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BRIEF COMMUNICATION

Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries

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Abstract

Introduction The negative impact of hypoglycaemic events on health-related quality of life (HRQoL) may be evaluated by attaching published disutilities to these events. It is suggested that the marginal negative impact of individual hypoglycaemic events on HRQoL may decrease as the overall frequency increases.

Methods Using disutility values from a large-scale (>8,000 respondents), time trade-off (TTO) study, nonlinear regression curves were fitted to the total disutility of different frequencies of non-severe daytime and nocturnal hypoglycaemic events. Nonparametric bootstrapping was applied to characterise the uncertainty of the marginal disutility.

Results Power function regression curves were estimated at $U_{\mathrm{d}} = 0.0141x^{0.3393}$ and $U_{\mathrm{d}} = 0.0221x^{0.3277}$. An increase from 0 to 1 hypoglycaemic event per year produced a utility decrease of 0.0141 and 0.0221 for non-severe daytime and nocturnal events, respectively. An increase from 25 to 26 events per year produced a marginal impact of 0.0006 and 0.0008 for non-severe daytime and nocturnal events, respectively.

Discussion These data concur with the noted phenomenon of "first being worst" as regards hypoglycaemic events. This finding may reflect a coping mechanism on the part of patients, a maximum limit for trading off remaining lifetime or the nature of the study.

Conclusion Applying nonlinear functions to the TTO data might improve the precision of the measured impact of hypoglycaemic events.

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Keywords Diabetes · Hypoglycaemia · Health-related quality of life · Disutility · Time trade-off

Abbreviations

TTO	Time trade-off
HRQoL	Health-related quality of life
QALY	Quality-adjusted life years
MID	Minimally reported difference

Introduction

The primary aim of diabetes treatment is to achieve good glycaemic control (i.e. to lower blood sugar levels) in order to reduce the risk of future complications. Unfortunately, intensive glucose lowering has been associated with increased rates of hypoglycaemic adverse events [1]. Hypoglycaemia, where blood sugar levels dip too low, can cause negative effects such as pounding heart, trembling, hunger, sweating, difficulty concentrating, confusion, unconsciousness or coma. In rare cases, hypoglycaemia can result in death [2]. Hypoglycaemic events may be non-severe (the individual is able to take remedial action) or severe (requiring third-party assistance) and can occur during the day or night [3, 4]. Although incidence is difficult to measure conclusively, one large-scale study has reported the overall incidence of hypoglycaemic events as 42.89 events per patient-year for type 1 diabetes (1.15 severe events per patient-year) and 16.36 events per patient-year for type 2 diabetes (0.35 severe events per patient-year) [5].

Hypoglycaemia can have a significant negative effect on patients' well-being and health-related quality of life (HRQoL) [6, 7]. This impact can be quantified using a health utility value: a value from 0 to 1 that represents health status, where 0 = dead and 1 = perfect health [8, 9]. Health utility values are used by health technology assessment agencies to calculate quality-adjusted life years (QALYs), in order to analyse cost-effectiveness of treatments [10–14]. Utility values may be calculated using a time trade-off (TTO) method, where respondents are asked to choose between living with a particular health problem for the rest of their life (t years) or living for fewer years but in full health (x years). Time x is then varied until the respondent is indifferent to the two scenarios, and the TTO value or utility is calculated (x/t).

Traditionally, when assessing the impact of hypoglycaemia, a constant impact of hypoglycaemic events on HRQoL has been assumed. For instance, in a recent study, Evans et al. [15] used the TTO approach to estimate the negative impact of hypoglycaemic events, assuming a constant impact of hypoglycaemic event. However, when applying these results to individual patient-level data, where there might be a large variation around the mean values, the distribution will in reality most likely be skewed. Some patients have few or no hypoglycaemic events at all, whereas other patients experience many events per year. Thus, the specific impact of a hypoglycaemic event may differ for individual patients depending on the frequency with which they experience such events.

In clinical practice, there is an acknowledgement of the phenomenon of "first being worst"; i.e. the negative effect of each individual hypoglycaemic event on HRQoL diminishes as the frequency of events increases. This phenomenon may, in health-economic terms, be referred to as diminishing marginal disutility.

This paper explores the possibility of estimating the marginal disutility of additional hypoglycaemic events, with a focus on non-severe events. The paper uses the previously published disutility data from Evans et al. [15]. Whereas Evans et al. used a weighted mean of the disutility impact of different hypoglycaemic event frequencies, this paper attempts to fit nonlinear curves to the same data. The focus is on non-severe hypoglycaemic events as severe events occur much less frequently and the case for decreasing marginal disutility is less obvious.

Materials and methods

Study methodology

This analysis was conducted on data from a recent large-scale, web-based, TTO study of 8,286 participants from the general population in the UK, USA, Canada, Germany and Sweden. Full details of the design, TTO methodology and initial results of this survey have been published elsewhere [15].

TTO values were estimated for different frequencies of hypoglycaemic events (one event quarterly, one monthly, one weekly and one weekly) for non-severe daytime and nocturnal events, respectively (Table 1) [15]. By subtracting the TTO values for the different frequencies of hypoglycaemic events from the baseline diabetes TTO values, the total disutility values for different frequencies of hypoglycaemic events were obtained. An advantage of the subtraction is that it accounts for unobserved characteristics influencing utility values of baseline and hypoglycaemic events.

Table 1 Time trade-off (TTO) values (95 % CIs, bootstrapped) for different frequencies of hypoglycaemic events [15]

Health state	0 Annually	1 Quarterly	1 Monthly	1 Weekly	3 Weekly
Total utility					
Baseline diabetes	0.844 [0.839–0.848]	–	–	–	–
Non-severe daytime hypoglycaemia	–	0.812 [0.802–0.822]	0.812 [0.802–0.822]	0.808 [0.799–0.817]	0.773 [0.762–0.784]
Non-severe nocturnal hypoglycaemia	–	0.809 [0.800–0.819]	0.804 [0.794–0.813]	0.775 [0.764–0.786]	0.729 [0.717–0.740]
Total disutility[a]					
Non-severe daytime hypoglycaemia		0.033081	0.029834	0.050429	0.081725
Non-severe nocturnal hypoglycaemia		0.045869	0.049901	0.072963	0.12205

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[a] Difference from baseline diabetes

Statistical analysis and regression curve fitting

Statistical analyses were carried out using SAS® version 9.2 statistical software. To capture a potentially nonlinear relationship between the frequency of hypoglycaemic events and disutility, two curves were fitted to the plotted estimated disutility values for each frequency of hypoglycaemic events based on a power function of the form $U_d = \alpha * x^{\beta}$. For this function, U_d represents disutility, x is the annual hypoglycaemic event rate and α and β are coefficients determining the slope and curvature of the function. This function was estimated using linear regression on the log-transformed values.

To ensure proper statistical inference, proper weighting of data is essential. Therefore, in order to fit curves that included both the low and high hypoglycaemic event frequencies, a weighting mechanism was used to allow each data point (one event quarterly, one monthly, one weekly or three weekly) to represent a range of values on the hypoglycaemia frequency scale. The data points of 4, 12, 52 and 156 annual events (one quarterly, one monthly, one weekly, three weekly) were each given a weight equal to the share of the range they represented.

It is essential to keep in mind that log-normal distribution is only one of many potential nonlinear specifications (others include polynomial functions or a dummy vector approach). Thus, as this distributional assumption might not have been met, nonparametric bootstrapping was used to simulate confidence intervals for the marginal impact of hypoglycaemic events. This method estimates the parameter's distribution by repeatedly resampling the original data set with replacement. For the present study, 10,000 iterations were performed [16].

Results

Log-transformed regression curves, fitted to the total disutilities, were estimated at $U_d = 0.0141x^{0.3393}$ and $U_d = 0.0221x^{0.3277}$ for non-severe daytime and non-severe nocturnal hypoglycaemic events, respectively (Fig. 1).

Using the incidence of non-severe hypoglycaemic events from Donnelly et al. [5] (41.74 non-severe events per patient-year for type 1 diabetes, 16.01 non-severe events per patient-year for type 2 diabetes) and assuming that 25 % of the events are nocturnal, would mean that a patient with type 1 diabetes with an average incidence would have a total utility loss of $(0.0141(0.75 * 41.74)^{0.3393} + 0.0221(0.25 * 41.74)^{0.3277}) = 0.0930$ and a patient with type 2 diabetes with an average iincidence would have a total utility loss of $(0.0141 (0.75 * 16.01)^{0.3393} + 0.0221(0.25 * 16.01)^{0.3277}) = 0.0676$.

The calculated marginal disutility of hypoglycaemic events is illustrated in Fig. 2. An increase from 0 to 1 hypoglycaemic event per year produced a utility decrease of 0.0141 for non-severe daytime, and 0.0221 for non-severe nocturnal events. An increase of one hypoglycaemic event from 25 events per year to 26 events per year produced a marginal impact of 0.0006 and 0.0008 for non-severe daytime and non-severe nocturnal hypoglycaemic events, respectively. An increase of one hypoglycaemic event per year from 100 events per year to 101 events per year produced an impact of 0.0002 and 0.0003 for non-severe daytime and non-severe nocturnal, respectively.

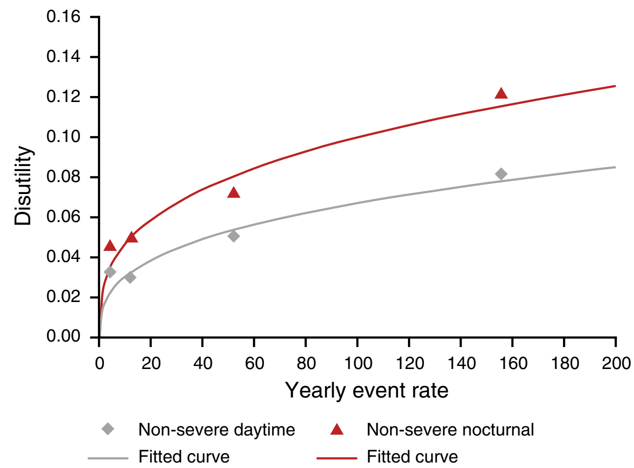

Fig. 1 Total disutility of non-severe daytime and non-severe nocturnal hypoglycaemic events, respectively, by yearly event rate. Curves fitted based on a power function of the form $U_d = \alpha * x^{\beta}$

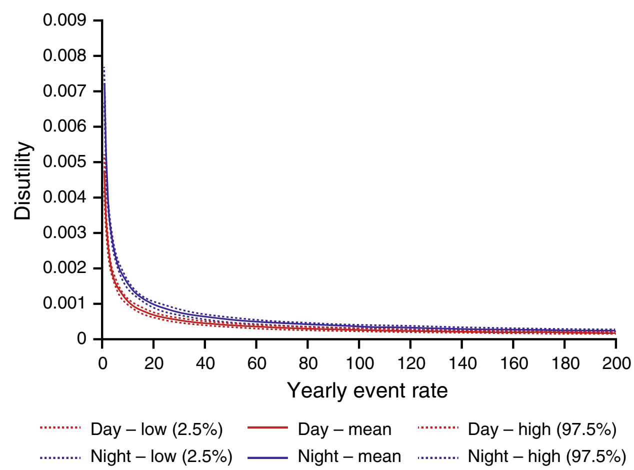

Fig. 2 Marginal disutility of non-severe daytime and non-severe nocturnal hypoglycaemic events, respectively, with increasing yearly event rate. Confidence intervals estimated by nonparametric bootstrapping

Discussion

It has been previously demonstrated using TTO disutility values that there is an increase in disutility associated with increasing frequency of non-severe hypoglycaemic events, irrespective of whether they occur in the daytime or at night [15]. This finding is in agreement with previous studies, which show an increasing negative impact on HRQoL with increasing frequency of hypoglycaemic events [17, 18]. Here, we illustrate that although the disutility of non-severe hypoglycaemic events increases as the frequency of events increases (Fig. 1), both daytime and, to a slightly lesser extent, nocturnal non-severe hypoglycaemic events are associated with marginally decreasing disutility (Fig. 2). Nocturnal hypoglycaemic events often occur when patients are sleeping and so they may therefore be less conscious of these events. The onset of nocturnal hypoglycaemia can be unpredictable and difficult to detect, which means these events can be difficult to avoid [19]. The slightly lesser curvature of the nocturnal curve was therefore to be expected.

The diminishing marginal disutility seen in this study may reflect a number of factors: patients learning to cope with hypoglycaemia; unwillingness to trade-off remaining lifetime after a certain point; or the nature of the study, where some respondents might pay more attention to the health-state descriptions than the actual frequencies. Unfortunately, it is not possible to further validate the results seen here as this study is the first to examine this phenomenon. There is, however, recognition of the phenomenon of ‘first being worst’ within clinical practice, where the impact of each hypoglycaemic event on HRQoL diminishes as frequency increases, and the patient learns to adapt. In contrast, there is research indicating that experience of hypoglycaemia increases the fear of future events and that this fear increases with the cumulative number of hypoglycaemic events; this would work against any reduction in marginal disutility [20].

It is well established that a nonlinear transformation can result in the consequence that the mean of the transformed values will not be the same as transforming the mean. Therefore, the mean disutility will not necessarily be the same as the disutility of the mean number of hypoglycaemic events [21–23]. This will be more pronounced if there is a large variation in the hypoglycaemic event frequencies and means that applying nonlinear functions to the data might improve the precision of the measured impact of hypoglycaemic events; for example, when using patient-level data. The exact curvature of the disutility function is, however, less obvious. Several functional forms, including power functions, polynomial functions, linear and log-linear functions were possible candidates and were explored. The power functions gave the best fit among those candidates assessed and possessed the practical properties of non-negative slopes and approaching zero for fewer events.

In addition to the functional form, the weighting mechanism could also potentially take other forms and an infinite number of possible weighting schemes could be used for the regression models. For this particular project, a weighting procedure was developed to adjust for the uneven representation of the full range of hypoglycaemia event frequencies. This procedure gives more weight to the higher frequencies to ensure that all ranges on the scale are well represented by the disutility function.

The analysis was conducted on data from a recent large-scale, web-based, TTO study. The web-based nature of this study made it possible to gather a large sample and hence to reduce the statistical uncertainty. However, because this method of data collection was used, the study is also limited by potential selection bias in relation to the patients in the survey panel. To be included in the survey panel, participants needed to be comfortable with computers and interested in online surveys, which may have excluded less literate or technology-literate individuals. Despite the wide representation in terms of age and gender, it is possible that participants could be biased in terms of other characteristics. Furthermore, a web-based approach, while facilitating respondent participation, does mean that help is not available if respondents have queries regarding the questions. Additionally, the lack of supervision may lead to some respondents not considering their answers well enough. Collectively, these design attributes may have led to inconsistencies within the responses. The development and validation of the TTO questionnaires are further described in Harris et al. [24].

Total disutility values were obtained by subtracting the TTO values for the different frequencies of hypoglycaemic events from the baseline diabetes TTO values. With this design, the utility differentials of hypoglycaemic events are not, per design, non-positive values and the differencing also accounts for unobserved characteristics. Nonparametric bootstrapping was used to estimate confidence intervals as the parametric assumptions are uncertain. However, in addition to sampling uncertainty, it is plausible that the differencing led to increased imprecision due to potential imperfect intra-rater reliability.

To date, published disutilities for hypoglycaemia include: 0.0033, 0.0036, 0.0052 for non-severe events [10, 18, 25], and 0.0118, 0.0121 for severe events [10, 25]. In an international TTO study examining the impact of hypoglycaemia on HRQoL, Evans et al. made a distinction between the effects of non-severe and severe hypoglycaemia and also between daytime and nocturnal events [15]. This paper adds to these findings and further elucidates the marginal disutility of individual hypoglycaemic events at increasing frequencies of hypoglycaemia.

The marginal impact of an additional hypoglycaemic event might appear small for patients who already have many hypoglycaemic events and the impact reported here is smaller than the previously reported minimally reported differences (MIDs) for utility estimates for generic instruments. Drummond et al., for example, reported an MID in utilities of 0.03 for the 15D instrument and the Health Utilities Index (HUI®), with the elaboration that utilities of 0.01 may be meaningful in some contexts [26]. In addition, Walters et al. reported MIDs for EQ-5D in the range of −0.011 to 0.140 and for SF-6D in the range of 0.011–0.097 [27], and Luo et al. [28] reported MIDs for EQ-5D in the range of 0.0001–0.175 with a mean and median of 0.04 and 0.038, respectively, and for SF-6D a range from 0–0.091 with mean and median of 0.027 and 0.016, respectively. For direct preference-based measures, Feeny [29] reported an MID of 0.05 for TTO and standard gamble. However, it is important to stress that the total impact of hypoglycaemic events on HRQoL is still large, and small improvements can have a large total impact on patients' quality of life. In addition, non-severe hypoglycaemic events have a demonstrable economic impact on both patients and the healthcare system [30] and so should be minimised wherever possible.

Conclusion

This study demonstrated how nonlinear functions can be applied to TTO data in order to take the diminishing marginal impact into consideration. This method might improve the precision of the measured impact of hypoglycaemic events and can be particularly useful if there is large variation in the hypoglycaemia data or if using individual level data.

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