were unlikely to be affected by expanded access to newer oral diabetes drugs because such medicines are generally not more potent than existing drugs in reducing HbA1c, however, such drugs might substantially lower the risk of hypoglycaemia and thereby improve DALYs averted through therapy, though their cost might preclude their use in many situations.

Several key assumptions should be noted. First, the projections of type 2 diabetes prevalence from the IDF are based on population projections and the existing relations between age, sex, urbanisation, and diabetes prevalence. Because dietary and physical activity environments can change in both obesogenic and disease-reducing ways, the IDF projections could be either optimistic or pessimistic in unpredictable directions. Second, the RECODE equations we used were previously derived and validated from US samples, though we recalibrated the baseline hazard rates of events here to match GBD estimates.7,23 The use of these equations assumes that the relation between underlying demographics (age, sex), biomarkers (blood pressure, HbA1c), and complications is consistent across countries, which might neglect some ethnic variations. Third, our estimates of hypoglycaemia risk are based on a logistic regression (incorporating risk factors such as age and insulin dose) internally cross-validated in the ACCORD study sample,7 but not externally validated in another study sample. Fourth, we used the distributions of bodyweight, HbA1c, and insulin use from available cohort studies in the absence of comprehensive longitudinal data of high quality across all countries. The cohort data available nevertheless represent more than 60% of the global population with type 2 diabetes and therefore constitute the largest assembled sample, to our knowledge, of comprehensive diabetes profiles compiled to date. As bodyweight and insulin usage guidelines change, insulin usage quantities are expected to change in turn. We do not know the extent to which insulin initiation might be delayed by improved lifestyle modifications or effective public health interventions. Additionally, we did not have sufficient data to estimate the degree to which different oral antidiabetes drugs have different durability in maintaining HbA1c reductions over time. We assumed similar durability across classes; data from the ADAPT trial suggest that thiazolidinediones might have more durability than sulfonylureas when used as monotherapy,20,21 but insufficient data are available regarding durability of add-on therapies to metformin to construct a risk equation for time to insulin initiation.2,22

Future research should consider how key barriers to availability and accessibility of diagnosis and therapy, in the African region in particular, might be overcome,20 and how ministries of health can best prepare for the anticipated large increase in need of insulin in the coming years. Meanwhile, our study has shown that insulin use 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 comorbidities—might help to balance the risks of insulin therapy with longer-term microvascular benefit.

Contributors
SB, JSY, and DB contributed to the study design, data collection, data analysis, and writing of the report. SK, JID, SHW, KJL, and JBS contributed to the literature search, study design, data interpretation and writing the report.

Declaration of interests
KJL receives financial support from the US Centers for Medicare and Medicaid Services to develop and evaluate publicly reported quality measures. SHW reports non-financial support for accommodation and subsistence for attendance to the Scottish Study Group for Diabetes in the Young biannual conference from Novo Nordisk. All other authors declare no competing interests.

Acknowledgments
This report was prepared using ACCORD research materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the ACCORD or the NHLBI. This research was undertaken as part of the ACCISS study, which is funded by The Leona M and Harry B Helmsley Charitable Trust and the Stichting ICF. The present analysis is the work of the authors alone and does not necessarily reflect the views of the funders. All conclusions are intended for educational and informative purposes and do not constitute an endorsement or recommendation from the funders. We thank Marie McDonnell of Brigham and Women’s Hospital (Boston, MA, USA) for her advice regarding insulin dosing recommendations. We also thank Alper Sonmez of Gulhane School of Medicine (Ankara, Turkey) and Ilhan Satman of Istanbul University (Istanbul, Turkey) for advice and feedback on earlier versions of this report.

References
4 Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients’ advice and feedback on earlier versions of this report.

www.thelancet.com/diabetes-endocrinology  Published online November 20, 2018  http://dx.doi.org/10.1016/S2213-8587(18)30303-6


Insulin use for type 2 diabetes: the challenges of predicting trends and modelling care

There is absolutely no question that the world is in the midst of a diabetes epidemic. The disease, which affected 5% of adults worldwide in 1980, currently affects 9% of all adults worldwide, with disproportionately higher numbers in the developing world. This high prevalence, plus the increased rates of cardiovascular disease, stroke, heart failure, blindness, renal failure, neuropathic pain, cirrhosis, cancers, and other chronic problems conferred by diabetes, account for about US$700 billion of annual health-care costs worldwide.

Although the burden of this serious chronic disease is daunting, research shows that some therapies can prevent type 2 diabetes, prevent the consequences of diabetes, and achieve remission, meaning the disease might have a much smaller effect in the future than it has today. Indeed, established and emerging therapies, plus changes in the way that living spaces in cities are built, might succeed in partly or completely reversing the epidemic. Clearly, this speculation is an extrapolation from what is known today; however, it is hardly an unreasonable one.

In The Lancet Diabetes & Endocrinology, Sanjay Basu and colleagues use a highly sophisticated approach to predict future insulin use for type 2 diabetes and the effect of alternative treatment algorithms on insulin need and the burden of complications. Using conservative projections of diabetes prevalence in adults over the next 12 years from the International Diabetes Federation (IDF), the investigators created a clearly described, rigorously designed, and flexible mathematical model that allowed them to estimate the number of insulin users and the amount of insulin that will be required worldwide by 2030 under various assumptions. For example, assuming that insulin would be widely available and used to target an HbA1c of 7%, and assuming that currently available non-insulin therapies would have a durability similar to sulfonylureas (ie, would fail at a similar rate and over a similar time period), the researchers estimated that roughly 15.5% of all people with type 2 diabetes would use insulin in 2030.

The investigators also estimated the benefits and risks that would accrue if the HbA1c target was reduced to 6.5% or increased to 8%. Benefits were estimated as disability-adjusted life years (DALYs) averted for diabetes-related eye, kidney, and nerve disease, and risks were estimated as DALYs caused by severe hypoglycaemia, finger-stick glucose monitoring, and injections. They concluded that compared with a universal HbA1c target of 7%, use of a target of 7% in people with type 2 diabetes younger than 75 years, and 8% in people aged 75 years and older, would use less insulin, and would increase the net DALYs averted by 44.2% because of reduced hypoglycaemia.

These comprehensive analyses explicitly accounted for various circumstances. Nevertheless, they are based on mathematical models that are in turn based on other mathematical models. They are also based on various assumptions, including that type 2 diabetes prevalence will continue to increase linearly as predicted by the IDF regression model, that new insulin preparations being developed will have the same risk of hypoglycaemia as those that are currently available, that no changes will occur in the concomitant use of other drugs that have been shown to mitigate the risk of hypoglycaemia as those that are currently available, that no changes will occur in the concomitant use of therapies that are now known to reduce kidney disease independently of insulin, and no discovery and widespread use of new therapies to prevent eye and nerve disease. Finally, these analyses are also based on the assumption that only eye, nerve, and kidney disease are responsive to HbA1c targets. The data, however, are not known for many other diabetes-related outcomes and controversy persists regarding the possible benefits of targeting HbA1c for ischemic heart disease, cirrhosis, cancers, cognitive decline, and other long-term consequences. Such considerations suggest that predictions about the future need to be viewed cautiously. Indeed, the rapid pace of diabetes-related research suggests that one or more of the foregoing assumptions will prove to be wrong. For example, any model in 1985 is unlikely to have accurately predicted the diabetes epidemic that was clearly apparent only 15 years later.
Regardless of these uncertainties, insulin is likely to maintain its place as a crucial therapy for type 2 diabetes, and as such a sufficient global supply needs to be estimated and ensured. Conclusions regarding the best glucose targets, however, might be more fragile in view of the overlapping CIs observed in these data,7 and the need to personalise therapy rather than base treatment decision only on age or sex. Finally, ongoing updates to models such as these, incorporating new data and trends as they accrue, might be the most reliable way of assuring their reliability and relevance to evidence-based care.

Hertzel C Gerstein

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton L8S4K1, ON, Canada gerstein@mcmaster.ca

I am the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. I have received research grant support from AstraZeneca, Eli Lilly, Merck, and Sanofi, honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi, and consulting fees from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Janssen, and Sanofi.