**Supplementary materials of “*Review and Estimation of Disutility for Joint Health States of Severe and Non-Severe Hypoglycemic Events in Diabetes*”.**

Supplementary Material 1: Literature Search Strategies

Supplementary Material 2: Methods of estimating disutility of the joint four health states: daytime NSHE, nocturnal NSHE, daytime SHE, and nocturnal SHE

Supplementary Material 3: Estimation of Disutility for Joint Two Health States of SHEs and NSHEs

Supplementary Material 4: Disutility Data for Construct Validity

Supplementary Material 5: Details of Studies Included in Literature Review

**Supplementary Material 1: Literature Search Strategies**

Database(s): **Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®**1946-Present  
Search Strategy:

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | utili\*.mp. | 942737 |
| 2 | disutili\*.mp. | 510 |
| 3 | EQ-5D.mp. or exp "European Quality of Life 5 Dimensions questionnaire"/ | 9402 |
| 4 | health utility index.mp. | 217 |
| 5 | 1 or 2 or 3 or 4 | 949535 |
| 6 | exp "quality of life"/ or quality?of?life.mp. | 212581 |
| 7 | exp quality adjusted life year/ or QALY\*.mp. | 18802 |
| 8 | quality?adjusted life?yea\*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] | 0 |
| 9 | patient?reported outcom\*.mp. | 17 |
| 10 | preference?based measu\*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] | 0 |
| 11 | healthy utility.mp. | 4 |
| 12 | 6 or 7 or 8 or 9 or 10 or 11 | 227975 |
| 13 | exp hypoglycemia/ or hypoglyc#emi\*.mp. | 38583 |
| 14 | hbA1c.mp. or exp hemoglobin A1c/ | 37579 |
| 15 | 13 or 14 | 72765 |
| 16 | exp diabetes mellitus/ or diabet\*.mp. | 742169 |
| 17 | 5 and 12 and 15 and 16 | 217 |
| 18 | limit 17 to (english language and full text and yr="2000 - 2021") | 52 |

Database(s): **Embase Classic+Embase**1947 to 2021 June 11  
Search Strategy:

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | utili\*.mp. | 1399082 |
| 2 | disutili\*.mp. | 1014 |
| 3 | EQ-5D.mp. or exp "European Quality of Life 5 Dimensions questionnaire"/ | 20417 |
| 4 | health utility index.mp. | 378 |
| 5 | 1 or 2 or 3 or 4 | 1413507 |
| 6 | exp "quality of life"/ or quality?of?life.mp. | 535159 |
| 7 | exp quality adjusted life year/ or QALY\*.mp. | 34331 |
| 8 | quality?adjusted life?yea\*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 2 |
| 9 | patient?reported outcom\*.mp. | 864 |
| 10 | preference?based measu\*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 12 |
| 11 | healthy utility.mp. | 9 |
| 12 | 6 or 7 or 8 or 9 or 10 or 11 | 538801 |
| 13 | exp hypoglycemia/ or hypoglyc#emi\*.mp. | 102204 |
| 14 | hbA1c.mp. or exp hemoglobin A1c/ | 127462 |
| 15 | 13 or 14 | 209776 |
| 16 | exp diabetes mellitus/ or diabet\*.mp. | 1285772 |
| 17 | 5 and 12 and 15 and 16 | 1051 |
| 18 | limit 17 to (english language and yr="2000 - 2021" and article) | 492 |

**Supplementary Material 2: Methods of estimating disutility of the joint four health states: daytime NSHE, nocturnal NSHE, daytime SHE, and nocturnal SHE**

Many studies use the multiple linear regression model to obtain the adjusted disutility (i.e., the coefficient of the variable) of hypoglycemia in diabetic patients. The dependent variable (i.e., the utility value) in the linear model is not bounded by the maximum utility of 1, so the constant coefficient and the predicted utilities can be greater than 1. The R2 of these models is often low, so it is difficult to use these models to calculate the baseline utility (i.e., diabetic patients without any complications). Furthermore, most studies grouped patients by hypoglycemia severity level, and do not estimate the cumulative impact of different frequencies of SHE and NSHE events on utility.

We chose a study that derived utilities for hypoglycemia using TTO in the general population (Evans et al. 2013) [1] to estimate the disutility for joint SHEs and NSHEs due to the following considerations:

* We expected that the health state utility should be impacted by the severity and frequency of hypoglycemic events, so we needed a study that reported disutilities for different severity levels and frequencies
* Evans et al provided the disutilities for daytime and nocturnal SHEs/NSHEs separately, which can be used for estimating the disutility for joint health states at the given frequencies of SHEs and NSHEs
* The health states included events which have short-term impact (e.g., shaky, hungry, irritable, sweaty, confused) and long-term impact (e.g., worrying about the effects on day-to-day life)
* The sample size is very large, with 8,286 participants from 5 countries
* Many published economic evaluations used this study to estimate disutility for hypoglycemic events

To illustrate the estimation of disutility in joint health states, we used the results of a recent survey study in 552 individuals with type 1 (N=94) and type 2 (N=456) diabetes in Canada [2]. This study showed that 83% of respondents with type 1 diabetes experienced at least one SHE in the last year or at least one NSHE in the past month (daytime: 80%; nocturnal 63%), as did 62% of respondents with type 2 diabetes (daytime: 59%; nocturnal 37%). Also, 54% of individuals with type 1 diabetes and 38% of those with type 2 diabetes experienced SHEs in the past year [2]. We assumed that the number of each type of hypoglycemic event follows a Poisson distribution. Based on the median, 10th percentile and 90th percentile of simulated data of hypoglycemic events for type 1 and type 2 diabetes, we created six hypothetical scenarios (Table 1). These scenarios captured diabetes with low, medium and high frequencies of NSHEs and SHEs. We first estimated the disutility for each type of event (the disutility values per event [1] multiplied by the corresponding frequency of events per year, or log-transformed estimates of disutility values associated with daytime and nocturnal NSHEs by Lauridsen et al [3]), and then estimated the disutility of joint health states with four types of events (daytime NSHE, nocturnal NSHE, daytime SHE, and nocturnal SHE) using four commonly-used non-parametric methods, below. The parametric estimator (the linear index) requires individual level data, and is not feasible for the present study.

Nonparametric methods to estimate joint health state utilities include the additive, minimum, and multiplicative methods, and adjusted decrement estimator (ADE) [4]. The disutility of a joint health state is the difference between the utility of the joint health state and baseline utility.

DJ = UJ – U0 (S2.1)

where DJ is the total reduction in health utility from hypoglycemia (i.e., disutility), U0 is the baseline utility for diabetes without any complications, and UJ is the joint utility for diabetes with different types of hypoglycemic events. In our study, disutility has a negative value, so the utility for a given condition is equal to the baseline utility plus the disutility (e.g., UJ = U0 + DJ), which is equivalent to baseline utility minutes an absolute value of disutility.

The additive method assumes that the conditions that affect the utility function independently with no overlap [4]:

DJ = DdNSHE + DnNSHE + DdSHE + DnSHE (S2.2)

where DdNSHE, DnNSHE, DdSHE and DnSHE denote the disutility due to daytime NSHE, nocturnal NSHE, daytime SHE, and nocturnal SHE, respectively.

The minimum utility method uses the largest disutility of the different types of hypoglycemic events in the joint health state, and assumes there is no cumulative burden from the other types of events. The health state with the minimum disutility is associated with the minimum value of health utility [4]:

DJ = Min (DdNSHE, DnNSHE, DdSHE, DnSHE) (S2.3)

The multiplicative method assumes that for each additional condition, the disutility impact is proportional to the disutility already experienced [4]:

(S2.4)

The ADE method incorporates terms that represent the additive, multiplicative, and minimum methods [5]: The original ADE was used for estimating the joint health utility for two conditions [6]: and we extended it to four conditions using the approach introduced by Thompson et al [4]: We ranked the four health state utilities (i.e., (U0 + DdNSHE), (U0 + DnNSHE), (U0 + DdSHE), and (U0 + DnSHE)), and estimated the joint utility for the health states with the two lowest utilities. We then estimated the joint utility of this utility and the third lowest utility. Using the same approach, we estimated the joint health utility of this utility and that of the remaining condition. We use the terms “joint two health states” to describe joint health states with two types of hypoglycemic events, and “joint four health states” when joint health states include four types of hypoglycemic events.

**Supplementary Material 3: Estimation of Disutility for Joint Two Health States of SHEs and NSHEs**

*Overview*

The American Diabetes Association Workgroup on Hypoglycemia has suggested five classifications for hypoglycemia: 1) severe hypoglycemia, 2) documented symptomatic hypoglycemia, 3) asymptomatic hypoglycemia, 4) probable symptomatic hypoglycemia, and 5) pseudo-hypoglycemia (presenting with the typical symptoms of hypoglycemia with a plasma glucose concentration slightly above 70 mg/dL) [7,8]. For our purpose of estimating disutility, we included the main predictors and excluded redundant predictors. We excluded asymptomatic hypoglycemia because it is not expected to be associated with an immediate reduction in HRQoL. We also grouped documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, and pseudo-hypoglycemia into non-severe hypoglycemic event (NSHE) since all three are associated with minor symptoms. We kept severe hypoglycemic events (SHEs) and NSHEs separate because there are substantial differences in frequency and health consequences between the two.

We assumed the total number of NSHEs and SHEs would jointly predict the disutility. We first estimated the disutility values associated with the total number of NSHEs and SHEs separately [1]. Then, we used the adjusted decrement estimator (ADE) [6] and multiplicative method [5] to estimate the utility of the joint diabetes-specific health states of having both NSHEs and SHEs. Finally, we applied our methods to six hypothetical hypoglycemia scenarios.

*Disutility of non-severe hypoglycemic events*

Given that daytime and nocturnal NSHEs are highly correlated, we combined them to estimate the total number of NSHEs. Nocturnal hypoglycemia is usually defined as hypoglycemia occurring between 12 AM and 6 AM (comprising 25% of a 24-hour day). In the reference case, we assumed that NSHEs occur randomly throughout the 24-hour day so the disutility of any NSHEs at a given frequency would be approximately equal to the weighted disutility of daytime NSHEs (75% weight) and nocturnal NSHEs (25% weight). For example, the disutility of NSHEs occurring once weekly was calculated to be −0.044 [−0.036 (disutility of weekly daytime NSHE) × 75% − 0.069 (disutility of weekly nocturnal NSHE) × 25%] [1]. We summarized the disutility values associated with hypoglycemic events by type and frequency as in Evans et al [1] (Table S1). In total, five observations (hypoglycemic frequency of 0, 4, 12, 52, and 156 events per year) were reported by Evans et al for NSHEs [1]. Using our approach of weighting daytime and nocturnal events, the corresponding disutilities would be 0, −0.033, −0.034, −0.044, and −0.082, respectively. In the sensitivity analysis, we assumed that NSHEs do not occur randomly and estimated the disutility for 15% and 35% nocturnal NSHEs.

We used six different methods to transform the total number of NSHEs per year (e.g., square root of the number of NSHEs) (Table S2). Then, we used the linear regression model to predict the disutility from the transformed number of events:

DN = β × TNSHE (S3.1)

where β is the coefficient in the linear regression model, DN is the disutility due to NSHEs, TNSHE is the transformed number of NSHEs per year. We omitted the intercept (i.e., intercept = 0) because the disutility would be 0 when there are no NSHEs.

We used R2 to evaluate the fit of the prediction models. We also evaluated goodness-of-fit using the sum of squares due to error (SSE) for the disutility from the five observations. A smaller SSE indicates a better-fitting model.

*Disutility of severe hypoglycemic events*

The disutility values of daytime and nocturnal SHEs were very similar in Evans et al [1] (Table S1). Therefore, we did not use the weighted disutilities as we did with NSHEs, but instead used the three observations (frequency of hypoglycemia at 0, 1, and 4 events per year for daytime SHEs) reported by Evans et al [1]. We used the same methods (Formula S3.1) as for NSHEs to develop and evaluate the prediction model.

*Joint disutility of severe and non-severe hypoglycemic events*

To date, there is no gold standard for estimating utilities for joint health states. However, some studies showed the ADE (Formula S3.2) by Hu and Fu can generate a less-biased prediction of utilities for joint health states compared with other methods [5,6]. This method incorporates terms that represent the additive, multiplicative, and minimum methods [5]:

Uij = Umin – Umin × (1 – Ui) × (1 − Uj) (S3.2)

where Uij is the mean joint utility for people with both health conditions i and j, Umin = min (Ui, Uj), Ui is the mean single utility for people with health conditions i, and Uj is the mean single utility for people with health condition j.

Based on Formula S3.2, we can express the joint utility of diabetes with both SHEs and NSHEs (USN) in Formula S3.3 below. In the study by Hu and Fu, the non-parametric estimator calculated the utility decrement of the joint health states [(1 – Ui) and (1 − Uj) for health conditions i and j, respectively] from a perfect health state (utility = 1). For diabetes-specific health states however, it may be more appropriate to calculate the utility decrement from the baseline utility for diabetes without any diabetes complications (0.844 in Evans et al [1]). As such, we modified the non-parametric estimator for calculating the joint health states of SHEs and NSHEs for diabetes as follows:

USN = Umin – Umin × (U0 – US) × (U0 − UN) = Umin × (1 – DS × DN)

Let US < UN, then

= (U0 – |DS|) × (1 – DS × DN) (S3.3)

where U0 is the baseline utility of diabetes without any diabetes complications, USN is the mean utility of diabetes with both SHEs and NSHEs, Umin = min (US, UN), UN is the mean utility of diabetes with NSHEs, US is the mean utility of diabetes with SHEs, DS is the mean disutility due to SHEs (let |DS| > |DN|), and DN is the mean disutility of diabetes due to NSHEs. Following Formula S2.1 above, we considered that the disutility has a negative value.

Note: Generally the disutility of a health state associated with SHEs is greater than the disutility of a health state associated with NSHEs, even if the frequency of NSHEs is very high [1]. Therefore, we assumed that the absolute value of disutilities of health states with SHEs will always be larger than the absolute value of the disutilities of health states with NSHEs (i.e., Umin = US = U0 + DS).

Then, we calculated the mean joint disutility of diabetes for both SHEs and NSHEs (DSN):

DSN = USN – U0 (S3.4)

We also used the multiplicative method, conditional on adjustment for baseline utility, to estimate the utility for the joint health states. The multiplicative method has been recommended for estimation of joint health state utility due to its smaller bias [4,5]. We applied this formula to our hypoglycemia case:

(S3.5)

where the notation is the same as in Formula S3.3, using Formula S3.4 to calculate the joint disutility.

*The best-fitting models for SHEs and NSHEs*

The β coefficient, R2, and SSE of the six prediction models for disutility due to NSHEs and SHEs are shown in Table S2. The best-fitting model (highest R2 and lowest SSE) used the cube root to transform the total number of NSHEs to predict disutility:

DN = −0.014533 × (S3.6)

where DN is the disutility due to NSHEs, and NN is the total number of NSHEs per year.

Based on this model (where 25% of all hypoglycemic events are nocturnal), we estimated that the disutility for 50 NSHEs per year is 0.054. When we varied the weighted disutility of nocturnal hypoglycemic events to 15% and 35%, the best-fitting models were still the cube root-transformed models. The predicted disutilities for 50 NSHEs were 0.051 and 0.056 for 15% and 35% nocturnal events, respectively. We therefore expected that the precision level of Formula S3.7 would be acceptable for most diabetes cases.

The best prediction model of severe hypoglycemia is presented below:

DS = −0.080460 × (S3.7)

where DS is the disutility due to severe hypoglycemia, and NS is the total number of SHEs per year.

Based on our model, the disutility of the first SHE is −0.08, while the marginal disutilities for the second, third, and fourth SHEs decrease, to −0.012, −0.008 and −0.006, respectively. These perfectly reflected the observed data of one and four SHEs per year (Table S1).

**Table S1: Disutility Values Associated with Hypoglycemic Events, by Type and Frequency**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type of Hypoglycemic Event** | **Frequency of Hypoglycemic Events** | | | | |
| **1/Year** | **4/Year** | **12/Year**  **(1/month)** | **52/Year**  **(1/week)** | **156/Year**  **(3/week)** |
| Non-severe daytime event | NA | −0.032 | −0.032 | −0.036 | −0.071 |
| Non-severe nocturnal event | NA | −0.035 | −0.040 | −0.069 | −0.115 |
| Severe daytime event | −0.082 | −0.105 | NA | NA | NA |
| Severe nocturnal event | −0.085 | −0.106 | NA | NA | NA |

Abbreviations: NA, not applicable.

Note: We estimated the disutility values based on Table 2 in Evans et al [1]. The disutility value is equal to the baseline utility (0.844 for diabetes without any hypoglycemic events) minus the utility of diabetes with different types and frequencies of hypoglycemic events.

**Table S2: Coefficient and Goodness of Fit Assessment for Six Models**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Non-Severe Hypoglycemia** | | | **Severe Hypoglycemia** | | |
| **β coefficient (SE)** | **R-squared** | **SSE** | **β coefficient (SE)** | **R-squared** | **SSE** |
| Model 1: D = β × N | −0.000575 (0.000133) | 0.823399 | 0.001927 | −0.029529 (0.009276) | 0.835189 | 0.002925 |
| Model 2†: D = β × log (N+1) | −0.014460 (0.001319) | 0.967780 | 0.000352 | −0.073542 (0.013631) | 0.935712 | 0.001141 |
| Model 3: D = β × | −0.006815 (0.000752) | 0.953509 | 0.000507 | −0.058400 (0.008344) | 0.960775 | 0.000696 |
| Model 4: D = β × | −**0.014533 (0.001014)** | **0.980908** | **0.000208** | −0.070650 (0.005056) | 0.989862 | 0.000180 |
| Model 5: D = β × | −0.020593 (0.001541) | 0.978093 | 0.000239 | −0.076831 (0.002585) | 0.997742 | 0.000040 |
| Model 6: D = β × | −0.025048 (0.002268) | 0.968235 | 0.000347 | −**0.080460 (0.000825)** | **0.999790** | **0.000004** |

Abbreviations: β coefficient in the linear regression model (dependent variable: transformed number of hypoglycemic events; dependent variable: disutility); D, disutility due to non-severe or severe hypoglycemic events; N, total number of non-severe or severe hypoglycemic events; SE, standard error; SSE, sum of squared errors.

†**:** We used log(N+1) to avoid log(0) for the first baseline observation (i.e., no hypoglycemic events).

Note: We also used mean absolute error to evaluate the model fit. The models identified as the best fit using mean absolute error were the same as those identified using R2 and SSE.

**Supplement 4: Disutility Data for Construct Validity**

Table S3: Disutility of Selected Diabetes Complications

|  |  |  |  |
| --- | --- | --- | --- |
| **Health State** | **CORE Model†** | **UKPDS 72‡** | **Takahara et al. 2019§** |
| **Baseline Utility (Diabetes With No Complications)** | **0.814** | **0.79** | **0.936** |
| **Disutility from baseline** |  |  |  |
| Myocardial infarction (year of event) | −0.129 | −0.06 | NA |
| Stroke (year of event) | −0.181 | −0.16 | −0.098 |
| Congestive heart failure | −0.181 | −0.11 | −0.031 |
| Gross proteinuria | 0 | NA | −0.017 |
| Proliferative diabetic retinopathy | −0.02 | NA | −0.003 |
| Severe vision loss/blindness | −0.08 | −0.08 (blindness in one eye) | −0.023 in one eye and −0.095 in both eyes |
| Amputation | −0.109 | −0.28 | −0.177 (major) |
| Major hypoglycemic event¶ | −0.0052 | NA | −0.025 (severe or nocturnal) |

Abbreviations: CORE, Center for Outcomes Research; NA, not available; UKPDS, United Kingdom Prospective Diabetes Study.

†:Based on data from Palmer et al from various sources [9].

‡:Based on data from Clarke et al, using the EQ-5D-3L [10].

§:Based on data from Takahara et al. 2019, using the Japanese EQ-5D-5L [11]. The coefficients of linear regression model were reported as the disutility due to the diabetic complications. The constant of the model was 1.013.

¶: Hypoglycemic event requiring third-party medical intervention.

**Supplement 5: Details of Studies Included in Literature Review**

Table S4: Details of Studies Investigating Utility and Disutility Due to Hypoglycemia in Patients with Type 1 and Type 2 Diabetes

|  |  |  |
| --- | --- | --- |
| **Author, Year, country†** | **Study details** | **Definition of hypoglycemia by level of severity** |
| Neuwahl et al., 2021, United States [12] | **Population:** Type 2 diabetes  **Recruitment:** The data of this study were from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Look AHEAD (Action for Health in Diabetes) trials and their follow-up studies.  **Period of recorded hypoglycemia:** in the past year  **Age, mean ± SD:** 51.6 ± NR (age at diagnosis)  **Sex:** 45.6% female  **Utility measure:** HUI-3  **Utility of total population, mean ± SD:** 0.74± NR  **Statistical model to estimate adjusted disutility:** a fixed-effects regression model  **R2 overall:** NR  **Conflicts of interest:** No | **Hypoglycemia:** events requiring any assistance (Note: the definition of hypo in this study was similar to the definition of severe hypoglycemia in most of the other studies) |
| Gordon et al., 2020, UK[13] | **Population:** Type 1 diabetes  **Recruitment:** Patients participated in DEPICT (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) clinical trial programme.  **Period of recorded hypoglycemia:** in the past 4 weeks  **Age, mean ± SD:** 43.42 ± 13.27  **Sex:** 54.3% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** 0.89 ± 0.15  **Statistical model to estimate adjusted disutility:** two-stage models  **Stage 1:** Log transformed number of symptomatic hypoglycemia, severe hypoglycemia (Yes/No) and other explanatory variables were used to predict the hypoglycemia fear survey (HFS) score using linear regression model  **Stage 2:** HFS score and other explanatory variables were used to predict utility using linear regression model  **R2 overall:** NR  **Conflicts of interest:** Yes | Same as defined by American Diabetes Association[7] |
| Yfantopoulos et al., 2020, Greece[14] | **Population:** Type 2 diabetes treated with insulin  **Recruitment:** Patients were recruited from one hospital centre and 57 private clinics.  **Period of recorded hypoglycemia:** in the past year  **Age, mean ± SD:** 67.02 ± 10.69  **Sex:** 55.2% female  **Utility measure:** EQ-5D-5L  **Utility of total population, mean ± SD:** 0.713 ± 0.239  **Statistical model to estimate adjusted disutility:** multiple linear regression model  **R2 overall:** 0.227  **Conflicts of interest:** No | **Severe hypoglycemia:** the events require hospitalization or assistance from another person |
| Zhang et al., 2020, United States[15] | **Population:** Type 2 diabetes treated with oral agents  **Recruitment:** This study was conducted at 75 hospitals from 9 cities in China. Survey questionnaires were used to collect data.  **Period of recorded hypoglycemia:** in the past 4 weeks  **Age, mean ± SD:** 59.60 ± 12.64  **Sex:** 49.13% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** 0.87 ± 0.15  **Statistical model to estimate adjusted disutility:** multiple linear regression model  **R2 overall:** NA  **Conflicts of interest:** No | NR |
| Shao et al., 2019, United States[16] | **Population:** Type 2 diabetes  **Recruitment:** The data of this study were from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.  **Period of recorded hypoglycemia:** NR  **Age, mean ± SD:** 62.61 ± NR  **Sex:** 39% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** NA  **Statistical model to estimate adjusted disutility:** multiple linear regression model  **R2 overall:** 0.086  **Conflicts of interest:** No | NR |
| Takahara et al., 2019, Japan[11] | **Population:** Type 1 (6.9%) and type 2 (93.1%) diabetes  **Recruitment:** This study was conducted at 13 centres. Patient recruitment was at the physician visits. The questionnaires were administered by the physicians  **Period of recorded hypoglycemia:** NR  **Age, mean ± SD:** 64 ± 12  **Sex:** 34.6% female  **Utility measure:** EQ-5D-5L  **Utility of total population, mean ± SD:** 0.901 ± 0.137  **Statistical model to estimate adjusted disutility:** multiple linear regression model  **R2 overall:** 0.400  **Conflicts of interest:** No | Patients had either or both of severe and/or nocturnal hypoglycemic episodes  **Severe hypoglycemia:** the events require assistance from another person  **Nocturnal hypoglycemia:** the events occur while sleeping |
| Pratipanawatr et al., 2019, Thailand[17] | **Population:** Type 2 diabetes treated with sulfonylurea  **Recruitment:** This study was conduced at 5 tertiary care hospitals in Thailand; patients were eligible for enrollment if they had a diagnosis of type 2 diabetes, were 30 years of age or older, and had been treated with sulfonylurea monotherapy or sulfonylurea and metformin combination therapy for at least 6 months before enrollment  **Period of recorded hypoglycemia:** in the past 6 months  **Age, mean ± SD:** no statistics of total population. No hypo, 66.2 ± 9.6; hypo, 63.9 ± 10.7  **Sex:** no statistics of total population. No hypo, 49.2% female; hypo, 54.0% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** NR  **Statistical model to estimate adjusted disutility:** multiple linear regression model  **R2 overall:** NR  **Conflicts of interest:** No | **Mild:** little or no interruption of your activities, no assistance required  **Moderate:** some interruption of your activities, no assistance required  **Severe:** required the assistance of others to manage symptoms (e.g., to bring food or drink)  **Very severe:** need medical assistance (e.g., called an ambulance) |
| Pagkalos et al., 2018, Greece[18] | **Population:** Type 2 diabetes treated with sulfonylurea  **Recruitment:** This study was conducted at the routine office visit in patients who had been treated with sulfonylurea monotherapy or sulfonylurea and metformin combination therapy  **Period of recorded hypoglycemia:** NR  **Age, mean ± SD:** 68.4 ± 11.4  **Sex:** 47% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** NR  **Statistical model to estimate adjusted disutility:** linear regression model  **R2 overall:** NR  **Conflicts of interest:** Yes | Mild, moderate, severe or very severe, as defined by  Vexiau et al.[19] |
| Pawaskar et al., 2018a, United States[20] | **Population:** Type 2 diabetes  **Recruitment:** Participants in the 2013 US National Health and Wellness Survey (NHWS) were recruited from an internet panel using a random stratified sampling  **Period of recorded hypoglycemia:** in the past 3 months  **Age, mean ± SD:** 60± NR  **Sex:** 39.6% female  **Utility measure:** SF-6D  **Utility of total population, mean ± SD:** NR  **Statistical model to estimate adjusted disutility:** NR  **R2 overall:** NR  **Conflicts of interest:** Yes | **Non-severe hypoglycemia:** with or without symptoms, no assistance required  **Severe hypoglycemia:** the events require assistance from healthcare professionals or other persons as defined by the American Diabetes Association Workgroup on Hypoglycemia[7] |
| Pawaskar et al., 2018b, Europe[21] | **Population:** Type 2 diabetes  **Recruitment:** Patients were selected from the 2013 NHWS conducted in France, Germany, Italy, Spain and UK. The NHWS is an Internet-based survey  **Period of recorded hypoglycemia:** in the past 3 months  **Age, mean ± SD:** no statistics of total population. No hypo, 60.7 ± 11.4; non-severe hypo, 59.3 ± 11.1; severe hypo, 56.2 ± 14.7  **Sex:** no statistics of total population. No hypo, 32.7% female; non-severe hypo, 38.3% female; severe hypo: 34.5% female  **Utility measure:** SF-6D  **Utility of total population, mean ± SD:** NR  **Statistical model to estimate adjusted disutility:** NR  **R2 overall:** NR  **Conflicts of interest:** Yes | **Non-severe hypoglycemia:** with symptoms, but no assistance required  **Severe hypoglycemia:** the events require assistance from healthcare professionals or other persons as defined by the American Diabetes Association Workgroup on Hypoglycemia[7] |
| Cvetanović et al., 2017, Serbia[22] | **Population:** Type 2 diabetes  **Recruitment:** consecutively selected adult patients from a Health Centre in Leskovac, Serbia.  **Period of recorded hypoglycemia:** NR  **Age, mean ± SD:** 65.1 ± 9.3  **Sex:** 62.8% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** 0.86 ± 0.09  **Statistical model to estimate adjusted disutility:** hierarchical multiple linear regression model  **R2 overall:** NR  **Conflicts of interest:** NR | **Hypoglycemia:** the presence of symptoms, with or without a self measured blood glucose concentration to confirm, as defined by the American Diabetes Association[7] |
| Peasgood et al., 2016, UK[23] | **Population:** Type 1 diabetes  **Recruitment:** Patients who participated in Dose Adjustment For Normal Eating (DAFNE) education program, longitudinal data: baseline and follow up visits at year 1 and year 2  **Period of recorded hypoglycemia:** in the past year  **Age, mean ± SD:** 39.3 ± 13.8  **Sex:** 48.6% female  **Utility measure:** EQ-5D-3L and SF-6D  **Utility of total population, mean ± SD:** EQ-5D-3L, 0.839 ± 0.231; SF-6D, 0.745 ± 0.137  **Statistical model to estimate adjusted disutility:** fixed-effects linear model  **Rho statistics:** EQ-5D-3L model, 0.746; SF-6D model, 0.679  **Conflicts of interest:** No | **Severe:** NR |
| Sheu et al., 2012, the Republic of China[24] | **Population:** Type 2 diabetes treated with oral antihyperglycaemic agents  **Recruitment:** This study was conduced at outpatient centres in China, South Korea, Malaysia, Taiwan (the Republic of China), and Thailand; patients were eligible for enrollement if they had a diagnosis of type 2 diabetes, were ≥ 30 years old at time of diagnosis, and had been treated with oral antihyperglycemic agents at the time of study entry for at least 6 months  **Period of recorded hypoglycemia:** in the past 6 months  **Age, mean ± SD:** 58.7 ± 10.2  **Sex:** 50.6% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** 0.89 ± 0.15  **Statistical model to estimate adjusted disutility:** multiple linear regression model  **R2 overall:** NR  **Conflicts of interest:** Yes | **Mild:** little or no interruption of your activities, no assistance required  **Moderate:** some interruption of your activities, no assistance required  **Severe:** required the assistance of others to manage symptoms  **Very severe:** need medical assistance |
| Solli et al., 2010, Norway[25] | **Population:** Type 1 (31.7%) and type 2 (68.3%) diabetes  **Recruitment:** questionnaire mailed to randomly selected patient members from the Norwegian Diabetes Association  **Period of recorded hypoglycemia:** NR  **Sex:** type 1, 53% female; type 1, 44%  **Age, mean ± SD:** type 1, 47 ± 14.9; type 2, 64 ± 11.7  **Utility measure:** EQ-5D-3L  **Utility of total population, mean (95%CI): Type 1,** 0.83 (0.79 to 0.87); Type 2, 0.81 (0.79 to 0.83)  **Statistical model to estimate adjusted disutility:** linear regression model  **R2 overall:** NR  **Conflicts of interest:** No | **Level 1:** intake of fluids containing sugar, no assistance required  **Level 2:** intake of fluids containing sugar, assistance from others required  **Level 3:** help from doctor required, but no hospital admission  **Level 4:** resulting in hospital admission  Episodes of hypoglycaemia with 4 levels of severity were added with severity weights (level 1 × 1, level 2 × 2, level 3 × 3, level 4 × 4) and divided in 3 groups 0, 1-11 and ≥12 |
| Marrett et al., 2009, United States[26] | **Population:** Type 2 diabetes patients treated with oral antihyperglycaemic agents  **Recruitment:** A representative sample of the US population was identified from the 2007 National Health and Wellness Survey, a cross-sectional internet-based survey  **Period of recorded hypoglycemia:** in the past 6 months  **Age, mean ± SD:** 58.1±11.1  **Sex:** 43.3% female  **Utility** **measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** NR  **Statistical model to estimate adjusted disutility:** mixed linear regression  **R2:** NR  **Conflicts of interest:** Yes | **Mild:** little or no interruption of activities and no assistance required  **Moderate:** some interruption of activities but no assistance required  **Severe:** required the assistance of others to manage symptoms  **Very severe:** need medical assistance |
| Vexiau et al., 2008, France[19] | **Population:** Type 2 diabetes treated with a sulphonylurea and metformin but no insulin  **Recruitment:** Patients were recruited by physicians at primary care centres  **Period of recorded hypoglycemia:** in the past 6 months  **Age, mean ± SD:** 62.1±10.7  **Sex:** 46.4% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** 0.77 ± 0.24  **Statistical model to estimate adjusted disutility:** linear regression model  **R2** in model A = 0.24; **R2** in model B = 0.27  **Conflicts of interest:** Yes | **Mild:** little or no interruption of activities and no need of assistance  **Moderate:** some interruption of activities but no need of assistance  **Severe:** need assistance of others to manage symptoms  **Very severe:** need medical assistance |
| Currie et al., 2006, UK[27] | **Population:** Type 1 (35.3%) and type 2 (64.7%) diabetes  **Recruitment:** The study data were from two self-completed postal survey. Patients in survey 1 were identified by their HbA1c test at primary and secondary care setting; patients in survey 2 were selected from the hospital in-patient records and outpatient records  **Period of recorded hypoglycemia:** in the past 3 months  **Age, mean ± SD:** type 1, 53.5 ± 18.2; type 2, 66.5 ± 12  **Sex:** type 1, 49.5% female; type 2, 40.6% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** Type 1, 0.684 ± 0.33; type 2, 0.655 ± 0.313  **Statistical model to estimate adjusted disutility:** two-stage models  **Stage 1:** Log transformed number of symptomatic hypoglycemia, severe hypoglycemia (Yes/No) and other explanatory variables were used to predict the HFS score using linear regression model  **Stage 2:** HFS score and other explanatory variables were used to predict utility using linear regression model  **R2** in stage 1 model: 0.23**; R2** in stage 2 model: 0.23  **Conflicts of interest:** Yes | **Mild:** sweating, dizziness, trembling in the hands, etc., and no need of assistance  **Moderate:** odd behaviour such as rudeness or laughter, aggressive behaviour, confusion etc., but no need of assistance  **Severe:** required the assistance of others |
| Lundkvist et al., 2005, Sweden[28] | **Population:** Type 2 diabetes  **Recruitment:** Patients’ routine follow-up visits at 7 primary care centres  **Period of recorded hypoglycemia:** in the preceding month  **Age, mean ± SD:** 65 ± 11  **Sex:** 40% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** NR  **Statistical model to estimate adjusted disutility:** linear regression model  **R2**: 0.063  **Conflicts of interest:** Yes | **Mild:** patients can manage by themselves (e.g., eating)  **Severe:** patients need help from another person |
| Davis et al., 2005, UK[29] | **Population:** Type 1 (31.5%) and type 2 (68.5%) diabetes  **Recruitment:** A self-completed postal survey was mailed to diabetic patients who were selected from the hospital in-patient records, outpatient records and respondents of a previous diabetes study  **Period of recorded hypoglycemia:** in the past 3 months  **Age group:** all type 1 and type 2, 18-40: N = 128; 41-65: N = 325; >65: N = 408  **Sex:** 44.8% female  **Utility measure:** EQ-5D-3L  **Utility of total population, mean ± SD:** NR  **Statistical model to estimate adjusted disutility:** NA (authors did not perform analysis to estimate the disutility due to hypoglycemia)  **R2**: NA  **Conflicts of interest:** Yes | **Mild:** sweating, dizziness, trembling in the hands, etc.  **Moderate:** odd behaviour such as rudeness or laughter, aggressive behaviour, confusion etc.  **Severe:** unconsciousness or need help from someone else  **Nocturnal:** symptoms between bedtime and breakfast |

Abbreviations: EQ-5D-3L: EuroQol – 5 dimension – 3 level; EQ-5D-5L: EuroQol – 5 dimension – 5 level; HUI-3, Health Utilities Index Mark 3; NA, not applicable; NR, not reported; SF-6D: short form – 6 dimension.

†: The country of the first author.

Table S5: Details of Studies Investigating Hypothetical Health States

|  |  |  |
| --- | --- | --- |
| **Author, Year, country†** | **Study details** | **Definition of hypoglycemia by severity level** |
| Shafie et al. 2018, Malaysia[30]‡ | **Population:** General population  **Recruitment:** 256 people from general public were interviewed. After excluding the illegible responders (e.g., inconsistency), 140 people were included in analyses  **Age, mean ± SD:** 25.74 ± 11.43  **Sex:** 69.3% female  **EQ-5D-3L utility of responders, mean ± SD:** NR  **Utility** **measure for hypothetical health states:** Time trade-off  **Statistical method to estimate disutility per hypoglycemic incident type:** the difference between the mean utility and the baseline diabetes state utility was divided by the number of annual events  **Conflicts of interest:** No | **Minor hypoglycaemic events:** The patient might feel shaky, dizzy, sweaty, or irritable  **Severe hypoglycaemic events:** The patients will need help from another person, possibly medical assistance |
| Shingler et al., 2015, UK[31] | **Population:** General population in UK  **Recruitment:** 100 people from general public were recruited. The sample aimed to  be broadly representative of the UK general public  **Age, mean ± SD:** 40.42 ± NR  **Sex:** 51% female  **EQ-5D-3L utility of responders, mean ± SD:** NR  **Utility** **measure for hypothetical health states:** Time trade-off  **Statistical method to estimate disutility per hypoglycemic incident type:** NA  **Conflicts of interest:** Yes | **Type 2 diabetes with moderate hypoglycemic events:** patients require regular medication and may occasionally experience some symptoms  **Type 2 diabetes with severe hypoglycemic events:** patients require regular medication and have spent a few days in hospital for an episode of illness |
| Harris et al., 2014, Canada[32]‡ | **Population:** General population in Canada (a subset of the Evans et al. study[1])  **Recruitment:** A cross-sectional internet-based survey using a representative sample of the Canadian general adult population  **Age, mean ± SD:** 46 ± NR  **Sex:** 48% female  **EQ-5D-3L utility of responders, mean ± SD:** 0.81 ± NR  **Utility** **measure for hypothetical health states:** Time trade-off  **Statistical method to estimate disutility per hypoglycemic incident type:** the average time trade-off value for each frequency, weighted according to the distribution of those specific hypoglycemic event frequencies among the survey participants with diabetes  **Conflicts of interest:** Yes | **Non-severe nocturnal event:** it occurs during the night, and can be treated by eating or drinking something that contains sugar  **Non-severe daytime event:** it occurs during the daytime. These symptoms usually do not last long after eating or drinking something that contains sugar  **Severe events:** people need help from another person, possibly medical assistance |
| Evans et al., 2013, UK[1]‡ | **Population:** General population in five countries (Canada, Germany, Sweden, UK and United States)  **Recruitment:** An internet-based survey using an existing panel of prospective participants  **Age, mean ± SD:** 46 ± 16  **Sex:** 49% female  **EQ-5D-3L utility of responders, mean ± SD:** 0.81 ± 0.25  **Utility** **measure for hypothetical health states:** Time trade-off  **Statistical method to estimate disutility per hypoglycemic incident type:** the average time trade-off value for each frequency, weighted according to the distribution of those specific hypoglycemic event frequencies among the participants with diabetes  **Conflicts of interest:** Yes | **Non-severe nocturnal event:** it occurs during the night, and can be treated by eating or drinking something that contains sugar  **Non-severe daytime event:** it occurs during the daytime. These symptoms usually do not last long after eating or drinking something that contains sugar  **Severe events:** people need help from another person, possibly medical assistance |
| Levy et al., 2008, Canada[33]‡ | **Population:** Respondents in Canada and UK without diabetes  **Recruitment:** Respondents without diabetes were recruited through newspaper advertisements. Data were collected through one-on-one interviews by the trained interviewer using standardized scripts  **Age, mean ± SD:** Respondents in Canada, 47 ± 16; respondents in UK, 46 ± 15  **Sex:** Respondents in Canada, 50% female; respondents in UK, 59% female  **EQ-5D-3L utility of responders:** NR  **Utility** **measure for hypothetical health states:** Time trade-off  **Statistical method to estimate disutility per hypoglycemic incident type:** linear regression model  **R2**: 0.29  **Conflicts of interest:** Yes | **Non-severe hypoglycemic episode:** if blood sugar becomes low the person feels shaky, dizzy and sweaty. This happens at different frequencies. It also has the long-term consequences, such as worrying about the symptoms and limiting travelling |

Abbreviations: NA, not applicable; NR, not reported; UK, United Kingdom

†: The country of the first author.

‡: We reported the main results from general population or people with no diabetes of the studies [1,30,32,33]. These studies also included the statistics from the respondents with diabetes, but the sample sizes of diabetic patients were smaller than those in the main analyses [1,30,32,33]. Generally, it is recommended to use the time trade-off utility from the general population (not patients) to reflect social preferences. Thus, we did not present the results from the diabetes patients in this table.

Table S6: Utility and Disutility from Studies Investigating Hypothetical Health States Using Time Trade-off

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author, Year** | **Population, N** | **Type of hypoglycemia** | **Unadjusted utility by frequency and type (i.e., number of a type of hypo events per year), mean (95%CI)** | **Disutility per type of hypo event, mean (95%CI)** |
| Shafie et | General | Diabetes, no hypo events | 0.64 (NR) |  |
| al. 2018, [30]†‡ | population,140 | Non-severe daytime hypo event | 4/Y: 0.35 (NR); 12/Y: 0.44 (NR); 52/Y: 0.22 (NR); 156/Y: 0.30 (NR) | 0.0354 (SD = 0.0740) |
|  |  | Non-severe nocturnal hypo event | 4/Y: 0.56 (NR); 12/Y: 0.43 (NR); 52/Y: 0.30 (NR); 156/Y: 0.16 (NR) | 0.0155 (SD = 0.0310) |
|  |  | Severe daytime hypo event | 1/Y: 0.17; 4/Y: 0.01 | 0.3619 (SD = 0.3676) |
|  |  | Severe nocturnal hypo event | 1/Y: 0.19; 4/Y: −0.05 | 0.3027 (SD = 0.3207) |
| Shingler et al., | General population, | Type 2 diabetes (T2DM), no hypo events | 0.92 (0.90 to 0.94) | -- |
| 2015[31] | 100 | T2DM with moderate hypoglycemic events | No frequency of hypo events specified, 0.81 (0.77 to 0.84) | -- |
|  |  | T2DM with severe hypoglycemic events | No frequency of hypo events specified, 0.77 (0.73 to 0.81) | -- |
| Harris et | General | Diabetes, no hypo events | 0.819 (0.807 to 0.830) | -- |
| al., 2014[32]† | population, 1696 | Non-severe daytime hypo event | 4/Y: 0.775 (0.750 to 0.801); 12/Y: 0.772 (0.746 to 0.797);  52/Y: 0.784 (0.760 to 0.807); 156/Y: 0.745 (0.720 to 0.770) | −0.0056 (−0.0043 to −0.0069) |
|  |  | Non-severe nocturnal hypo event | 4/Y: 0.788 (0.765 to 0.811); 12/Y: 0.769 (0.742 to 0.796);  52/Y: 0.754 (0.731 to 0.777); 156/Y: 0.713 (0.685 to 0.741) | −0.0076 (−0.0061 to −0.0091) |
|  |  | Severe daytime hypo event | 1/Y: 0.741 (0.714 to 0.768); 4/Y: 0.724 (0.696 to 0.747) | −0.0592 (−0.0495 to −0.0691) |
|  |  | Severe nocturnal hypo event | 1/Y: 0.732 (0.703 to 0.758); 4/Y: 0.711 (0.686 to 0.739) | −0.0616 (−0.0518 to −0.0714) |
| Evans et | General | Diabetes, no hypo events | 0.844 (0.839 to 0.848) | -- |
| al.,2013[1]† | population, 8286 | Non-severe daytime hypo event | 4/Y: 0.812 (0.802 to 0.822); 12/Y: 0.812 (0.802 to 0.822);  52/Y: 0.808 (0.799 to 0.817); 156/Y: 0.773 (0.762 to 0.784) | −0.004 (−0.004 to −0.005) |
|  |  | Non-severe nocturnal hypo event | 4/Y: 0.809 (0.800 to 0.819); 12/Y: 0.804 (0.794 to 0.813);  52/Y: 0.775 (0.764 to 0.786); 156/Y: 0.729 (0.717 to 0.740) | −0.007 (−0.006 to −0.007) |
|  |  | Severe daytime hypo event | 1/Y: 0.762 (0.751 to 0.773); 4/Y: 0.739 (0.739 to 0.750) | −0.057 (−0.053 to −0.061) |
|  |  | Severe nocturnal hypo event | 1/Y: 0.759 (0.749 to 0.770); 4/Y: 0.738 (0.726 to 0.748) | −0.062 (−0.058 to −0.066) |
| Levy et | Canada | Diabetes, no hypo events | 0.88 (0.62 to 1.00) | -- |
| al., 2008[33]† | General population, 78 | Non-severe hypo event | 3 to 4/Y: 0.85 (0.55 to 1.00); 12/Y: 0.77 (0.38 to 1.00);  52/Y: 0.66 (0.22 to 1.00) | -- |
|  | UK general | Diabetes, no hypo events | 0.97 (0.85 to 1.00) | -- |
|  | population, 75 | Non-severe hypo event | 3 to 4/Y: 0.94 (0.80 to 1.00); 12/Y: 0.90 (0.74 to 1.00);  52/Y: 0.83 (0.64 to 1.00) | -- |
|  | All, 153 | Non-severe hypo event | -- | −0.0032 (SE: 0.0002) |

Abbreviations: CI, confidence interval; hypo, hypoglycemia; NR, not reported; SD, standard deviation; SE, standard error; Y, year.

†: We reported the main results from general population or people with no diabetes of the studies [1,32,33]. These studies also included the statistics from the respondents with diabetes, but the sample sizes of diabetic patients were smaller than those in the main analyses [1,32,33]. Generally, it is recommended to use the time trade-off utility from the general population (not patients) to reflect social preferences. Thus, we did not present the results from the diabetes patients in this table.

‡: This study did not report the mean utilities of different health states in the text or tables, but presented the main results in Figure 2. We estimated the utilities from this figure.

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