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Incidence and costs of hypoglycemia in insulin-treated diabetes in Switzerland: A health-economic analysis

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ABSTRACT

Aims: We assess the incidence and economic burden of severe and non-severe hypoglycemia in insulin-treated diabetes type 1 and 2 patients in Switzerland.
Methods: We developed a health economic model to assess the incidence of hypoglycemia, the subsequent medical costs, and the production losses in insulin-treated diabetes patients. The model distinguishes between severity of hypoglycemia, type of diabetes, and type of medical care. We used survey data, health statistics, and health care utilization data extracted from primary studies.
Results: The number of hypoglycemic events in 2017 was estimated at 1.3 million in type 1 diabetes patients and at 0.7 million in insulin-treated type 2 diabetes patients. The subsequent medical costs amount to 38 million Swiss Francs (CHF), 61 % of which occur in type 2 diabetes. Outpatient visits dominate costs in both types of diabetes. Total production losses due to hypoglycemia amount to CHF 11 million. Almost 80 % of medical costs and 39 % of production losses are due to non-severe hypoglycemia.
Conclusions: Hypoglycemia leads to substantial socio-economic burden in Switzerland. Greater attention to non-severe hypoglycemic events and to severe hypoglycemia in type 2 diabetes could have a major impact on reducing this burden.

1. Introduction

Hypoglycemia is a considerable public health problem, due to its impact on quality of life of people with diabetes and its substantial economic implications.[1] Hypoglycemia is a common side effect of insulin therapy for diabetes mellitus type 1 and 2 and constitutes a major obstacle to achieving optimal glycemic control. Many people reduce their insulin dose after a hypoglycemic event, because of the fear of overdosing and recurrent hypoglycemic events. This can lead to poor glycemic control and increase the risk of severe long-term complications of diabetes.[2,3]

Hypoglycemic events are classified as non-severe or severe.[4] Non-severe events can be self-managed and are more frequent than severe hypoglycemic events.[5] Severe events require third party assistance, which may be provided by medical professionals or by laypersons.

The frequency of hypoglycemia is higher in people with type 1 diabetes and increases with the duration of diabetes, age and insulin treatment.[6–8] People with insulin-treated type 2 diabetes seek more frequently medical care after a hypoglycemic event compared to people with type 1 diabetes.[9] People with type 2 diabetes are also usually older and less experienced in managing their hypoglycemic events.[9,10]

Several studies have evaluated the incidence and costs of hypoglycemia in a number of countries using different methodologies.[1,2,10–12] The epidemiology, treatment and costs of diabetes in Switzerland have also previously been estimated for Switzerland.[13–16] However, incidence, treatment and cost of hypoglycemia are unknown in Switzerland.

Switzerland may be interesting from an international perspective, as the country has one of the most expensive and generous healthcare systems with universal coverage and virtually no waiting time.[17] Yearly per capita health care spending amounted in 2020 to 7179 purchasing power adjusted US-Dollars,[18] the third highest among the OECD countries after the US and Germany.

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The aim of this study is to assess the socio-economic burden of hypoglycemia in adults with insulin-treated type 1 or type 2 diabetes in Switzerland in 2017. We built a health-economic model distinguishing by type of diabetes, severity of hypoglycemic event, and type of medical care required. The model combines different data sources including survey data and health care claims extracted from individual studies, Swiss population surveys, and hospital registries. While other antidiabetic drugs can also cause hypoglycemia, the study focused on insulin, as it is the most relevant risk factor for hypoglycemia.

2. Materials and methods

2.1. Health economic model

We developed a health economic model assessing the incidence, treatment and costs of hypoglycemia in Switzerland in 2017. The model proceeds in two steps (see Fig. 1):

A first step assesses the number of people with diabetes treated with insulin (alone or in combination with other antidiabetic drugs), distinguishing by age-groups (18–64 and 65+) and type of diabetes (type 1 and type 2).

A second step assesses the number of hypoglycemic events by severity, need of medical care and type of medical care required. Although non-severe hypoglycemic events do not require, by definition, any medical or third-party assistance, some people visit an outpatient care physician in the days following an event. Severe hypoglycemic events requiring medical care can be treated in different settings: 1) in outpatient care, 2) on the spot by ambulance staff, and 3) in hospital. Hospital care includes 4) ambulatory care in the emergency department only or 5) inpatient care following an emergency department visit (defined as at least one over-night-stay). Severe and non-severe hypoglycemic events may also lead to more frequent self-measurements of blood glucose (SMBG) in the days following the event. This leads to a higher consumption of SMBG strips and lancets for the measuring devices, which were accounted for in the medical costs.

Cost of hypoglycemia were assessed in terms of medical costs and production losses for the year 2017. They were calculated from a societal perspective, including all private and public payers. Medical costs were calculated by multiplying the number of hypoglycemic events in each healthcare setting with the respective prices. Production losses were calculated as the value of the work time lost due to hypoglycemia, in terms of absence from work. These losses were calculated by multiplying the hours of productive time lost by economically active patients in working age with the hourly Swiss gross wage. We also considered that non-severe hypoglycemic events do not regularly lead to absence from work.

The model has an identical structure in patients with type 1 and type 2 diabetes but differs with respect to the model parameters. The model was programmed in Microsoft Excel 10.

2.2. Sources of input parameters

Table 1 shows the model input parameters used to calculate the incidence of hypoglycemia and the probabilities of using different types of medical care (the numbers in the first column of the table refer to the model stage shown in Fig. 1).

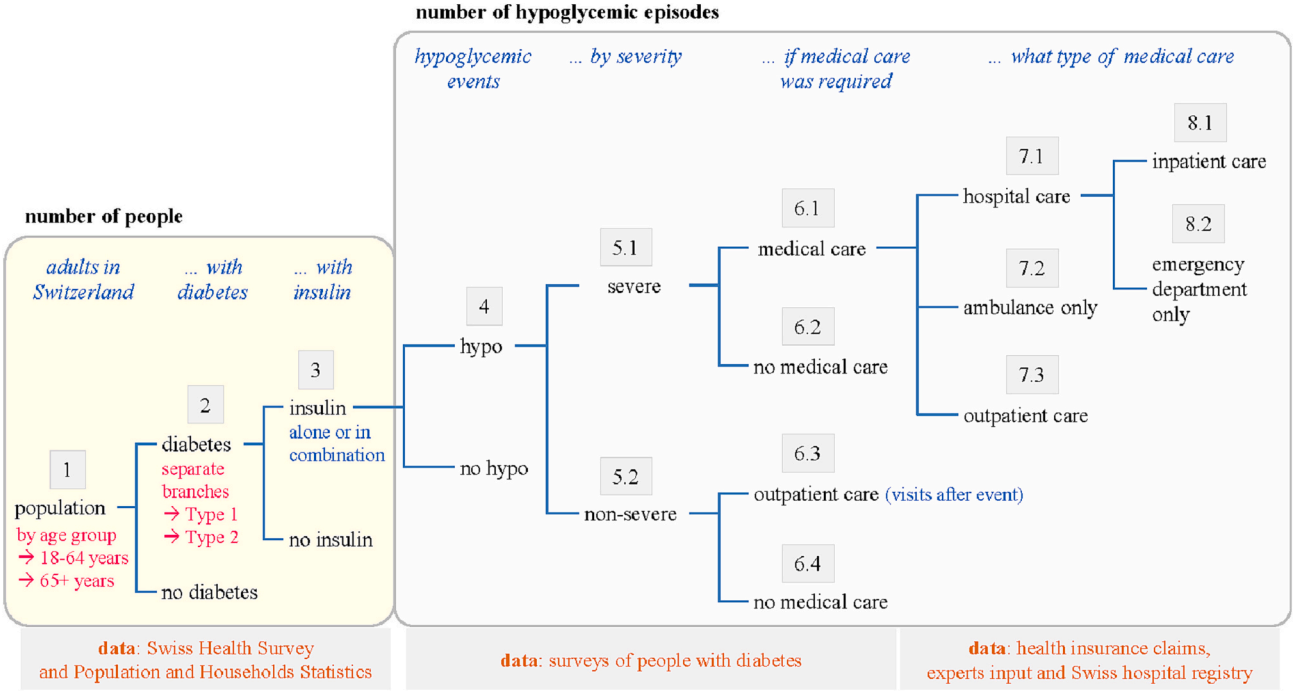


Fig. 1. Overview of the health economic model.
The model first calculates the prevalence of insulin-treated diabetes (stages 1–3) and then the incidence of hypoglycemic events of different severities and requiring different types of medical care (stages 4–8).

Table 1
Model parameters for calculation of incidence and type of treatment of hypoglycemia.

Model stage	Model parameter	Source of parameter value		Parameter value in model	
		Type 1 DM	Type 2 DM	Type 1 DM	Type 2 DM
1	Size of adult population (2017)	Population and Households Statistics[19]		18–64 years old: 5′481′577 Over 65 years old: 1′550′947	
2	Overall prevalence of type 1 and type 2 diabetes in the adult population	Authors' calculation based on the Swiss Health Survey 2017[20]		18–64 years old: 0.31 % ≥65 years old: 0.50 % ≥18 years old: 0.35 %	18–64 years old: 2.41 % ≥65 years old: 9.63 % ≥18 years old: 4.00 %
3	Prevalence of insulin-treated type 1 and type 2 diabetes by age-group (2017)			18–64 years old: 0.31 % ≥65 years old: 0.50 % ≥18 years old: 0.35 %	18–64 years old: 0.55 % ≥65 years old: 2.36 % ≥18 years old: 0.95 %
4–5.1	Number of severe events per person-year	Meta-analysis[6,7,12,39–43]	Meta-analysis[7,12,43–48]	0.77	0.35
4–5.2	Number of non-severe events per person-year	Meta-analysis[7,12,41–43]	Meta-analysis[7,12,41,43,47,48]	70.12	15.33
6.1	Severe: share of events with medical care	de Groot et al. 2018[11] and Hammer et al. 2009[10] regarding only Germany		22.68 %	42.64 %
6.2	Severe: share of events with no medical care	100 % minus % in stage 6.1		77.32 %	57.36 %
6.3	Non-severe: share of events with medical care	Geelhoed-Duijvestijn et al. 2013[3] regarding only Switzerland		4.90 %	15.73 %
7.1	Severe: share of hospital care within medical care	69.91 % of the share in type 2 by Curkendall et al. 2011[21]	Curkendall et al. 2011[21]	21.09 %	30.17 %
7.2	Severe: share of ambulance only within medical care	MedStat 2017[22] and experts' input from the canton hospital of St. Gallen		0.71 %	1.00 %
7.3	Severe: share of outpatient care only within medical care	100 % minus % in stage 7.1 minus % in stage 7.2		78.20 %	68.83 %
8.1	Severe: share of inpatient care within hospital care	69.91 % of the share in type 2 by Curkendall et al. 2011[21]	Curkendall et al. 2011[21]	14.48 %	20.71 %
	Correction factor for lower inpatient care use by people with type 1 diabetes	Authors' calculation based on stage 7.1 and stage 8.1 regarding type 2 diabetes and on MedStat 2017[22] regarding type 1 diabetes		69.91 % (132 people)	
8.2	Severe: share of emergency department only within hospital care	100 % minus % in stage 8.1	Curkendall et al. 2011[21]	85.52 %	79.29 %

DM: diabetes mellitus. MedStat: Swiss hospital registry.

Number of insulin-treated diabetes patients (stage 3). The prevalence of insulin-treated type 1 and type 2 diabetes in the two age-groups was calculated by combining information from the Swiss Population and Households Statistics (STATPOP)[19] and the Swiss Health Survey[20] (SHS) for 2017. The STATPOP covers the entire population in Switzerland and allows to identify the total number of people by age-groups. The SHS is a large representative population survey, which allows to identify the prevalence of diagnosed diabetes mellitus, distinguish between type 1 and type 2 diabetes based on self-reported type of diabetes and type of drug use. Since a substantial number of respondents gave contradictory responses on their type of diabetes, our calculation of the number of respondents with type 1 diabetes included only those declaring type 1 diabetes and current insulin use.

Number of hypoglycemic events (stages 4 and 5). The rate of hypoglycemic events per person-year, by severity and type of diabetes, was calculated based on studies identified in a structured literature review we conducted (see Appendix A.1). Although we identified two studies reporting the incidence of hypoglycemic events in Switzerland, we decided to include international studies in our calculations too, since the sample size of the Swiss studies was relatively small and incidence rates varied remarkably (Fig. A.2). We pooled the studies using self-reported survey data and a variance indicator of their estimated rates with four statistical meta-analyses (one for each combination of type 1 or type 2 diabetes with severe or non-severe, Table A.2). We carried out meta-analyses to account for the sample size and the precision of the estimated rate. For studies reporting more than one rate (e.g. for different levels of awareness) we first calculated the weighted mean.

Share of events requiring medical care (stage 6). The parameters used for the calculation of hypoglycemia-induced health care utilization by insulin-treated diabetes patients were drawn from the literature and calibrated to Swiss data. The proportion of events requiring medical care was drawn from studies using survey data. The allocation of these events to different types of medical care was based on studies using claims data. Swiss studies were used where available. The proportion of non-severe hypoglycemic events requiring medical care were obtained from a Swiss survey reported in Geelhoed-Duijvestijn et al. 2013.[3] The proportion of severe hypoglycemic events requiring medical care was obtained as the weighted mean of two studies using a Dutch[11] and a German[10] survey, since these countries have relatively similar levels of health care provision compared to Switzerland.

Type of medical care required (stages 7 and 8). The probabilities of using different types of medical care differed by type of diabetes.

For patients with type 2 diabetes we proceeded as follows: 1) The share of severe events requiring hospital care (stage 7.1), inpatient care (stage 8.1) and emergency department only (stage 8.2), was based on a large US claims-based study.[21] 2) The share of events treated at the scene by ambulance staff (stage 7.2) was calculated based on information provided by the cantonal hospital of St. Gallen (the main tertiary referral center in Eastern Switzerland). 3) The share of events treated in outpatient care (stage 7.3) was defined as the remaining severe events requiring medical care.

For patients with type 1 diabetes, we found no studies of comparable data quality. Therefore, we estimated the share of type 1 patients with hospital care (stage 7.1) and inpatient care (stage 8.1) with re-calculation: Starting with the documented number of inpatient visits due to hypoglycemia in type 1 (according to MedStat 2017), we used the respective shares of people with type 2 diabetes in stage 7.1 and 8.1 to derive the respective shares of type 1 patients (see Appendix A.3.1).[22] The resulting correcting factor of 80.56 % appears plausible considering that people with type 2 diabetes are more prone in seeking hospital care compared to those with type 1 diabetes.[9] The share of events treated at the scene by ambulance staff and the share of events treated in outpatient care was calculated as for type 2 diabetes.

Unit costs of healthcare services and production losses. Table 2 summarizes the input parameters used to calculate the medical costs and production losses:

- Unit costs of treatments were drawn from Swiss data sources for 2017. The price of an additional SMBG was drawn from the medical devices list (MiGEL).[23] The number of additional SMBG conducted following a non-severe hypoglycemic event was drawn from a Swiss survey.[3] We conservatively assumed that a similar number of additional tests was conducted following a severe hypoglycemic event.
- The mean cost of an outpatient care consultation of patients with insulin-treated diabetes was provided by SWICA, a large and representative Swiss health insurer. For the treatment of severe hypoglycemia, an emergency lump-sum was added. Due to lack of data, we assumed that 90 % of severe and 20 % of non-severe hypoglycemic events led to a home treatment by a physician and the rest to a patient visit in the physician's office.
- The cost of ambulance services was calculated as the mean of the 2017 tariffs of the canton of St. Gallen[24] and of the city of Zurich.[25]
- The cost of an emergency department visit was calculated as the weighted mean of the cost of a standard emergency department visit and of a hospital-associated emergency primary care unit with general practitioners, according to a Swiss study.[26] We assumed that 75 % of emergency department treatments were carried out in standard emergency departments. The share of patients admitted to hospital by ambulance was based on MedStat 2017 for inpatient stays.[22] Due to lack of information, we assumed that the share of hospital admissions by ambulance for patients treated in the emergency department equaled to the one for patients treated in inpatient care.
- The costs of inpatient treatments were calculated based on MedStat[22] in combination with SwissDRG cost-weights.[27] Hypoglycemic events were identified by ICD-10-GM codes E16, E10.6, E11.6, E13.6 and E14.6. The DRG cost-weight of a single stay was multiplied with the average cost of inpatient stays in 2017.
- The percentage of diabetes patients with work time lost and the number of work hours lost due to non-severe hypoglycemia were extracted from a Swiss survey.[3] The number of work hours lost due to severe hypoglycemia was drawn from a Swedish study.[28] The labor force participation rate and the hourly wage were drawn from the Swiss Federal Statistical Office.[29,30]

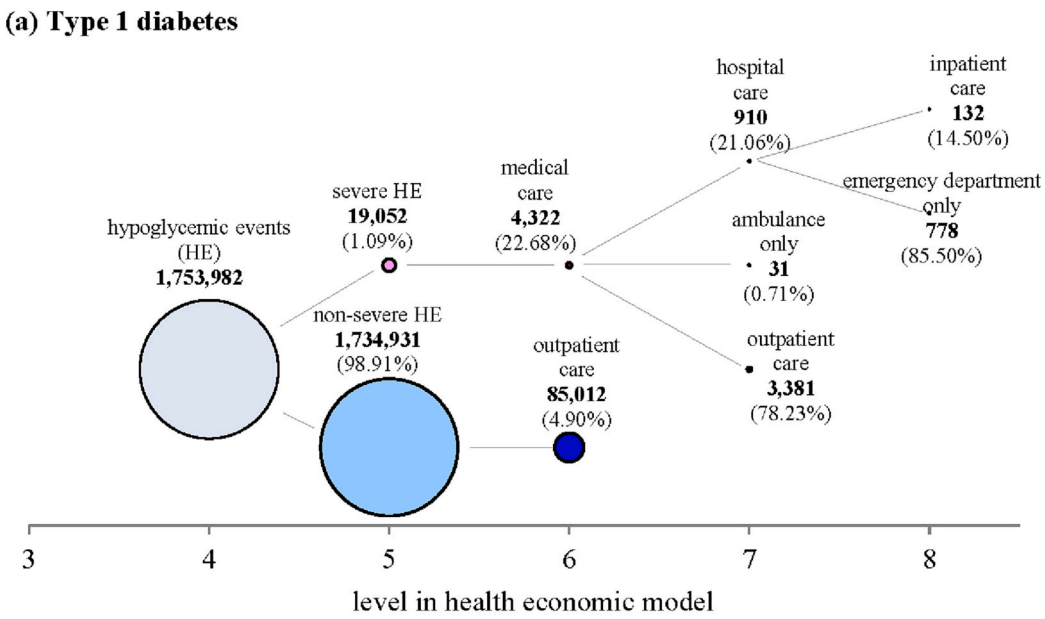
Table 2
Values and sources of cost parameters.

Model parameter	Source of parameter value	Parameter value in model
Cost parameters regarding the medical costs		
Price per SMBG strip	MiGEL[23] (21.03.01.01.1 from	CHF 0.80
Price per SMBG lancet	01.01.2017B)	+ CHF 0.13
Overall price per SMBG	MiGEL[23] (21.03.05.00.1 until 01.03.2018B,C)	= CHF 0.93
Number of additional glucose measurements	Geelhoed-Duijvestijn et al. 2013[3]	2.90
Non-severe: outpatient visit	SWICA health insurance assumption: 80 % office visit and 20 % home visit	CHF 153.71
Severe: outpatient visit	SWICA health insurance assumption: 10 % office visit and 90 % home visit	CHF 235.69
Ambulance	Mean of the 2017 tariffs of the canton of St. Gallen[24] and of the city of Zurich[25]	CHF 1316.67
Emergency department only	Eichler et al. 2014[26] assumption: 75 % of emergency treatments carried out in standard emergency departments	CHF 470.25
Cost of inpatient stays		
Type 1 diabetes age 18–64	Authors' calculation based on MedStat 2017[22] (hypoglycemia main diagnosis) and SwissDRG 2017[27]	CHF 6317.62
Type 1 diabetes age ≥65		CHF 7376.51
Type 2 diabetes age 18–64		CHF 7647.95
Type 2 diabetes age ≥65		CHF 8161.17
% admitted by ambulance		
Type 1 diabetes age 18–64	Authors' calculation based on MedStat 2017[22]	20.62 %
Type 1 diabetes age ≥65		2.78 %
Type 2 diabetes age 18–64		22.15 %
Type 2 diabetes age ≥65		9.52 %
Cost parameters regarding the production losses		
Percentage with work time lost due to a non-severe event	Geelhoed-Duijvestijn et al. 2013[3]	5.90 %
Number of work hours lost due to…		
Non-severe event	Geelhoed-Duijvestijn et al. 2013[3]	1.27
Severe event not requiring medical care	Jönsson et al. 2006[28]	1.80
Severe event requiring outpatient care	Jönsson et al. 2006[28]	2.21
Severe event requiring hospital or ambulance only care	Jönsson et al. 2006[28]	54.12
Labor force participation rate	Swiss Federal Statistical Office[29]	84.00 %
Average hourly wage	Swiss Federal Statistical Office[30]	CHF 60.05

SMBG: self-measurements of blood glucose. MiGEL: list with medical devices. MedStat: Swiss hospital registry.

2.3. Sensitivity analyses

To test the robustness of our results we conducted two types of sensitivity analysis and one scenario analysis. The probabilistic sensitivity analysis varied all model parameters within their predefined distributions in 1000 random draws (details in Appendix A.3.2). The outcomes of this sensitivity analysis were used to determine the 95 % confidence intervals of our main results. The univariate sensitivity analysis assessed the impact of single model parameters on the overall results by changing each parameter at a time by ±20 %. The scenario analysis assessed the impact of using only the Swiss rates of hypoglycemic events per person-year (Fig. A.2).



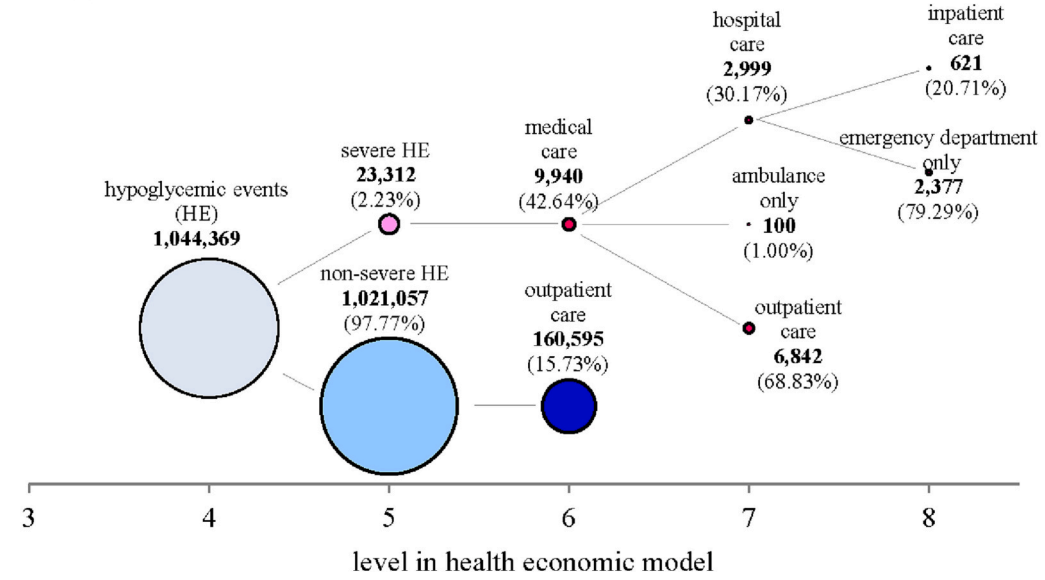


Fig. 2. Estimated annual incidence of hypoglycemic events by severity and type of medical care required.
Sample size type 1 diabetes = 24,742; sample size type 2 diabetes = 66,605. The size of the circles is proportional to the incidence of hypoglycemic events in each type of hypoglycemia severity and type of medical care required. The horizontal axis marks the respective levels of the epidemiological model. The percentages are in respect to the value of the previous circle (level).

3. Results

3.1. Incidence of hypoglycemia

Our estimations show that in 2017 there were 91,347 adult insulin-treated patients with diabetes in Switzerland. Among those, 24,742 type 1 diabetes patients experienced 1,753,982 hypoglycemic events, and 66,605 type 2 diabetes patients experienced 1,044,369 hypoglycemic events (Fig. 2).

3.2. Health care utilization

Overall, about 9 % of the hypoglycemic events were estimated to require medical care (Fig. 2). Of the hypoglycemic events requiring medical care 66 % occurred in patients with type 2 diabetes and 95 % of them were non-severe. In patients with type 1 diabetes 69 % of the hypoglycemic events requiring medical care occurred in the age-group 18–64 years. In patients with type 2 diabetes 45 % of hypoglycemic events requiring medical care occurred in the same age-group. Table A.5 in the Appendix gives additional details on the estimated number of hypoglycemic events distinguished by diabetes type, age-groups, hypoglycemia severity and required medical care. Among all severe events requiring medical care, 72 % were managed in outpatient care and 27 % in the hospital. The estimated proportion of events that were treated directly by the paramedic team at the scene (0.9 %) is low in Switzerland compared to other countries, such as England.[31] Patients with type 2 diabetes experiencing severe hypoglycemic events had almost three times as many hospital visits compared to people with type 1 diabetes.

3.3. Medical costs and production losses

The estimated total cost of insulin-induced hypoglycemia amounted to 70.68 million Swiss Francs[1] (CHF) as a sum of direct medical costs (79 %) and production losses (21 %). The 18–64 age-group accounted for half of medical costs and all production losses (see Table A.6 in the

[1] In 2017 a Swiss Franc was worth 1.022 US-Dollars or 0.866 Euros.[32]

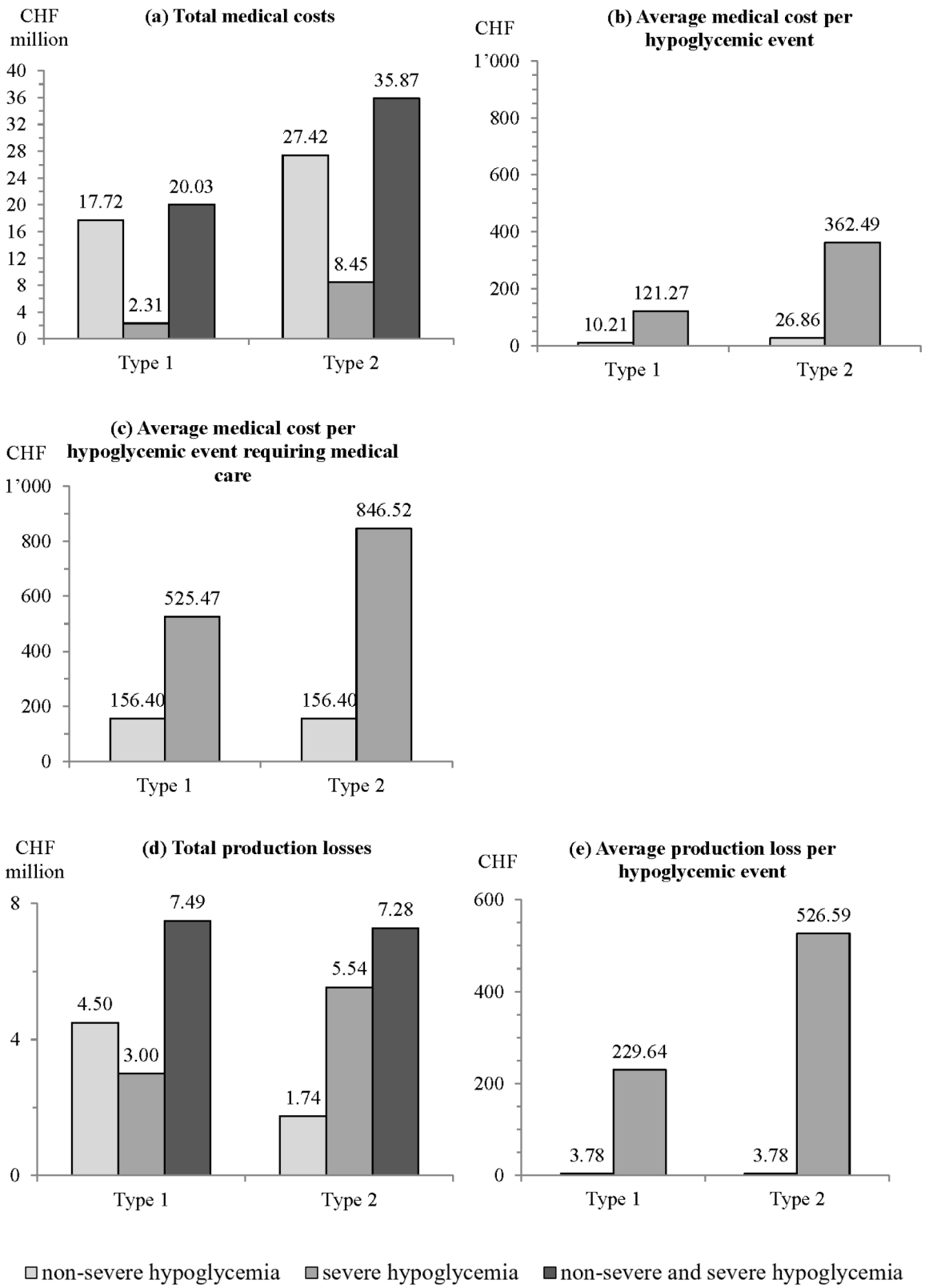


Fig. 3. Estimated medical costs and production losses by severity of hypoglycemia and type of diabetes.

Appendix for a detailed overview of the costs per diabetes type for each age-group, hypoglycemia severity and type of medical care required).

Fig. 3 shows the estimated distribution of medical costs and production losses by severity of hypoglycemia and type of diabetes:

- The total medical costs amounted to CHF 55.91 million. Of these, CHF 35.87 million (64 %) are attributed to type 2 diabetes and 45.15 million (81 %) to non-severe events (Panel a).
- The average medical cost per hypoglycemic event is higher in type 2 diabetes compared to type 1 diabetes and for severe compared to non-severe events (Panel b). The average medical cost per severe hypoglycemic event amounted to CHF 121.27 in type 1 diabetes and to CHF 362.49 in type 2 diabetes. The average medical cost per non-severe hypoglycemic event amounted to CHF 10.21 in type 1 diabetes and to CHF 26.86 in type 2 diabetes.
- The average cost per hypoglycemic event requiring medical care varied from CHF 156.40 for non-severe events in both diabetes types to CHF 846.52 for severe events in type 2 diabetes (Panel c).
- The total production losses amounted to CHF 14.78 million. Of these, CHF 7.49 million (51 %) are attributed to type 1 diabetes and 8.53 (58 %) to severe events (Panel d).
- The average production losses per severe hypoglycemic event are higher in type 2 diabetes amounting to CHF 526.59 (Panel e). This is mainly attributed to the higher number of severe events in type 2 diabetes treated in hospitals.

Fig. A.3 in the Appendix illustrates the estimated distribution of medical costs of hypoglycemia by type of diabetes and type of medical care (Panel a) and by severity of hypoglycemia and type of care (Panel b):

- Outpatient care visits dominate medical costs in both types of diabetes. Additional SMBG constitute a high share of medical costs, especially in type 1 diabetes. In type 2 diabetes, inpatient care constitutes the second largest cost component with 14 %.
- Regarding severity of hypoglycemia, 81 % of medical costs are attributed to non-severe hypoglycemia. Of these, 84 % are due to outpatient care visits and 16 % to additional SMBG. 19 % of medical costs are attributed to severe hypoglycemia. Of these, 75 % are due to hospital care, while ambulance services, outpatient care visits and additional SMBG together account for the remaining 25 %.

3.4. Sensitivity analyses

The results of the probabilistic sensitivity analyses are reported in the Appendix. Tables A.5 and A.6 show the 95 % confidence intervals of the main outcomes.

The parameters with the strongest effect on the number of hypoglycemic events requiring medical care are the share of non-severe hypoglycemic events requiring medical care in type 2 diabetes and the number of non-severe events per person-year in type 2 diabetes (Panel a in Fig. A.4). The parameters with the strongest effect on medical costs are the cost of an outpatient visit due to a non-severe event and the share of non-severe events in type 2 diabetes requiring medical care (Panel b in Fig. A.4). A 20 % reduction in the cost of an outpatient visit would, for example, decrease the overall medical costs by 14 % and a 20 % reduction in the share of non-severe events in type 2 diabetes requiring medical care would decrease the overall medical costs by 10 %. The parameters with the strongest effect on production losses are the hourly wage and the number of work hours lost due to the severe event requiring hospital or on the scene treatment by the ambulance staff (Panel c in Fig. A.4).

Among the parameters based on international data, the share of severe events requiring medical care in type 2 diabetes and the share of severe events requiring hospital care have the largest effect on the results (Fig. A.4). A ± 20 % change of the share of severe events requiring medical care in type 2 diabetes would change the overall medical costs by ±3 % and the overall production losses by ±6 %. The estimate we used is rather conservative compared to Spain[10] and similar compared to Great Britain.[9,10] A ± 20 % change of the share of severe events requiring hospital care would change the overall medical costs by ±2 % and the overall production losses by ±7 %. The estimate we used is comparable to other European studies based on survey data[10] and smaller compared to some other US studies based on claims data with a much smaller sample size.

The scenario analysis shows that, if we had used only the Swiss rates of hypoglycemic events per person-year (Fig. A.2), the total medical costs would be 42 % to 43 % higher and the total production losses 2 % to 8 % higher. Consequently, our main results appear conservative.

4. Discussion

This study illustrates the substantial socio-economic burden of hypoglycemia in insulin-treated patients with type 1 and type 2 diabetes in Switzerland. It shows the estimated incidence of hypoglycemia and quantifies the subsequent medical costs in different healthcare settings as well as production losses due to absence from work. Incidence of non-severe hypoglycemia is estimated at 70.12 events per person year in type 1 diabetes patients and at 15.33 events in type 2 diabetes patients. The cost of severe and non-severe hypoglycemia is estimated at CHF 55.91 million in medical costs and CHF 14.78 million in production losses. These medical costs correspond to 6 % of total costs of diabetes in Switzerland.[16]

Interestingly, non-severe events are a considerable driver of the costs of hypoglycemia. Although severe events require more medical care, the much higher incidence of non-severe events results in 81 % of medical costs and in 42 % of production losses.

Our estimations show that hypoglycemic events in patients with type 2 diabetes dominate costs due to their higher use of medical care, in particular inpatient care and the more frequent outpatient visits for non-severe hypoglycemic events. As previously observed,[9] this may be due to the better self-management skills of patients with type 1 diabetes, who are mostly younger and less affected by comorbidities. In both types of diabetes, medical treatments in outpatient care settings and additional SMBG due to hypoglycemic events constitute a high share of medical costs.

The average production loss due to a severe hypoglycemic event is substantial, estimated at CHF 252 and CHF 815 in type 1 and type 2 diabetes respectively. Although the impact of hypoglycemic events on quality of life and life years were not assessed in this study, it is likely to contribute substantially to the clinical and social impact of hypoglycemia.

Our study has several strengths. To our knowledge, it is the first study to develop a health economic model of the incidence and socio-economic burden of hypoglycemia in insulin-treated diabetes in Switzerland. It is also the first study to estimate population prevalence

data of insulin-treated diabetes mellitus and to distinguish between diabetes types and age-groups in Switzerland. A second strength is the combination of data from numerous sources, including the treated prevalence of diabetes (from the Swiss health survey), the incidence of hypoglycemia (from patient survey data), the number of hospitalizations due to hypoglycemia (from hospital registry data) and the cost of medical care (from health insurance claims data). A third strength is that we weighted the information provided by survey data regarding the rate of hypoglycemic episodes per person-year for the sample size and standard errors by applying meta-analyses. Finally, our health economic model may also be applied in other countries, by adjusting the model parameters to the country-specific values.

Our study also has some limitations. First, the distinction between the prevalence of type 1 and type 2 diabetes is associated with some uncertainty, as it was based on patient-reported data and patients sometimes are not aware of their type of diabetes. Switzerland, however, lacks other population data on diabetes type. Second, based on the data available in Switzerland it is not possible to estimate the costs of hypoglycemia distinguishing between different insulin regimens, especially in type 2 diabetes. Third, where information was not available, we estimated the health care utilization in type 1 diabetes by combining the health care utilization of type 2 diabetes and the real-world number of inpatient stays in Switzerland according to MedStat (see Appendix A.3.1). This combination of different sources is common in health economic modelling and its consequences were explored in the sensitivity analyses. Fourth, although most of the model parameters were based on Swiss data, some parameters had to be extracted from other European countries and the US. Where possible we used information from countries with healthcare systems comparable to Switzerland's. Table A.7 in the Appendix provides an overview of the country of data origin. Despite the uncertainty regarding the representativity of these parameters for Switzerland, it is important to mention again that the costs for inpatient care in type 1 diabetes were based on the actual number of inpatient stays due to hypoglycemia in Switzerland in 2017. Fifth, the use of continuous blood glucose measurements in type 1 diabetes, and to lesser extent in intensified insulin-treated type 2 diabetes, has reduced the amount of SMBG leading to reduced costs due to hypoglycemia but increased overall costs of diabetes treatment. Sixth, it is also worth mentioning that in the past years the treatment of type 2 diabetes has changed considerably, as new drugs have entered the market. The new drugs in the classes of Glucagon-Like Peptide-1 (GLP-1) receptor agonists and Sodium glucose linked transporter-2 (SGLT-2) inhibitors can be used as monotherapy, in which case they do not cause hypoglycemia.[33,34] When they are used in combination with insulin therapy, basal insulin is often sufficient for achieving a better glycemic control and hypoglycemia-prone intensive insulin treatment can be avoided. We could not analyze the effect of the increasing usage of these new antidiabetic drugs on the incidence of hypoglycemic events in our study, since the combination therapies of these new drugs with insulin were not so frequently used in 2017. Thus, we might overestimate the incidence of hypoglycemic events in our type 2 diabetes population in the light of the current treatment guidelines for type 2 diabetes in 2023.[35]

Compared to other European countries, the estimated medical costs per severe hypoglycemic event in Switzerland seem to be lower in type 1 diabetes and at the average European level in type 2 diabetes. The Netherlands[11] and Spain[10,36] exhibit the highest costs, followed by Germany,[14] the UK,[14,36] Switzerland and Denmark.[37] The estimated medical costs per non-severe hypoglycemic events in Switzerland are at the average in type 1 diabetes and twice to almost eleven times higher in type 2 diabetes compared to other European countries.[11,36] In the USA most studies focus on severe hypoglycemia in type 2 diabetes and show that the medical costs are much higher than in Europe.[1,38] Cross-country and –study comparisons are difficult due to differences in the definition and incidence of hypoglycemia, the type of costs considered, the different types of medical care used, the overall differences in per-capita health care expenditures, and the different perspectives from which the costs were calculated. Cross-country differences in the production losses are influenced by differences in the hourly wage and the estimated working hours lost.

This study suggests that insulin treatment in diabetes mellitus can lead to high rates of health care utilization for managing hypoglycemia with considerable medical costs and production losses. The results of this study can be helpful for policy makers and health care organizations seeking to develop cost-effective interventions aiming to decrease the incidence of hypoglycemia in insulin-treated patients. Such a reduction could lead to better glucose control, to higher wellbeing and potentially save some of the substantial estimated costs from avoidable health care use and production losses. This would in turn reduce the socio-economic burden on the patients, as well as on the healthcare system. The results can also be key for physicians in establishing the proper treatment and prevention regimen of their diabetes patients, as it highlights the subgroups in which the incidence of hypoglycemia is the highest. Hence, physicians should actively ask their patients and help them take preventive measures (e.g. dietary changes, insulin dosage according to planned physical activity) in order to avoid future hypoglycemic events.

In conclusion, medical costs of hypoglycemia in insulin-treated patients are estimated at CHF 55.91 million, 64 % of which occur in type 2 diabetes. Outpatient visits were responsible for a large proportion of the costs in both types of diabetes. Thus, prevention of non-severe and severe hypoglycemic events using new treatments and technologies might reduce the burden and total costs of diabetes care.

Statement of funding sources

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Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A

A.1. Literature review

We systematically searched for studies reporting the rate of severe and non-severe hypoglycemic events per person-year in insulin-treated type 1 and type 2 diabetes. We searched the electronic databases MEDLINE and COCHRANE-library, including the University of York Centre for Review and Dissemination Library, using four electronic interfaces (PubMed, Cochrane, CRD and Google Scholar). We searched for papers in English or German, based on pre-specified search terms and inclusion/exclusion criteria (Table A.1).

Our searches retrieved 547 potentially relevant studies (Fig. A.1). The papers selected included studies based on surveys of people with diabetes. Of the 19 studies included only 13 were used, as the rest did not report a measure of precision of the estimated incidence rate, such as a confidence interval or standard deviation, which is required for the meta-analysis.

Table A.1
Inclusion criteria.

Study design	Observational studies or Randomized controlled trials using survey data (e.g. self-declared incidence of hypoglycemia) Any length of follow-up; any sample size Language restriction: published in English and German Year of publication: from 2004 Publication status: published journal articles
Setting	Any study setting (e.g. primary care sector; diabetes care in specialized centers) Geographical study location: high-income countries to ascertain health care services comparable to Switzerland
Population	Diabetes patients with insulin treated diabetes mellitus Age $\geq$ 18 years; any sex
Intervention	Insulin as stand-alone therapy or insulin in combination with oral antidiabetic agents
Control intervention (comparator)	If outcome of comparison is a ratio, the net-effect between the two groups needs to be insulin or insulin and oral antidiabetic agents. Otherwise, the comparator is not of interest.
Outcome measure	Number of hypoglycemic events per person-year

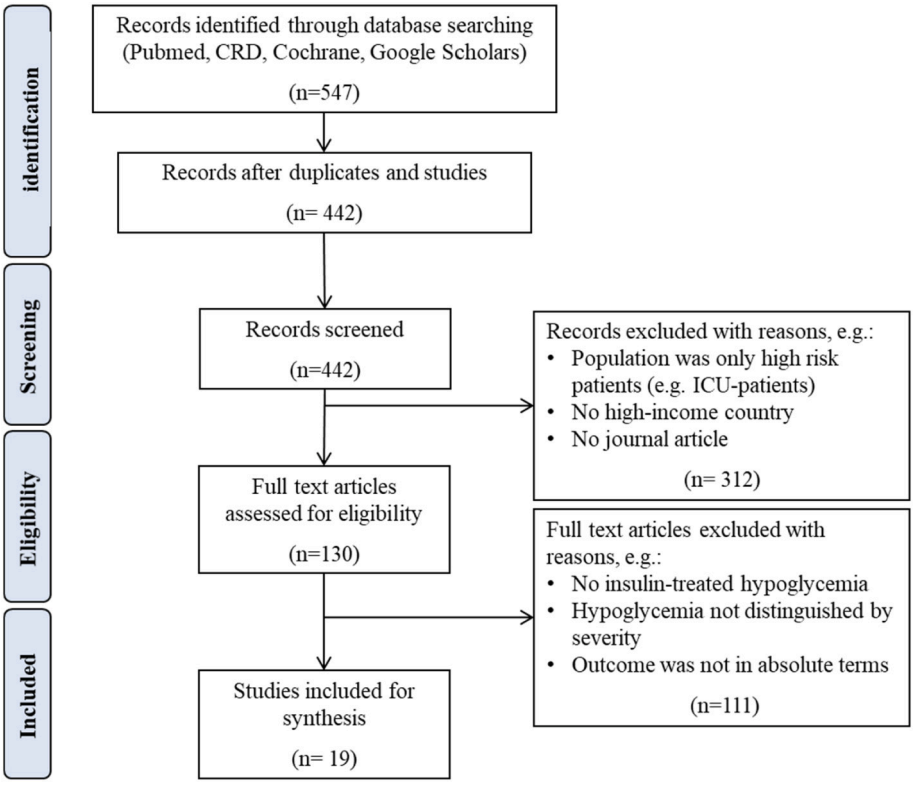


Fig. A.1. PRISMA flow diagram of the literature review.

A.2. Number of hypoglycemic events

Our literature review showed that the incidence of hypoglycemia varies widely (Fig. A.2). Differences in the results between studies may be attributed to differences in the measurement and definitions of hypoglycemia, in the diabetes population (e.g. age, drug regimens, duration of insulin treatment, comorbidity status, type of diabetes), or in potential recall bias. The rate of hypoglycemic episodes is, for example, higher in studies based on surveys or patient diaries than in studies based on health insurance claims, hospital data, or on documented blood glucose values.

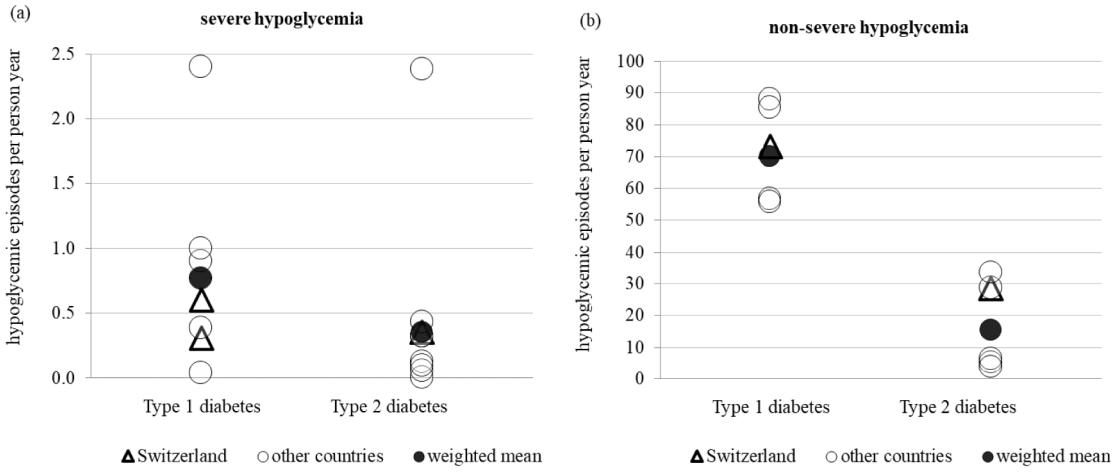


Fig. A.2. Rate of hypoglycemic events per person-year according to different sources.

Table A.2
Results of meta-analyses regarding the rate of hypoglycemic events per person-year.

Diabetes type	Hypoglycemia severity	Hypoglycemic events per person-year	95 % CI	Number of studies	References
Type 1	Severe	0.77	0.48–1.05	8	6,7,12,39–43
	Non-severe	70.12	57.47–82.77	5	7,12,41–43
Type 2	Severe	0.35	0.23–0.47	8	7,12,43–48
	Non-severe	15.33	10.45–20.21	6	7,12,41,43,47,48

We applied random-effects model allowing the real effect to vary among the studies.

A.3. Study protocol

A.3.1. Health care use

The probabilities of using different types of medical care for treating a severe hypoglycemic event differs by type of diabetes. As there are no data on Switzerland regarding these probabilities, we searched for published studies reporting this information. For this aim, we only considered studies, in which the population constituted of insulin-treated adult type 1 or type 2 diabetes patients, and which used health care claims and not survey data. For type 2 diabetes, we chose to follow a large US claims-based study.[21] For type 1 diabetes, we did not find any studies of comparable data quality (e.g. big sample size). However, for type 1 diabetes we know the exact number of inpatient visits due to hypoglycemia in each age-group in Switzerland in 2017 from MedStat 2017.[22] We, therefore, calibrated the share of severe events in type 1 diabetes treated in the hospital and the share of these events hospitalized, by combing the exact number of inpatient visits with the respective shares in type 2 diabetes. Similarly, as for type 2, the share of severe events in type 1 diabetes treated at the scene by ambulance staff was calculated based on information provided by the cantonal hospital of St. Gallen (the main tertiary referral center in Eastern Switzerland). The share of events treated in outpatient care was defined as the remaining severe events requiring medical care (Table A.3).

Table A.3
Model parameters for calculation of incidence and type of treatment of hypoglycemia in type 1 diabetes by age-group.

Number in model	Model parameter	Source of parameter value	Parameter value in model
		Type 1 DM	Type 1 DM
18–64			
7.1	Severe: share of hospital care within medical care	72.41 % of the share in type 2 by Curkendall et al. 2011[21]	21.84 %
7.2	Severe: share of ambulance only within medical care	MedStat 2017[22] and experts' input from the canton hospital of St. Gallen	0.71 %
7.3	Severe: share of outpatient care only within medical care	100 %-7.1–7.2	77.45 %
8.1	Severe: share of inpatient care within hospital care	72.41 % of the share in type 2 by Curkendall et al. 2011[21]	15.00 %
	Correction factor for lower inpatient care use by people with type 1 diabetes	Authors' calculation based on 7.1 and 8.1 regarding type 2 DM and on MedStat 2017[22] regarding type 1 DM	72.41 % (97 people)
8.2	Severe: share of emergency department only within hospital care	100 %-8.1	85.00 %
≥65			
7.1	Severe: share of hospital care within medical care	64.15 % of the share in type 2 by Curkendall et al. 2011[21]	19.35 %
7.2	Severe: share of ambulance only within medical care	MedStat 2017[22] and experts' input from the canton hospital of St. Gallen	0.71 %
7.3	Severe: share of outpatient care only within medical care	100 %-7.1–7.2	79.94 %
8.1	Severe: share of inpatient care within hospital care	64.15 % of the share in type 2 by Curkendall et al. 2011[21]	13.29 %
	Correction factor for lower inpatient care use by people with type 1 diabetes	Authors' calculation based on 7.1 and 8.1 regarding type 2 DM and on MedStat 2017[22] regarding type 1 DM	64.15 % (35 people)
8.2	Severe: share of emergency department only within hospital care	100 %-8.1	86.71 %
≥18 (all)			
7.1	Severe: share of hospital care within medical care	69.91 % of the share in type 2 by Curkendall et al. 2011[21]	21.09 %
7.2	Severe: share of ambulance only within medical care	MedStat 2017[22] and experts' input from the canton hospital of St. Gallen	0.71 %
7.3	Severe: share of outpatient care only within medical care	100 %-7.1–7.2	78.20 %
8.1	Severe: share of inpatient care within hospital care	69.91 % of the share in type 2 by Curkendall et al. 2011[21]	14.48 %
	Correction factor for lower inpatient care use by people with type 1 diabetes	Authors' calculation based on 7.1 and 8.1 regarding type 2 DM and on MedStat 2017[22] regarding type 1 DM	69.91 % (132 people)
8.2	Severe: share of emergency department only within hospital care	100 %-8.1	85.52 %

DM: diabetes mellitus. MedStat: Swiss hospital registry.

A.3.2. Sensitivity analysis

We conducted a probabilistic sensitivity analysis in order to estimate the precision of our main results. The probabilistic sensitivity analysis varied all model parameters randomly within their predefined distributions 1000 times. The type of the distribution of each model parameter was defined based on the type of the parameter, following the handbook by Briggs et al.[49] (Table A.4). For the definition of each distribution the mean and standard error is required. For parameters without information on their variability (e.g. standard error or confidence interval) from the literature, the standard error was set at 20 % of the mean.

Table A.4
Assumptions on distributions of model parameters.

Type of parameter	Distribution
Incidence rate	Normal
Parameters with 0,1 range, such as shares and prevalence	Beta
Cost parameters	Gamma

A.4. Additional results

Table A.5
Estimated hypoglycemic events per diabetes type, age-group, hypoglycemia severity and type of medical care required in 2017 (95 % CI).

Model stage	Type 1 diabetes						Type 2 diabetes					
	Age 18–64		Age ≥ 65		Age ≥ 18		Age 18–64		Age ≥ 65		Age ≥ 18	
4	All events											
	1,201,614	(1,178,361–1,206,951)	552,368	(549,195–569,469)	1,753,982	(1,721,605–1,758,364)	471,023	(464,874–475,770)	573,346	(565,512–577,295)	1,044,369	(1,037,112–1058,619)
5.1	Severe											
	13,052	(12,875–13,281)	6000	(5936–6186)	19,052	(18,751–19,293)	10,514	(10,362–10,614)	12,798	(12,724–13,011)	23,312	(22,934–23,457)
6.1	Severe, medical care											
	2961	(2919–3017)	1361	(1353–1412)	4322	(4252–4381)	4483	(4425–4537)	5457	(5415–5541)	9940	(9774–10,004)
7.1	Severe, medical care, hospital											
	647	(635–663)	263	(262–276)	910	(897–929)	1352	(1335–1369)	1646	(1634–1672)	2999	(2949–3019)
7.2	Severe, medical care, ambulance on the spot											
	21	(19–23)	10	(9–11)	31	(26–31)	45	(39–45)	55	(54–63)	100	(100–116)
7.3	Severe, medical care, outpatient											
	2293	(2259–2337)	1088	(1081–1128)	3381	(3323–3427)	3086	(3049–3126)	3756	(3723–3810)	6842	(6717–6876)
8.1	Severe, medical care, hospital - inpatient											
	97	(94–99)	35	(34–36)	132	(129–135)	280	(277–284)	341	(338–346)	621	(611–626)
8.2	Severe, medical care, hospital - ED											
	550	(541–564)	228	(227–240)	778	(767–795)	1072	(1058–1085)	1305	(1296–1326)	2377	(2338–2393)
5.2	Non-severe											
	1,188,562	(1,165,404–1,193,752)	546,368	(543,230–563,312)	1,734,931	(1,702,724–1,739,202)	460,509	(454,415–465,254)	560,549	(552,662–564,410)	1,021,057	(1,013,953–1,035,388)
6.3	Non-severe, outpatient care											
	58,240	(55,626–58,522)	26,772	(25,838–27,367)	85,012	(82,453–86,917)	72,430	(71,712–73,894)	88,165	(86,899–89,447)	160,595	(159,235–163,871)

ED: emergency department.

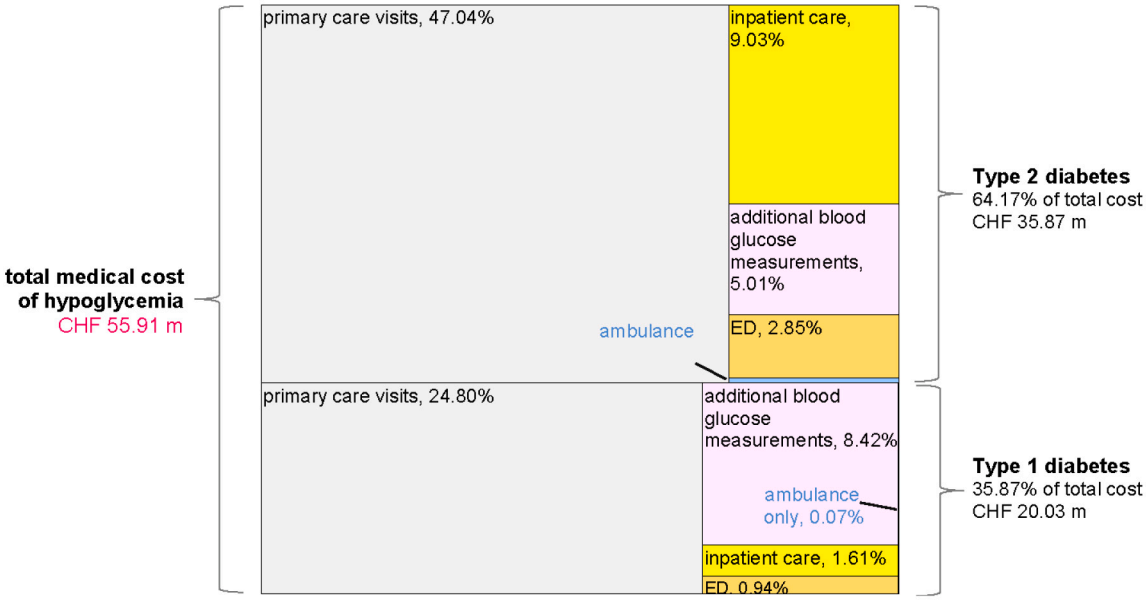
Table A.6
Estimated costs of hypoglycemia per diabetes type, age-group, hypoglycemia severity and type of medical care required in millions 2017 CHF (95 % CI).

Model stage		Type 1 + 2 diabetes		Type 1 diabetes						Type 2 diabetes					
		Age ≥ 18		Age 18–64		Age ≥ 65		Age ≥ 18		Age 18–64		Age ≥ 65		Age ≥ 18	
Medical costs															
4	Overall	55.91	(37.07–81.01)	13.79	(6.86–25.29)	6.24	(2.42–12.45)	20.03	(10.00–35.59)	16.22	(10.04–25.67)	19.65	(12.23–29.75)	35.87	(22.94–55.23)
5.1	**Severe**	**10.76**	**(7.41–14.39)**	**1.65**	**(0.85–2.79)**	**6.64**	**(0.28–1.27)**	**2.31**	**(1.20–3.79)**	**3.86**	**(2.28–5.93)**	**4.59**	**(2.73–6.73)**	**8.45**	**(5.07–11.96)**
	SMBG	0.11	(0.06–0.20)	0.04	(0.01–0.07)	0.02	(0.01–0.03)	0.05	(0.02–0.10)	0.03	(0.01–0.05)	0.03	(0.02–0.06)	0.06	(0.03–0.11)
7.2	Ambulance only	0.17	(0.01–0.61)	0.03	(0.00–0.18)	0.01	(0.00–0.07)	0.04	(0.00–0.20)	0.06	(0.00–0.26)	0.07	(0.00–0.33)	0.13	(0.00–0.59)
7.3	Outpatient care	2.41	(1.44–3.77)	0.54	(0.26–0.99)	0.26	(0.10–0.50)	0.80	(0.39–1.39)	0.73	(0.38–1.20)	0.89	(0.47–1.47)	1.61	(0.86–2.61)
8.1	ED	2.12	(1.33–3.16)	0.41	(0.18–0.77)	0.12	(0.04–0.25)	0.52	(0.25–0.95)	0.82	(0.47–1.25)	0.78	(0.42–1.20)	1.59	(0.92–2.47)
8.2	Inpatient care	5.95	(3.80–8.45)	0.64	(0.24–1.30)	0.26	(0.09–0.57)	0.90	(0.39–1.71)	2.22	(1.17–3.66)	2.83	(1.50–4.44)	5.05	(2.91–7.56)
5.2	**Non-severe**	**45.15**	**(26.51–69.71)**	**12.14**	**(5.44–23.50)**	**5.58**	**(2.01–11.66)**	**17.72**	**(7.93–32.91)**	**12.37**	**(6.92–21.00)**	**15.06**	**(8.12–24.67)**	**27.42**	**(15.12–45.78)**
	SMBG	7.39	(3.86–12.37)	3.19	(1.50–5.82)	1.47	(0.55–2.95)	4.65	(2.33–8.20)	1.24	(0.58–2.20)	1.50	(0.70–2.72)	2.74	(1.33–4.68)
6.3	Outpatient care	37.75	(19.93–61.68)	8.95	(3.06–19.41)	4.12	(1.21–9.19)	13.07	(4.42–27.37)	11.13	(5.94–19.50)	13.55	(6.92–23.00)	24.69	(13.12–41.93)

Model stage		Type 1 + 2 diabetes		Type 1 diabetes		Type 2 diabetes	
		Age 18–64		Age 18–64		Age 18–64	
Production losses							
4	Overall	14.77	(8.18–24.03)	7.49	(3.54–13.38)	7.28	(4.04–12.09)
5.1	Severe	8.53	(4.61–14.58)	3.00	(1.32–5.59)	5.54	(2.66–9.62)
5.2	Non-severe	6.24	(2.74–12.12)	4.50	(1.90–9.25)	1.74	(0.77–3.37)

SMBG: self-measurements of blood glucose. ED: emergency department.

(a) Total medical costs by type of diabetes and type of medical care



(b) Total medical costs by type of hypoglycemia severity and type of medical care

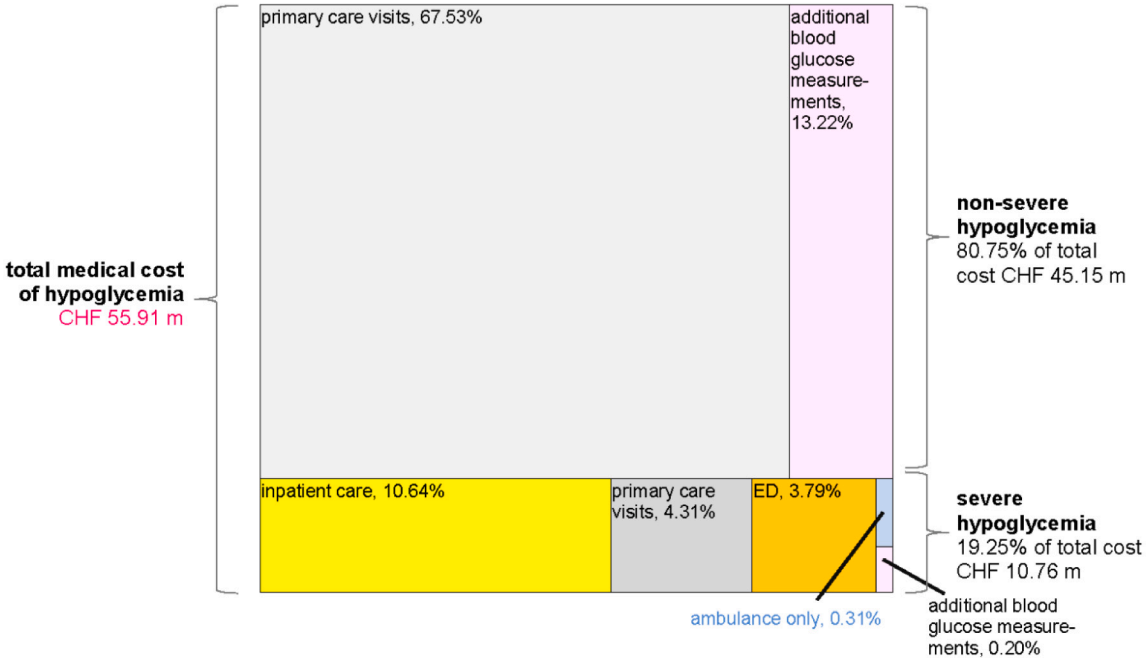
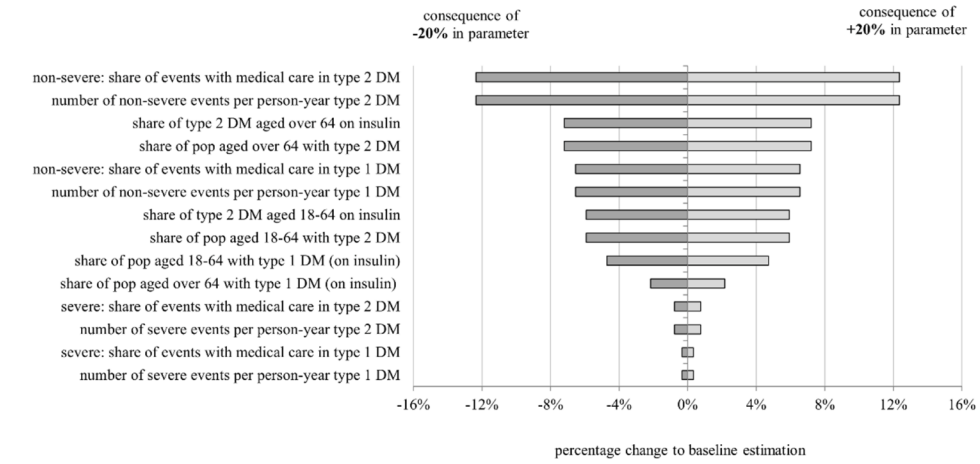
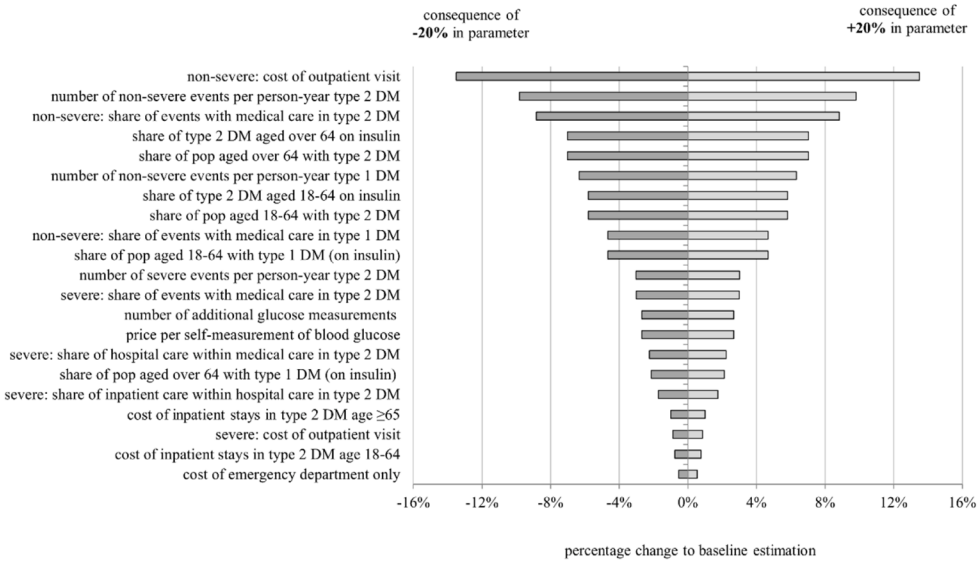


Fig. A.3. Estimated total medical costs of hypoglycemia by type of diabetes and medical care and by severity and type of medical care. m: million. ED: emergency department.

(a) Number of hypoglycemic events requiring medical care



(b) Overall medical costs



(c) Overall production losses

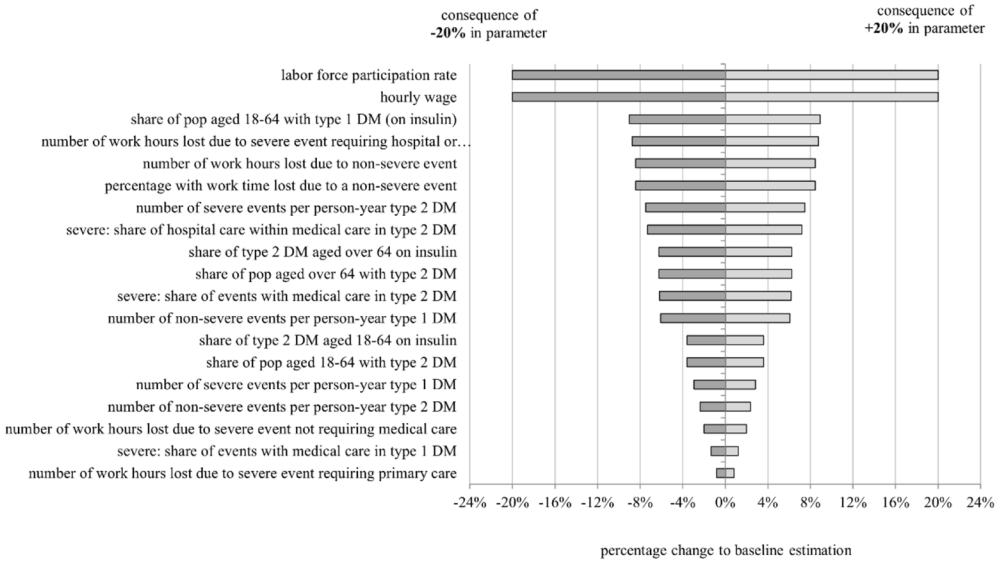


Fig. A.4. Univariate sensitivity analysis.
DM: diabetes mellitus. pop: population.

A.5. Overview of sources

Table A.7
Country of origin of model parameters.

Model parameter	Country of data origin
Parameters for calculation of incidence and type of treatment of hypoglycemia	
Size of adult population (2017)	Switzerland
Overall prevalence of type 1 and type 2 diabetes in the adult population	Switzerland
Prevalence of insulin-treated type 1 and type 2 diabetes by age-group (2017)	Switzerland
Number of severe events per person-year	MANY including Switzerland
Number of non-severe events per person-year	MANY including Switzerland
Severe: share of events with medical care	Netherlands and Germany
Non-severe: share of events with medical care	Switzerland
Severe: share of hospital care within medical care	USA
Severe: share of ambulance only within medical care	Switzerland
Severe: share of outpatient care only within medical care	100% minus above two
Severe: share of inpatient care within hospital care	USA
Severe: share of emergency department only within hospital care	100% minus above
Model parameter	country of data origin
Cost parameters regarding the medical costs	
Price per SMBG strip Price per SMBG lancet Overall price per SMBG	Switzerland
Number of additional glucose measurements	Switzerland
Non-severe: outpatient visit	Switzerland
Severe: outpatient visit	Switzerland
Ambulance	Switzerland
Emergency department only	Switzerland
Cost of inpatient stays	
Type 1 diabetes age 18–64	Switzerland
Type 1 diabetes age ≥65	Switzerland
Type 2 diabetes age 18–64	Switzerland
Type 2 diabetes age ≥65	Switzerland
% admitted by ambulance	
Type 1 diabetes age 18–64	Switzerland
Type 1 diabetes age ≥65	Switzerland
Type 2 diabetes age 18–64	Switzerland
Type 2 diabetes age ≥65	Switzerland
Cost parameters regarding the production losses	
Percentage with work time lost due to a non-severe event	Switzerland
Number of work hours lost due to…	
Non-severe event	Switzerland
Severe event not requiring medical care	Sweden
Severe event requiring outpatient care	Sweden
Severe event requiring hospital or ambulance only care	Sweden
Labor force participation rate	Switzerland
Average hourly wage	Switzerland

The model parameters are color coded. Green means that the country of data origin is Switzerland and orange that the country of data origin is not Switzerland. DM: diabetes mellitus. MedStat: Swiss hospital registry. SMBG: self-measurements of blood glucose. MiGEL: list with medical devices.

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