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Research and Applications

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Combining uncertainty-aware predictive modeling and a bedtime *Smart Snack* intervention to prevent nocturnal hypoglycemia in people with type 1 diabetes on multiple daily injections

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Abstract

Objective: Nocturnal hypoglycemia is a known challenge for people with type 1 diabetes, especially for physically active individuals or those on multiple daily injections. We developed an evidential neural network (ENN) to predict at bedtime the probability and timing of nocturnal hypoglycemia (0-4 vs 4-8 h after bedtime) based on several glucose metrics and physical activity patterns. We utilized these predictions *in silico* to prescribe bedtime carbohydrates with a *Smart Snack* intervention specific to the predicted minimum nocturnal glucose and timing of nocturnal hypoglycemia.

Materials and methods: We leveraged free-living datasets collected from 366 individuals from the T1DEXI Study and Glooko. Inputs to the ENN used to model nocturnal hypoglycemia were derived from demographic information, continuous glucose monitoring, and physical activity data. We assessed the accuracy of the ENN using area under the receiver operating curve, and the clinical impact of the *Smart Snack* intervention through simulations.

Results: The ENN achieved an area under the receiver operating curve of 0.80 and 0.71 to predict nocturnal hypoglycemic events during 0-4 and 4-8 h after bedtime, respectively, outperforming all evaluated baseline methods. Use of the *Smart Snack* intervention reduced probability of nocturnal hypoglycemia from 23.9 ± 14.1% to 14.0 ± 13.3% and duration from 7.4 ± 7.0% to 2.4 ± 3.3% *in silico*.

Discussion: Our findings indicate that the ENN-based *Smart Snack* intervention has the potential to significantly reduce the frequency and duration of nocturnal hypoglycemic events.

Conclusion: A decision support system that combines prediction of minimum nocturnal glucose and proactive recommendations for bedtime carbohydrate intake might effectively prevent nocturnal hypoglycemia and reduce the burden of glycemic self-management.

Key words: nocturnal hypoglycemia; type 1 diabetes mellitus; multiple daily injections; artificial intelligence; evidential regression.

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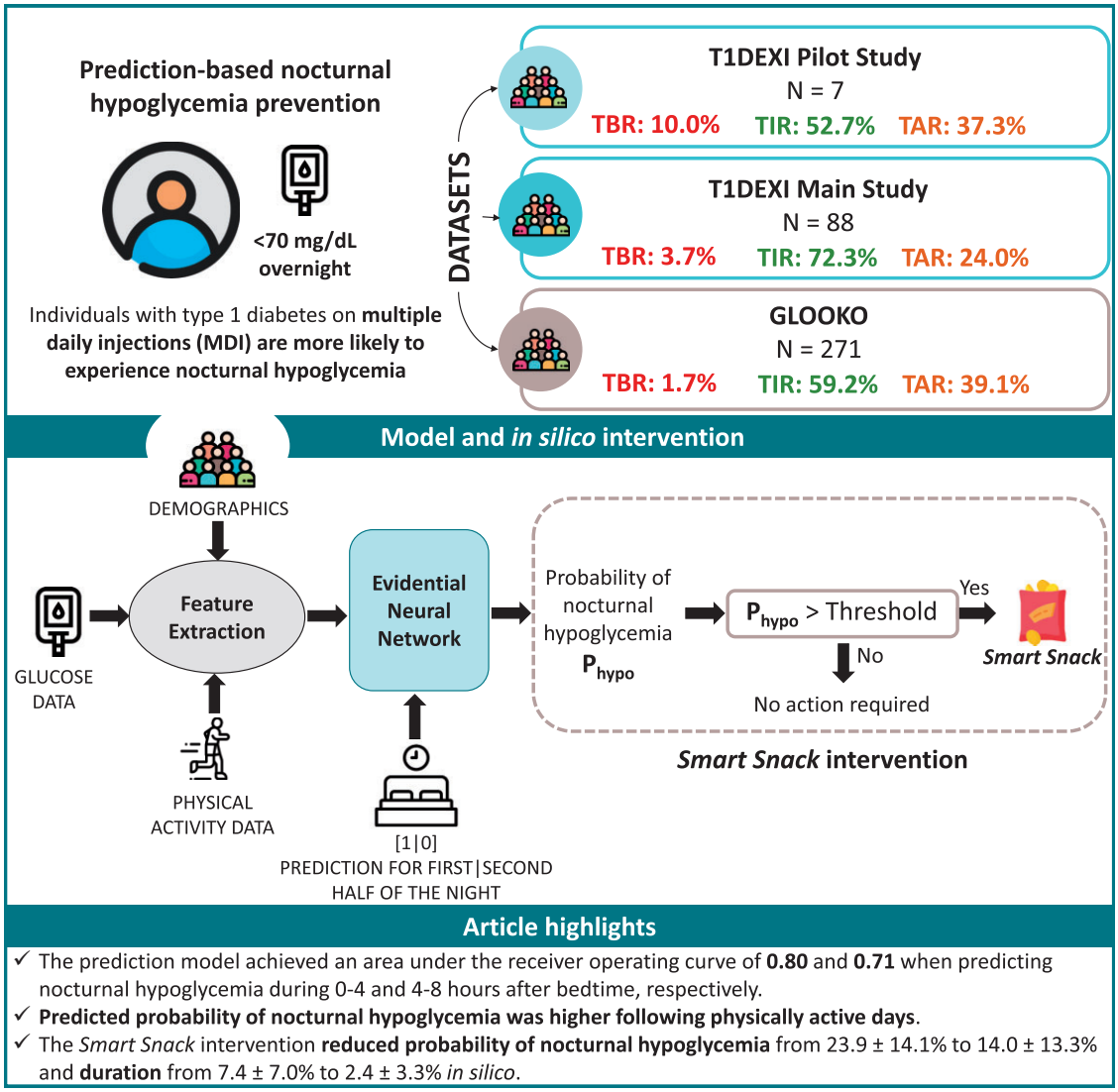
Graphical Abstract



Background and significance

Nocturnal hypoglycemia accounts for more than 50% of level-two hypoglycemia events (glucose <54 mg/dL) in persons with type 1 diabetes (T1D).[1,2] Increased levels of late day physical activity (PA) dramatically increase risk for nocturnal hypoglycemia.[3] However, this risk can be difficult to predict because of individual variation in whole body insulin sensitivity post-exercise[4] and the variability in the blunting of the counterregulatory responses to ensuing hypoglycemia after exercise, which may be impacted by several variables such as recent hypoglycemia events, sex, and the intensity of exercise.[5–8] Even with the use of intermittently scanned or real-time continuous glucose monitoring (CGM), nocturnal hypoglycemia can be difficult to manage clinically as individuals are unlikely to recognize symptoms while sleeping and may not awaken to hypoglycemia alarms from CGM systems.[9,10]

Although advanced insulin therapies are now available, most people with T1D continue to use multiple daily injections (MDI), with or without CGM.[11,12] A recent study showed that MDI users using CGM spent more time with glucose <54 mg/dL and experienced more nocturnal hypoglycemia than standard pump or hybrid closed-loop (HCL) users.[12]

Parallel approaches have emerged to separately prevent or predict nocturnal hypoglycemia. Guidelines recommend modifications to insulin doses and carbohydrate consumption without bolus insulin administration following exercise to help lower the risk of post-exercise nocturnal hypoglycemia,[13–15] but these guidelines rely heavily on user experiences, their perceived risk for nocturnal hypoglycemia, and actions to make adjustments within the appropriate time period. While there have been several publications demonstrating methods for predicting nocturnal hypoglycemia,[16–23] these algorithms do not estimate the risk and timing of nocturnal hypoglycemia relative to exercise based on known risk factors (eg, antecedent exercise intensity, duration, and recent glucose trends) nor do they provide predictive uncertainty. A system that both predicts nocturnal hypoglycemia and suggests

Table 1. Description of datasets used for model training and testing.

Characteristic	Dataset		
	T1DEXI study		Glooko
	Pilot study	Main study	
Participants, *N*	7	88	271
Nights with data, *N*	210	2278	41 666
Physical activity data	Yes	Yes	No
Demographics			
Biological sex (female/male/unknown), *N*	2/5/0	55/33/0	79/66/126
Age (mean±SD) at baseline, years	28 ± 11	38 ± 14	26 ± 18
Overall glucose control, average [range] at the participant level			
Time in target range 70-180 mg/dL, %	52.7 [38.1, 66.4]	72.3 [26.5, 98.7]	59.2 [2.6, 100.0]
Time above range >180 mg/dL, %	37.3 [21.3, 55.1]	24.0 [0.0, 73.5]	39.1 [0.0, 97.4]
Time below range <70 mg/dL, %	10.0 [1.3, 15.7]	3.7 [0.0, 15.8]	1.7 [0.0, 15.4]
Overnight hypoglycemia (11:00 PM-7:00 AM), average [range] at the participant level			
Probability of nocturnal hypoglycemia, %	44.8	24.3	16.2
Time in overnight glucose <70 mg/dL, %	15.1 [2.1, 33.3]	3.9 [0.0, 18.5]	2.1 [0.0, 53.8]
Time in overnight glucose <70 mg/dL, min	73 [10, 160]	18 [0, 80]	9 [0, 94]
Time in overnight glucose <54 mg/dL, %	7.2 [0.9, 18.2]	1.0 [0.0, 10.0]	0.4 [0.0, 8.1]
Time in overnight glucose <54 mg/dL, min	34 [5, 88]	5 [0, 44]	2 [0, 39]

prophylactic carbohydrate consumption at bedtime after a predominantly sedentary day or an active day has the potential to reduce exposure to nocturnal hypoglycemia safely and effectively and lower the patient burden for glycemic self-management.

Objective

To develop a unified approach to nocturnal hypoglycemia prediction and prevention using an algorithm that predicts the probability of an event and provides an estimated time frame for its occurrence and a measure of uncertainty. This information is passed to a *Smart Snack* algorithm to recommend carbohydrate intake at bedtime. This system aims to help people with T1D on MDI to avoid nocturnal hypoglycemia, and it is evaluated *in silico*.

Materials and methods

Datasets

We used free-living data from 366 individuals from the T1DEXI Study and Glooko Inc. (Mountain View, CA, USA) (refer to Table 1 for details). The T1DEXI Study is a large real-world observational study conducted at-home, involving the collection of glucose management data from 497 people with T1D to study the effects of different types of exercise (ie, cardio, interval, and strength) on glycemic control. Participants from the T1DEXI Study were recruited from around the United States. An Institutional Review Board approved the T1DEXI Study and electronic informed consent was obtained from each participant. The study had 2 phases: the initial pilot data collection[24] followed by the subsequent main data collection.[25] The T1DEXI dataset included data from physically active adults (mean age 37 ± 14 years; HbA1c 6.6 ± 0.8% [49 ± 8.7 mmol/mol]) on MDI, standard insulin pump, or HCL therapies, who wore an unblinded CGM and a fitness tracker during 4 weeks (dataset available at https://doi.org/10.25934/PR00008428). In brief, participants performed randomly assigned structured exercise sessions and reported PA, food intake, and insulin dosages (in the case of MDI users). The outcomes of the study included the change in glucose during exercise and differences in time in rage 70-180 mg/dL between physically active versus sedentary days.[25]

Although the T1DEXI dataset contains data from participants on various insulin treatment modalities; in this work, we exclusively employed data from participants on MDI therapy ($N = 7$ from the pilot phase and $N = 88$ from the main phase) as this group represents the target population for the prediction-based intervention developed in this research.

The Glooko dataset comprises glucose and insulin data from MDI users ($N = 271$) who lived in the United States. Demographic data in the Glooko dataset were limited to age and biological sex. Glooko provided the de-identified dataset for the study with required consent from patients and healthcare providers.

For algorithm development and testing, the participants from the T1DEXI and Glooko datasets were split in an 80:20 ratio such that 80% of the data was used only for model development while the remaining 20% was used for testing. We did not expect any institutional bias in either the T1DEXI dataset or the Glooko dataset because participants were not recruited directly by any single institution but rather were recruited from around the United States. The T1DEXI dataset included labeled PA and sleep data. Distribution of bedtimes from the T1DEXI Study was used to estimate bedtime in the Glooko dataset. We ensured that there were no insulin boluses reported in the 8 h after the estimated bedtimes.

Feature extraction and selection

Glucose features were derived from CGM (eg, glucose statistics, low/high blood glucose index, continuous overlapping net glycemic action,[26] percentage time in clinically relevant glucose ranges,[27] and long continuous glucose rises or drops) and calculated across different time frames prior to bedtime (ie, previous 7 nights, daytime [7:00 AM to bedtime], 1-24 h, and 30 min) and at bedtime. A maximum allowable threshold of 30% missing CGM data was employed during feature calculation to ensure that each participant had sufficient data represented in the dataset. Data in the training and test sets

were well balanced and had equivalent distributions to mitigate the influence of potential outliers.

Agglomerative clustering[28] was used for feature selection. Glucose features were clustered based on the features' pairwise mutual information (MI),[12] such that correlated features were grouped together. The optimal number of clusters was determined to be 69 by maximizing the Silhouette score.[29] From each cluster, the feature with maximum MI with nocturnal hypoglycemia was included in the model. Other widely used approaches such as Lasso[30] could have been used for feature selection. However, Lasso performs erratically when features are correlated.[31]

Missing values of glucose features and the duration of PA were imputed with the median value of the features in the training dataset and standardization was used for feature scaling. Scaling of continuous features was done by subtracting the feature mean from the unscaled feature value and then dividing by the feature standard deviation. Table S1 shows the mean and standard deviation values used for feature scaling.

We did not apply sampling or data augmentation methods to address dataset imbalance due to the relatively moderate nature of this imbalance (ie, ∼100:10 in our training dataset).[32] Furthermore, the use of imbalance correction techniques may not consistently lead to substantial enhancements in accuracy and might yield poorly calibrated models that overestimate the probability of infrequent events[33] such as nocturnal hypoglycemia in T1D.

Evidential regression

We optimized a fully connected evidential neural network (ENN)[34] to predict, at bedtime, the minimum nocturnal glucose along with associated predictive uncertainty. Although a universally accepted definition of nocturnal hypoglycemia has not been established, in this study we conservatively defined nocturnal hypoglycemia as occurring when minimum nocturnal glucose levels drop below 70 mg/dL during either the initial or later 4-h period following bedtime. Evidential regression has been used previously for personalized short-term glucose prediction.[35] The evidential regression framework presented by Amini et al.[34] and adopted in this work is presented in more detail in the Supplementary Material.

The architecture of the ENN (input layer: 81 units, hidden layers: 8 and 4 units, evidential output layer: 4 units) and training hyperparameters (starting learning rate: 2.4×10^{-3}, batch size: 128, and evidential penalty λ: 2.6×10^{-3}) were found via Bayesian optimization using 5-fold participant-level cross-validation on the training dataset. One output of the ENN (γ) in the Supplementary Material, is an estimation of the minimum glucose overnight. The 3 other outputs of the ENN (υ, α, β) were used to estimate the uncertainty of the minimum glucose estimate (see Supplementary Material). An indicator variable was used to specify whether the minimum overnight glucose is in hours 0-4 or 4-8 relative to bedtime.

Model parameters were optimized using the Adam optimizer.[36] Early stopping was used to prevent overfitting in the cross-validation runs. This means that training was halted before completing a usually very large set number of training epochs if the performance of the model as measured by the area under the receiver operating characteristic curve (AUROC) on the validation subset started to degrade.

Nocturnal hypoglycemia prediction evaluation metrics

AUROC, sensitivity, and specificity as well as the area under the precision-recall curve (AUPRC) were used to assess prediction accuracy. Risk thresholds for predicting nocturnal hypoglycemia were selected by maximizing the harmonic mean of the specificity and sensitivity on the training dataset to balance type I (false positives) and type II (false negatives) errors. In this application, both type I and type II errors are undesirable. Type I errors will result in high glucose levels and possibly weight gain if unnecessary treatments are indicated based on false positive predictions while type II errors will result in possibly preventable nocturnal hypoglycemia events.

Smart Snack intervention

Consumption of a bedtime snack was recommended if there was a predicted high likelihood of nocturnal hypoglycemia. The snack content was designed in collaboration with clinicians to address both the severity and timing of hypoglycemia. The carbohydrate content of the snack varied from 15 to 30 g based on the predicted minimum nocturnal glucose. Rapid-acting carbohydrates were recommended when the likelihood of a hypoglycemia event exceeded a target threshold in the first 4 h of sleep. A mixed macronutrient snack with protein, fat, and fiber was recommended to delay carbohydrate absorption and address hypoglycemia if the ENN predicted a high likelihood of hypoglycemia that again exceeded a threshold in the latter half of the night. The thresholds for likelihood of hypoglycemia were determined through hyperparameter tuning during training.

In silico evaluation of hypoglycemia prediction and *Smart Snack* intervention

The effect of the *Smart Snack* intervention was evaluated in a virtual population of 20 adults with T1D. We matched 20 participants from a 4-arm automated insulin delivery study that we published previously[37] to the most similar virtual adults in the Oregon Health & Science University virtual population using total daily insulin requirements and body weight.[38] Each virtual adult participated in an *in silico* 3-arm crossover study with 77 days per arm, including (1) standard basal and bolus regimens without *Smart Snack* intervention, (2) *Smart Snack* intervention based on ENN predictions, and (3) *Smart Snack* intervention using knowledge of actual overnight glucose values (the Oracle forecast method).[17] Varying insulin dosing regimens were imposed on the participants to reflect the impact of the intervention in a more real-world situation. The final *in silico* dataset reflects 4620 days of virtual participant outcomes. Glycemic outcomes are based on virtual participant CGM data and reported for the overnight period defined as 11 PM-7 AM, as well as for the 24 h following bedtime at 11 PM. Bedtime was fixed for the *in silico* trial.

Results

Figure 1 shows the top-20 glucose features along with the MI with nocturnal hypoglycemia. PA features included exercise type, duration, intensity, and timing. Demographic features were age and biological sex. Table S1 shows all input features.

Figure 2 shows prediction error versus evidential uncertainty and demonstrates that uncertainty increased with

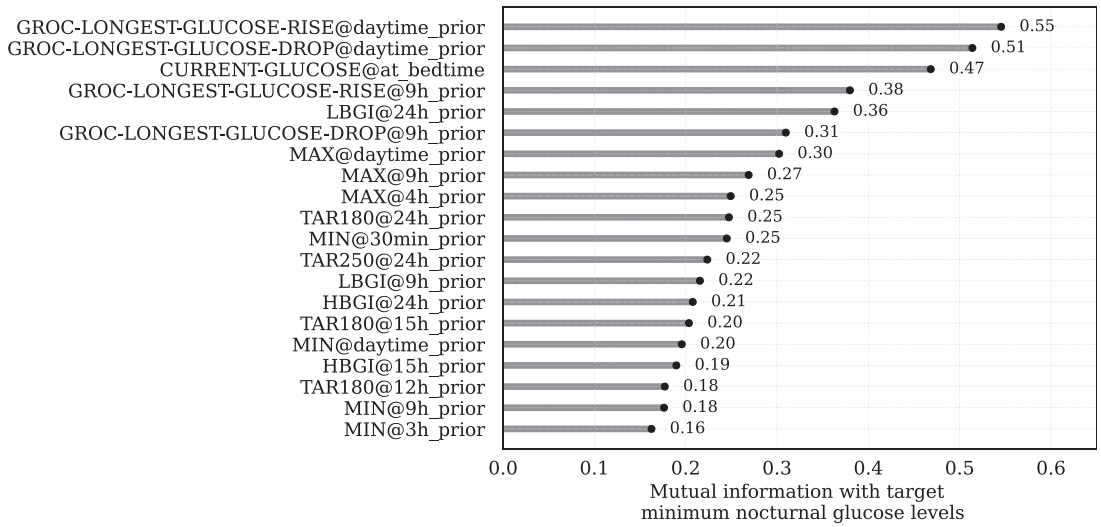


Figure 1. Top 20 glucose features used to train the prediction algorithm ranked by their average mutual information with the target minimum nocturnal glucose during the first half and latter half of the night. GROC, glucose rate of change; MIN, minimum CGM glucose; MAX, maximum CGM glucose; LBGI, low blood glucose index; HBGI, high blood glucose index; TAR[180|250], percentage time above range >180 mg/dL | >250 mg/dL. Features above are defined in Table S1.

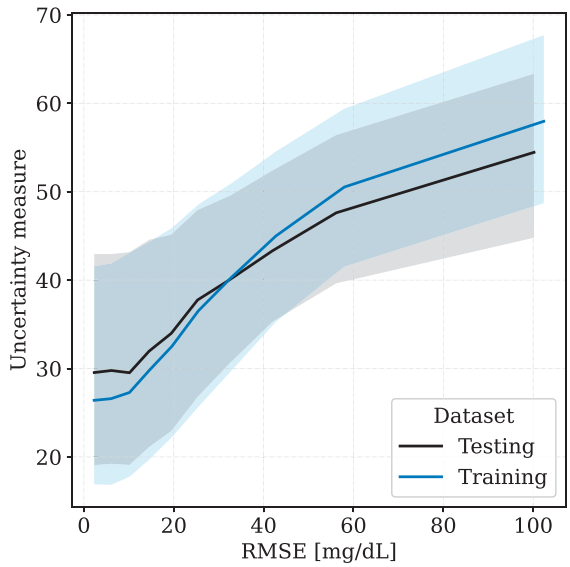


Figure 2. Association between prediction RMSE and evidential uncertainty for the training (blue) and the testing (black) datasets. Median (bold line) and interquartile range of uncertainty measure (shadow area) are shown. RMSE, root-mean-square error.

increased error in the estimation of the minimum nocturnal glucose as expected.

The ENN predicts the probability of hypoglycemia during the 0-4 h and the 4-8 h after bedtime. Figure 3A shows that the algorithm forecasted a higher likelihood of hypoglycemia during the latter half of the night compared with the first part of the night ($P < .001$). Higher likelihood of hypoglycemia was also forecasted on physically active days (ie, days with labeled exercise events) compared with sedentary days ($P < .001$) as presented in Figure 3B. There was 46.2% and 41.7% higher predicted probability of nocturnal hypoglycemia following physically active days relative to sedentary days in the training and testing data, respectively. Because of these differences, different thresholds were applied for predicting nocturnal hypoglycemia during the first half versus the latter half of the night, and for active versus sedentary days. The threshold is $p_{TH}^{(S,1)} = 0.112$ for nocturnal hypoglycemia prediction during the first half of the night and $p_{TH}^{(S,2)} = 0.167$ for nocturnal hypoglycemia prediction during the latter half of the night on sedentary days. Similarly, for active days, the threshold is $p_{TH}^{(A,1)} = 0.159$ for nocturnal hypoglycemia prediction during the first half of the night and $p_{TH}^{(A,2)} = 0.211$ for nocturnal hypoglycemia prediction during the latter half of the night. Customizing these thresholds through hyperparameter tuning resulted in a 25% improvement in median participant-level specificity (0.77 vs 0.52) at the expense of a 5% drop in participant-level sensitivity (0.81 vs 0.86) in predicting nocturnal hypoglycemia on active days.

To illustrate the operation of the algorithm, let us consider that a person is going to sleep at 11:00 PM and runs the algorithm to determine whether they should take a snack before bedtime to avoid hypoglycemia. At 11:00 PM, a feature vector is constructed including features derived from CGM, PA data, and demographics. Additionally, an input variable indicating that the model is tasked to return predictions for the first half of the night is used. The resulting feature vector and the indicator input variable are used to predict the minimum nocturnal glucose and the associated predicted uncertainty. Following this prediction, the algorithm generates a probability value p for the likelihood of the minimum nocturnal glucose falling below 70 mg/dL. If PA has been recorded during the day, an alert indicating a high likelihood of nocturnal hypoglycemia during the first half of the night will be triggered if $p > p_{TH}^{(A,1)}$ and a bedtime snack recommendation will be provided. If the alert is triggered for the first half of the night, no further predictions are performed. However, if $p \leq p_{TH}^{(A,1)}$ a new prediction will be initiated using the previously calculated feature vector, but with the indicator input

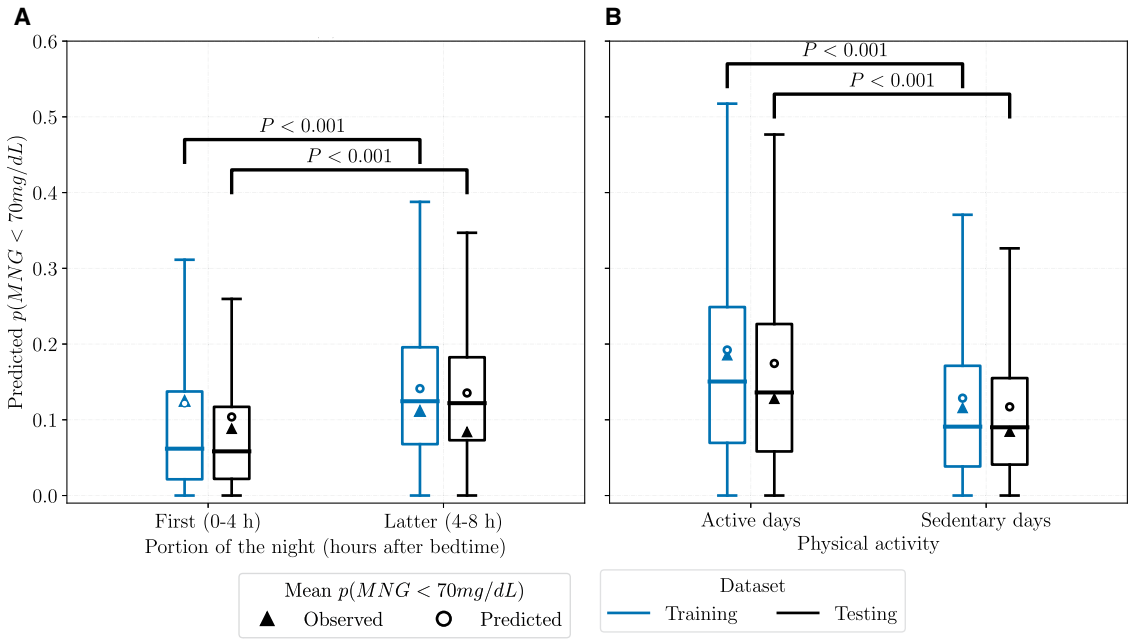


Figure 3. Predicted probability of nocturnal hypoglycemia stratified by (A) portion of the night and (B) active versus sedentary days. Predicted probability of nocturnal hypoglycemia is higher during the latter half of the night compared with the first part of the night (training: 0.14 vs 0.12, testing: 0.14 vs 0.10, $P < .001$). Predicted probability of nocturnal hypoglycemia is higher for nights following active days (training: 0.19 vs 0.13, testing: 0.17 vs 0.12, $P < .001$). MNG, minimum nocturnal glucose.

Table 2. Results of nocturnal hypoglycemia prediction methods on the hold-out testing dataset.

Nocturnal hypoglycemia time frame	Performance metric	Models			
		Elastic net	Support vector regression (SVR)	Extreme gradient boosting (XGBOOST)	Proposed evidential neural network
First half of the night 0-4 h after bedtime	AUROC	0.74	0.77	0.75	**0.80**
	Sensitivity	0.61	0.61	0.61	**0.67**
	Specificity	0.75	**0.79**	0.77	0.77
	AUPRC (chance level = 0.09)	0.32	0.38	0.32	**0.43**
Latter half of the night 4-8 h after bedtime	AUROC	0.64	0.67	0.64	**0.71**
	Sensitivity	0.51	0.52	0.51	**0.58**
	Specificity	0.69	**0.73**	0.67	0.72
	AUPRC (chance level = 0.09)	0.17	0.20	0.18	**0.22**
Nocturnal hypoglycemia regardless of event timing	Sensitivity	0.65	0.63	0.62	**0.68**
	Specificity	0.71	**0.75**	0.69	0.74

The best performance for each metric is highlighted in bold.

variable set such that the model returns predictions for the second half of the night. If the probability of nocturnal hypoglycemia $p > p_{TH}^{(A,2)}$, an alert for high likelihood of nocturnal hypoglycemia during the second half of the night is triggered and a bedtime snack recommendation will be provided. But if $p \leq p_{TH}^{(A,2)}$, the risk of nocturnal hypoglycemia is considered to be low enough to not trigger an alert. This same process is applied for sedentary days using corresponding probability thresholds $p_{TH}^{(S,1)}$ and $p_{TH}^{(S,2)}$.

Table 2 shows the higher performance of the proposed ENN algorithm when compared with Elastic Net,[31] Support Vector Regression,[39] and XGBOOST,[40] based on predictions made on the testing dataset which included the actual nocturnal glucose measurements that were used as ground truth. We chose comparator models such that various machine learning algorithms of different levels of complexity were evaluated, and we included the SVR model as the family of Support Vector Machine methods has been used in the past for predicting nocturnal hypoglycemia with promising results.[16,17,19,22,23] For a more objective comparative assessment of the accuracy of the prediction methods, the ENN and all comparator models were trained and tested on the same datasets described herein in the Methods/Datasets section.

The impact of the *Smart Snack* intervention *in silico* (mean±SD) is presented in Table 3. The statistical significance of the differences in glucose control outcomes was assessed using the Wilcoxon signed-rank test. ENN predictions in conjunction with the *Smart Snack* intervention resulted in 41% lower probability of nocturnal hypoglycemia relative to the no intervention baseline (14.0% vs 23.9%). Moreover, the ENN-based *Smart Snack* intervention

Table 3. Evaluation of the *Smart Snack* intervention *in silico*.

Study arm	Probability of nocturnal hypoglycemia (<70 mg/dL)	% Time-in-hypoglycemia (<70 mg/dL) *Mean*±*SD*		% Time-in-range (70-180 mg/dL) *Mean*±*SD*		% Time-in-hyperglycemia (>180 mg/dL) *Mean*±*SD*	
		Nighttime	24 h	Nighttime	24 h	Nighttime	24 h
No intervention	23.9 ± 14.1%	7.4 ± 7.0%	3.6 ± 2.3%	60.10 ± 9.7%	54.8 ± 10.0%	32.5 ± 11.8%	41.6 ± 10.3%
Evidential neural network+ *Smart Snack*	14.0 ± 13.3%[a]	2.4 ± 3.3%[a]	1.8 ± 1.2%[a]	60.7 ± 11.1%[b]	54.4 ± 9.8%[b]	36.9 ± 12.3%[a,b]	43.8 ± 10.3%[a,b]
Oracle+*Smart Snack*	13.5 ± 10.3%	2.8 ± 3.5%	2.2 ± 1.9%	65.1 ± 11.1%	56.1 ± 9.5%	32.2 ± 12.5%	41.6 ± 10.7%

Statistical significance indicates *P*-value <.05 as evaluated by Wilcoxon signed-rank test.
[a] Statistically significant with respect to control arm.
[b] Statistically significant with respect to Oracle *Smart Snack*.

significantly reduced %time-in-hypoglycemia as compared to no intervention, both in the overnight period (2.4% vs 7.4%) and during the 24 h following bedtime (1.8% vs 1.2%), with no change in %time-in-range. Using the Oracle forecasting method to recommend carbohydrates based on absolute knowledge of future nocturnal hypoglycemia resulted in comparable %time-in-hypoglycemia of 2.8%, and higher %time-in-range during the overnight period and the 24 h following bedtime given that the Oracle forecasting method does not produce Type I errors possibly leading to hyperglycemia.

Discussion

We demonstrate the performance of a proposed ENN framework and explore the clinical impact of utilizing this algorithm with a *Smart Snack* approach to recommend carbohydrates before bed, after both sedentary days and physically active days, if indicated. The ENN algorithm performs better than baseline methods in terms of AUROC and sensitivity in predicting nocturnal hypoglycemia. The SVR model achieved the highest specificity (1%-2% higher than the specificity of the ENN). However, comparator models lack the capability to estimate predictive uncertainty. The proposed algorithm provides uncertainty assessments that are well correlated with the prediction error (Figure 2), enabling the identification of scenarios where model predictions might be inaccurate. For instance, the uncertainty of the ENN predictions is optimized to be higher in scenarios when the model is applied to individuals with features (eg, demographic or glucose dynamics features) that significantly differ from those individuals whose data were used for model development.

The existing literature describes alternative approaches for estimating prediction uncertainties in neural networks using Bayesian techniques, such as mean–variance estimation,[41] Monte Carlo dropout,[42] and ensemble methods.[43] These methods generate prediction distributions by introducing noise to the model inputs, randomly dropping out a proportion of the neurons in a neural network or building ensembles of models with diverse parameters. However, the framework of evidential learning adopted in this study is different from these Bayesian strategies. Instead of placing a prior distribution on model inputs or parameters, it directly places a prior distribution on the likelihood function of the target variable, allowing a more flexible representation of uncertainty, as the likelihood function can capture both epistemic and aleatoric uncertainty.[34]

Our results suggest that the ENN algorithm might help avoid 68% of nocturnal hypoglycemic events, with a specificity of 74% (ie, 1.8 false positives per week). As expected, the accuracy of the algorithm is lower in predicting hypoglycemia that occurs in the latter half of the night (Table 2).

The prediction algorithm was equally effective in predicting nocturnal risk after both sedentary and physically active days. It is also worth noting that physically active days appeared to significantly increase the predicted risk for nocturnal hypoglycemia, which is consistent with other in clinical data observations for youth living with T1D who did or did not perform afternoon exercise.[44]

In our previous work on nocturnal hypoglycemia prediction,[17] we described an SVR algorithm that was trained and validated using data collected from people with T1D on sensor-augmented pump therapy (SVR_{PUMP}). We tested the SVR_{PUMP} on the MDI testing dataset. SVR_{PUMP} achieved sensitivity and specificity of 0.65 and 0.64 in predicting nocturnal hypoglycemia, respectively. The optimal glucose features found on data from pump users are comparable to MDI users. However, the SVR model trained with MDI (SVR_{MDI}) data and additional PA features yielded an overall sensitivity of 0.63 and a specificity of 0.75, which was worse than the ENN (Table 2). Although there was a slight decrease in sensitivity for the SVR_{MDI}, the additional features and the training data resulted in an 11% improvement in specificity, compared with the SVR_{PUMP}. This demonstrates the importance of training the model on MDI data if the algorithm is to be used by people on MDI therapy.

We further explored the impact of utilizing our algorithm and Smart Snack in an *in silico* clinical trial. We demonstrate that consuming a *Smart Snack* in response to the ENN predictions reduced both nocturnal hypoglycemia and hypoglycemia the following day; and this reduction was comparable to that of the Oracle method, which had full knowledge of nocturnal hypoglycemia prior to bedtime. These findings lend support for use of the ENN as an effective decision support tool to help people living with T1D avoid overnight hypoglycemia.

In the context of a real-world clinical application, the prediction-based recommendation system presented here can be integrated into a mobile health app for MDI users.[45] This integration involves automated processing of an individual's glucose measurements from a CGM sensor and PA data from a smartwatch or fitness tracker paired with the smartphone running a decision support app. The core functionality of the module for prevention of overnight low glucose encompasses preemptive alerts and personalized bedtime *Smart Snack* suggestions. These recommendations are triggered when there is

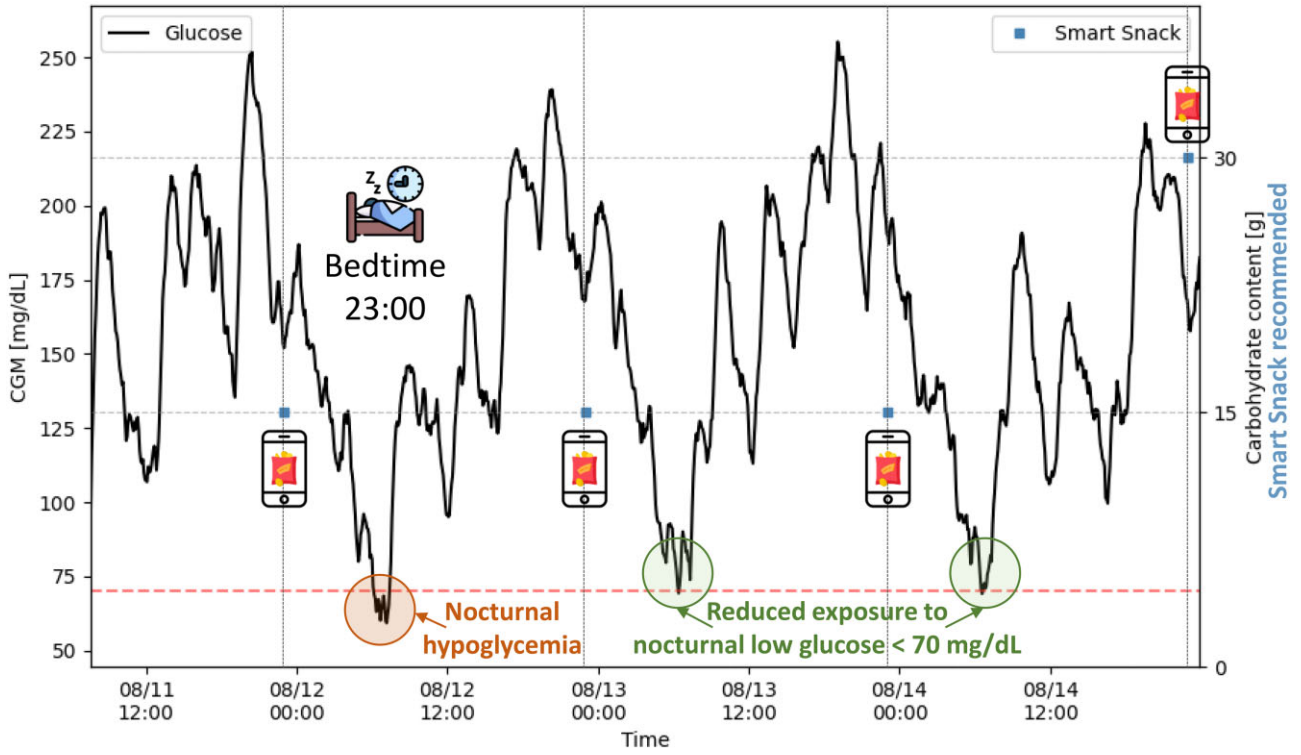


Figure 4. Illustration of a clinical application of the evidential regression-based decision support tool integrated into a mobile health app to predict probability of nocturnal hypoglycemia and provide bedtime snacks to help reduce exposure to overnight low glucose. Icons sourced from www.flaticon.com.

a heightened predicted probability of a nocturnal hypoglycemia event (refer to Figure 4 for an illustrative overview of the tool's functionality). The effectiveness of the proposed *Smart Snack* intervention in reducing nocturnal hypoglycemia for individuals with T1D using MDI therapy warrants further evaluation in clinical studies.

The prediction modeling work presented here has limitations that should be acknowledged. One limitation is that nocturnal period (ie, bedtime) was not standardized and our assessment of participants' bedtime may be inaccurate because the Glooko dataset did not include bedtime logs nor sleep information from its users. We therefore leveraged sleep information present in the T1DEXI Study data, as estimated from wearable data, to define a distribution of bedtimes that was used to generate training and testing examples.

Another limitation of this analysis arises from the definition of physically active days, which relied on participants' self-reported activity levels rather than activity captured by body-worn heart rate sensors and accelerometry. Thus, there is a potential for days featuring undisclosed (ie, incidental, not logged) PA to be inaccurately categorized as sedentary.

Conclusion

We leveraged advances in evidential machine learning to develop a model capable of predicting the probability and timing of nocturnal hypoglycemia. Information on risk and timing are key for making informed decisions regarding proactive measures to avoid nocturnal hypoglycemia.

The evidential learning approach applied in this study provides an estimation of predictive uncertainty, enabling identification of scenarios where the model is likely to fail; and therefore, improving the models' robustness and reliability. This system, in conjunction with our provider-informed *Smart Snack* algorithm, significantly reduced hypoglycemia overnight and in the following day in an *in silico* trial.

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Author contributions

C.M.-L., P.G.J., L.M.W., and J.R.C. designed the study. M.G. designed the bedtime snack, C.M.-L. and V.R.-E. processed the datasets and developed analysis and visualization tools. C.M.-L. developed the uncertainty-aware nocturnal hypoglycemia risk prediction algorithm and performed formal performance evaluation. C.M.-L. and N.S.T. developed the *in silico* clinical trial framework. C.M.-L., V.R.-E., N.S.T., L.M.W., J.R.C., S.R.P., M.A.C., C.K.M., M.C.R., R.L.G., and P.G.J. analyzed results. C.M.-L. wrote the first draft and revisions of the manuscript. C.M.-L., V.R.-E., N.S.T., L.M.W., J.R.C., S.R.P., M.A.C., C.K.M., M.C.R., R.L.G., and P.G.J. edited the manuscript. C.M.-L. acquired funding and administered the project.

Supplementary material

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

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Conflicts of interest

P.G.J. and J.R.C. have a financial interest in Pacific Diabetes Technologies Inc., a company that may have a commercial interest in the results of this research and technology. M.C.R. reports consulting fees from the Jaeb Center for Health Research, Eli Lilly, Zealand Pharma, and Zucara Therapeutics; speaker fees from Sanofi Diabetes, Eli Lilly, Dexcom Canada, and Novo Nordisk; and stock options from Supersapiens and Zucara Therapeutics. For all other authors, no competing interests exist.

Data availability

The dataset from the T1DEXI Study is accessible via this link: https://doi.org/10.25934/PR00008428. The Glooko dataset employed in this research is not available for public distribution in accordance with data sharing agreements.

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