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Use of machine learning to identify characteristics associated with severe hypoglycemia in older adults with type 1 diabetes: a post-hoc analysis of a case–control study

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ABSTRACT

Introduction Severe hypoglycemia (SH) in older adults (OAs) with type 1 diabetes is associated with profound morbidity and mortality, yet its etiology can be complex and multifactorial. Enhanced tools to identify OAs who are at high risk for SH are needed. This study used machine learning to identify characteristics that distinguish those with and without recent SH, selecting from a range of demographic and clinical, behavioral and lifestyle, and neurocognitive characteristics, along with continuous glucose monitoring (CGM) measures.

Research design and methods Data from a case–control study involving OAs recruited from the T1D Exchange Clinical Network were analyzed. The random forest machine learning algorithm was used to elucidate the characteristics associated with case versus control status and their relative importance. Models with successively rich characteristic sets were examined to systematically incorporate each domain of possible risk characteristics.

Results Data from 191 OAs with type 1 diabetes (47.1% female, 92.1% non-Hispanic white) were analyzed. Across models, hypoglycemia unawareness was the top characteristic associated with SH history. For the model with the richest input data, the most important characteristics, in descending order, were hypoglycemia unawareness, hypoglycemia fear, coefficient of variation from CGM, % time blood glucose below 70 mg/dL, and trail making test B score.

Conclusions Machine learning may augment risk stratification for OAs by identifying key characteristics associated with SH. Prospective studies are needed to identify the predictive performance of these risk characteristics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe hypoglycemia in older adults with type 1 diabetes is associated with significant morbidity and mortality, and previous work by Weinstock *et al* identified the characteristics that distinguish older adults with a recent history of severe hypoglycemia from those without across a wide range of potentially important variables.

WHAT THIS STUDY ADDS

⇒ This study aimed to harness machine learning methods to uncover the relative importance of those variables, including demographic, clinical, lifestyle, and neurocognitive characteristics, and continuous glucose monitoring (CGM) measures associated with a history of severe hypoglycemia among older adults with type 1 diabetes.

⇒ The individual-level characteristics associated with a history of severe hypoglycemia were hypoglycemia unawareness, hypoglycemia fear, glycemic variability as measured by CGM (coefficient of variation), % time blood glucose below 70 mg/dL, and trail making test B score.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows how machine learning models can be applied to prioritize risk characteristics for severe hypoglycemia.

⇒ The results may inform future risk stratification tools for older adults designed to aid care providers in providing data-driven, individualized counseling related to severe hypoglycemia.

INTRODUCTION

Older adults with type 1 diabetes are a growing population within the USA.[1] Although hypoglycemia is a concern at any age for people with type 1 diabetes, older adults are at substantially higher risk of hypoglycemia compared with younger adults. It has previously been reported that the incidence of one or more episodes of severe hypoglycemia (SH) in patients over age 65 within a 12-month period is 16.1%.[2] For older adults who have had type 1 diabetes for 40 years or more, the incidence of SH can be as high as 18.6% within 1 year.[2] Another study has shown that older adults over age 60 with type

1 diabetes have double the risk for SH compared with their younger counterparts.[3]

Among older adults, episodes of SH are associated with significant morbidity, including hospitalization, falls, fractures, altered mentation, and seizures.[1 4] In addition to the acute effects of hypoglycemia, in older adults the risk of other long-term side effects is also increased, including decreases in cognitive function.[5] SH episodes may affect cognition in older adults with type 1 diabetes related to language, executive function, and episodic memory, potentially because the brains of older adults are more susceptible to harm from SH compared with younger adults.[6] Avoiding these episodes is thus a priority of care.[7]

The increasing risk of SH with age may be attributed to changes to cognitive status,[8] metabolism and insulin sensitivity, higher prevalence rates of hypoglycemia unawareness, frailty, and functional impairments, as well as polypharmacy.[7] However, a challenge for mitigating the risk of SH on an individual level is that its etiology among older adults is both complex and multifactorial. Previous work by Weinstock *et al*[4] collected comprehensive data from older adults with type 1 diabetes in a case–control design and found that SH events were associated with increased hypoglycemia unawareness and glucose variability, with cases and controls having similar mean hemoglobin A1c (HbA1c) and mean continuous glucose monitoring (CGM)-measured glucose levels. Given that there are potentially many characteristics which may impact the risk for SH, spanning demographic and clinical characteristics, behavioral and lifestyle characteristics, neurocognitive characteristics, and CGM measures, there is a need to identify singular and sets of individual-level characteristics which may serve to identify older adults at high risk of SH.

Machine learning methods can "mine" high-dimensional data to uncover complex relationships between multiple potential risk characteristics and outcomes with fewer assumptions than traditional methods. We hypothesized that these methods could complement findings from traditional statistical analyses such as those by Weinstock *et al*[4] to provide insight into how different risk characteristics may be prioritized in a clinical setting to identify older adults at highest risk for SH; this is an important step toward risk stratification to tailor efforts to reduce significant morbidity and possible mortality associated with SH in this population. Building on the work of Weinstock *et al* that identified factors to distinguish older adults with a recent history of SH from those without from a wide range of potentially important variables, this study aimed to understand the relative importance of those characteristics. The long-term objective of this study is to generate new insights that may improve clinical tools for enhanced risk stratification to identify older adults at risk of SH.

RESEARCH DESIGN AND METHODS

Study design

This study used a data set from a prior case–control study to identify risk characteristics for SH in older adults with type 1 diabetes.[4] The random forest algorithm was used to classify (ie, identify) cases versus controls based on individual-level characteristics (ie, covariates). Participants in the original case–control study consented to taking part in the study.[4]

Data source

The data set for this study was initially used by Weinstock *et al* to identify risk characteristics for SH in older adults age 60 and older with diabetes duration of at least 20 years.[4 9] The original study was a case–control study with 201 participants from 18 T1D Exchange Clinical Network centers.[10] Cases were participants who reported an SH event within the past 12 months of study participation and controls did not have SH in the past 3 years. An SH event was defined as a hypoglycemic event leading to altered mentation or loss of consciousness and requiring the assistance of another individual to provide resuscitative assistance through carbohydrates, glucagon, or other means. Potential participants were excluded if they were current CGM users, recipients of pancreatic transplants, with life expectancy of less than 1 year, moderate or advanced dementia, or chronic kidney disease with a glomerular filtration rate of less than 30 mL/min/1.73 m^2.[4]

Measures

All data collection procedures are described in detail in Weinstock *et al*.[4] Demographic variables of interest included sex, race/ethnicity, education level, insurance type, and household size. Race/ethnicity was included as a social construct rather than to reflect differences in biology. Clinical variables of interest included body mass index, exercise, frequency of blood glucose monitoring, mean daytime and nocturnal blood glucose from CGM and blood glucose variability, HbA1c, insulin delivery system and dosing, medications, C peptide levels, creatinine, and hospitalization for diabetic ketoacidosis. Information on cognition, psychomotor skills, frailty, fear of hypoglycemia, hypoglycemia unawareness, and social support was also collected using a variety of survey and physical testing methods, described in the following.

Hypoglycemia unawareness was measured using the Clarke Hypoglycemia Awareness Questionnaire.[11] As noted in Weinstock *et al*,[4] the Clarke questionnaire includes questions about recent hypoglycemic events, which invalidates the use of the total score for this analysis. More recently, the Clarke score has been deconstructed into two subscales: SH experience and hypoglycemia awareness status.[12] To proxy hypoglycemia unawareness, removed from history of SH, we generated a raw score for the questionnaire elements that measures hypoglycemia awareness status and excluded the items that measure SH experience. Fear of hypoglycemia was

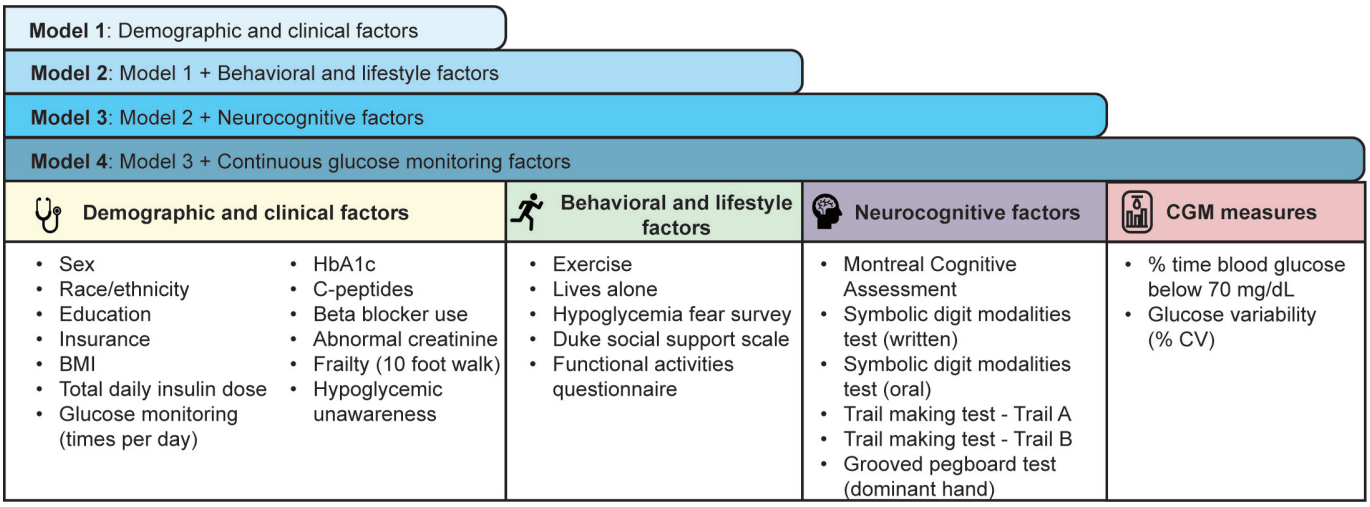

Figure 1 Models. We tested four models that were successively more complex, incorporating more individual-level characteristics that may be associated with severe hypoglycemia. BMI, body mass index; CGM, continuous glucose monitoring; CV, coefficient of variation; HbA1c, hemoglobin A1c.

assessed using the Hypoglycemia Fear Survey.[13] Neurocognitive testing was completed twice, 2 weeks apart. Mental status testing included the Montreal Cognitive Assessment.[14] Psychomotor testing was completed using the Symbol Digit Modalities Test.[15] Executive functioning was done using two trail making tests (trail making tests A and B).[16 17] Verbal memory was tested using the Hopkins Verbal Learning Test.[18] The grooved pegboard test was used to assess fine motor dexterity and speed.[19] Social support was assessed using the Duke Social Support Index.[20] Frailty was assessed using the timed 10-foot walk test. CGM data were blinded in the original study with SEVEN PLUS CGM devices worn by participants for 14 days with calibration daily. CGM was worn on average for 277 hours by case participants and 294 hours by control participants. The specific way in which each of these variables was operationalized in the model is shown in online supplemental table S1.

Statistical analysis

Successively complex (ie, richer) models were examined to incorporate demographic and clinical characteristics, behavioral and lifestyle characteristics, neurocognitive characteristics, and CGM measures (figure 1). The rationale for this approach was to use clinically accessible measures for model 1, exclusively. Subsequent models, models 2–4, include measures that require more time, tools, or resources to collect.

Stratified by case–control status and for the overall study population, we used descriptive statistics to summarize the characteristics of the study population. Binary and categorical characteristics were described using counts and percentages; numerical characteristics were described using the median, minimum, and maximum.

Because of missingness in the variables, we implemented multiple imputation[21] on the full analytic data set. Multiple imputation models the missing values conditional on the observed values. The model, in turn, is used to impute multiple likely values for the missing values and thus yields multiple imputed data sets. For our analysis, we generated 10 imputation data sets.

After multiple imputation, we split the observations into those to be included in the testing data set (test set) and those to be included in the training data set (training set). Observations included in the test set were chosen by randomly selecting 40% of the observations with complete data. Observations not in the test set were included in the training set. Overall, the train–test split was 78%/22%. Because observations included in the test set were complete cases, that is, information across the imputation data sets for the test cases was identical, the test set was exactly the single data set consisting of data for the test cases. In contrast, the training set consisted of the ten multiple imputation data sets subsetted on the observations selected as training cases.

To mitigate overfitting, we used feature selection techniques before fitting the machine learning models. First, we used correlation matrices to identify redundant characteristics and considered characteristics with an absolute correlation greater than 0.75 as redundant. Second, we used recursive feature elimination to identify the characteristics to include in our models to optimize accuracy.

Random forests[22] were trained on the training set and assessed on classification performance. For each of the four models considered, we fit a random forest on each of the imputation data sets in the training set. A random forest is a machine learning method that can be characterized as an ensemble of weak learners.[23] In the case of random forests, the weak learners are simple trees—the trees are the "learners," or models, and they are called weak because individual trees on average have poor predictive power and performance. Ensembling, in the context of random forests, means that many trees are constructed and each tree "votes" to contribute to the final prediction yielded from the forest of trees.

The "random" part of random forests refers to the injection of randomness in tree construction, for example, which characteristics are included in the tree and which ensures that the forest of trees has some heterogeneity and in turn improves performance. In our analysis, for each model, after training (ie, fitting) a random forest to each imputation set, we use the fitted model to classify observations in the test set as cases or controls. To assess model performance, sensitivity, specificity, and precision were calculated and averaged across the imputation sets.

Random forests naturally generate variable importance. In our analysis, we used the mean decrease in the Gini index to identify the importance of each variable. This metric is based on the idea of node purity. A node in a decision tree is a split point and each split is based on a variable. Node purity is a measure of the homogeneity of the labels at a particular node; the more homogeneous the labels the purer the node. The mean decrease in the Gini index captures the extent to which a particular variable, on average, decreases the impurity of a split among the constituent trees, or equivalently, the information gain from the use of that particular variable. The larger the mean decrease in the Gini index, the more important the variable across trees in the random forest.

Data and resource availability

The data set analyzed in the current study is publicly available from the Jaeb Center for Health Research database at https://public.jaeb.org/datasets/diabetes.[9] Analyses were conducted using the R statistical programming language.[24] The mice package[25] was used for multiple imputation, the caret package[26] was used to construct the test and training sets, and the randomForest package[27] was used to train the random forests. Git was used for version control; the code repository is stored on GitHub (https://github.com/nikkifreeman/T1D_SH_key_predictors).

RESULTS

Participant characteristics

This study used data for 191 participants from the Weinstock *et al* data set. Eight cases and four control participants were excluded due to missing demographics (two cases), having less than 7 days of CGM data (three cases), having less than 24 hours of night-time CGM (three cases, three controls), and not having CGM data (one control). The final analytic data set included 95 case participants and 96 controls; their characteristics are described in table 1.

The groups were similar in demographic characteristics based on sex, race/ethnicity, education, insurance status, annual income, and household size, with the majority being non-Hispanic white participants between 60 and 75 years old with at least some college education. There were differences between groups related to a variety of clinical characteristics. On average, the case participants monitored their blood glucose more frequently than the control group. Those in the case group had a greater percentage of time with hypoglycemic range blood glucose and had greater variability in their blood glucose measurements throughout the day and night. The case group also scored higher on frailty testing. Conversely, those in the control group scored lower on measures of hypoglycemia unawareness compared with controls. The testing for various functional modalities also showed differences among groups, with those in the control group demonstrating higher cognition, psychomotor skills, and dexterity.

Feature selection and model evaluation

Feature selection procedures revealed redundancy between two variables, the symbol digit modalities written test and the symbol digit modalities oral test. The controlled univariate analysis of the two tests in Weinstock *et al*[4] indicated a stronger signal for the written test than the oral test (p=0.001 vs p=0.01), so we dropped the oral test score as a covariate in our analysis. Recursive feature elimination did not provide compelling evidence for dropping additional variables from any of our models; thus, no additional variables were eliminated from our analyses (full results in online supplemental figure S2). Performance metrics for the fitted random forests, across all four models, are shown in table 2. The richer models, that is, models 2, 3, and 4, which had more variables as inputs, were more sensitive than model 1, and model 1 was more specific than the richer models. Precision was similar across models 1, 2, 3, and 4.

Modeling results

Figure 2 depicts the top five individual-level characteristics associated with having experienced an episode of SH from models 1–4 based on the mean decrease in the Gini index (full results in online supplemental figure S3). In model 1, which examined demographic and clinical characteristics, hypoglycemia awareness, HbA1c, glucose monitoring frequency, frailty, and insurance emerged as the most important for discerning between older adults with and without a history of SH. In model 2, where behavioral and lifestyle characteristics were added, hypoglycemia fear and the Duke Social Support Index additionally emerged as key characteristics, displacing frailty and insurance. In model 3, in which neurocognitive characteristics were added, the top five characteristics were hypoglycemia unawareness, hypoglycemia fear, the results of the Symbol Digit Modalities Test (written), the results of the trail making test - test A, and the results of trail making - test B. Finally, in model 4, which additionally included CGM measures, glucose variability as measured by % coefficient of variation and the per cent of time blood glucose below 70 mg/dL emerged as key variables associated with SH history.

DISCUSSION

We used a machine learning method and data from 191 older adults with type 1 diabetes to identify the

Table 1 Study participants, by case and control status

Participant characteristics	Overall (N=191)	Case participants (n=95)	Control participants (n=96)
Demographic and clinical characteristics			
Sex, n (%)			
Female	90 (47.1)	48 (50.5)	42 (43.8)
Male	101 (52.9)	47 (49.5)	54 (56.3)
Race/ethnicity, n (%)			
Non-Hispanic white	176 (92.1)	89 (93.7)	87 (90.6)
Other	15 (7.9)	6 (6.3)	9 (9.4)
Education, n (%)			
High school or less	22 (11.5)	13 (13.7)	9 (9.4)
Any college	117 (61.3)	54 (56.8)	63 (65.6)
Advanced degree	50 (26.2)	27 (28.4)	23 (24.0)
Missing	2 (1.0)	1 (1.1)	1 (1.0)
Insurance, n (%)			
Government and commercial	68 (35.6)	34 (35.8)	34 (35.4)
Only commercial	58 (30.4)	24 (25.3)	34 (35.4)
Only government	61 (31.9)	35 (36.8)	26 (27.1)
None	3 (1.6)	1 (1.1)	2 (2.1)
Missing	1 (0.5)	1 (1.1)	0 (0)
BMI, n (%)			
Underweight or normal weight	69 (36.1)	34 (35.8)	35 (36.5)
Overweight	72 (37.7)	35 (36.8)	37 (38.5)
Obese	46 (24.1)	24 (25.3)	22 (22.9)
Missing	4 (2.1)	2 (2.1)	2 (2.1)
Total daily insulin dose (units/kg), n (%)			
<0.40	45 (23.6)	19 (20.0)	26 (27.1)
0.40–0.60	79 (41.4)	40 (42.1)	39 (40.6)
>0.60	50 (26.2)	24 (25.3)	26 (27.1)
Missing	17 (8.9)	12 (12.6)	5 (5.2)
Glucose monitoring (times per day), n (%)			
0	1 (0.5)	1 (1.1)	0 (0)
1–3	22 (11.0)	5 (5.3)	16 (16.7)
4	43 (22.5)	20 (21.1)	23 (24.0)
5–6	68 (35.6)	37 (38.9)	31 (32.3)
7–9	40 (20.9)	19 (20.0)	21 (21.9)
≥10	18 (9.4)	13 (13.7)	5 (5.2)
HbA1c	7.7 (3.3, 11.5)	7.7 (3.3, 11.0)	7.65 (5.4, 11.5)
Detectable C peptide, n (%)			
<0.017	147 (77.0)	75 (78.9)	72 (75.0)
≥0.017	42 (22.0)	18 (18.9)	24 (25.0)
Missing	2 (1.0)	2 (2.1)	0 (0)
Beta-blocker use, n (%)	58 (30.4)	39 (41.1)	19 (19.8)
Missing	2 (1.0)	1 (1.1)	1 (1.0)
Abnormal creatinine, n (%)			
≤1.1 female/≤1.2 male	164 (85.9)	76 (80.0)	88 (91.7)

Continued

Table 1 Continued

Participant characteristics	Overall (N=191)	Case participants (n=95)	Control participants (n=96)
>1.1 female/>1.2 male	25 (13.1)	17 (17.9)	8 (8.3)
Missing	2 (1.0)	2 (2.1)	0 (0)
Frailty (10-foot walk in seconds)	3.0 (2.0, 7.5)	3.25 (2.0, 7.5)	3.0 (2.0, 6.5)
Missing, n (%)	2 (1.0)	1 (1.1)	1 (1.0)
Hypoglycemia unawareness*	2.82 (0.0, 6.0)	3.73 (0.0, 6.0)	1.94 (0.0, 6.0)
Missing, n (%)	3 (1.6)	2 (2.1)	1 (1.0)
Behavioral and lifestyle characteristics			
Exercise (days per week)	5.0 (0.0, 7.0)	5.0 (0.0, 7.0)	5.0 (0.0, 7.0)
Missing, n (%)	2 (1.0)	2 (2.1)	0 (0)
Lives alone, n (%)	44 (23.0)	23 (24.2)	21 (21.9)
Hypoglycemia Fear Survey	14.0 (5.0, 24.0)	14.0 (5.0, 24.0)	14.0 (5.0, 22.0)
Missing, n (%)	2 (1.0)	2 (2.1)	0 (0)
Duke Social Support Index	29.0 (15.0, 33.0)	28.0 (15.0, 33.0)	29.0 (19.0, 33.0)
Missing, n (%)	1 (0.5)	1 (1.1)	0 (0)
Functional Activities Questionnaire	0 (0, 30.0)	0 (0.0, 30.0)	0 (0.0, 30.0)
Neurocognitive characteristics			
Montreal Cognitive Assessment	26.0 (13.0, 31.0)	26.0 (13.0, 31.0)	26.0 (18.0, 30.0)
Missing, n (%)	1 (0.5)	1 (1.1)	0 (0)
Symbol Digit Modalities Test (written)	38.0 (12.0, 71.0)	35.0 (12.0, 66.0)	43.0 (17.0, 71.0)
Missing, n (%)	8 (4.2)	4 (4.2)	4 (4.2)
Symbol Digit Modalities Test (oral)	44.0 (16.0, 74.0)	41.0 (16.0, 74.0)	47.0 (19.0, 74.0)
Missing, n (%)	9 (4.7)	4 (4.2)	5 (5.2)
Trail making test – trail A	36.0 (15.0, 120.0)	39.0 (15.0, 82.0)	34.0 (16.0, 120.0)
Trail making test – trail B	92.0 (38.0, 300.0)	102 (39.0, 300.0)	84.5 (38.0, 257.0)
Missing, n (%)	6 (3.1)	2 (2.1)	4 (4.2)
Grooved pegboard test (dominant hand)	92.0 (59.0, 278.0)	97.0 (64.0, 261.0)	86.0 (59.0, 278.0)
Missing, n (%)	2 (1.0)	1 (1.1)	1 (1.0)
CGM measures			
% time blood glucose <70 mg/dL	6.50 (0.0, 29.9)	6.85 (0.21, 23.1)	5.40 (0.0, 29.9)
Coefficient of variation	43.5 (27.2, 60.0)	46.4 (28.0, 59.2)	41.7 (27.2, 60.0)

*Hypoglycemia unawareness was measured using the Clarke Hypoglycemia Awareness Questionnaire,[11] which recently has been deconstructed into two subscales: SH experience and hypoglycemia awareness status.[12] We generated a raw score for the questionnaire elements that measure hypoglycemia awareness status and excluded the items that measure SH experience.
BMI, body mass index; CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c; SH, severe hypoglycemia.

individual-level characteristics that were most strongly associated with having experienced an episode of SH, exploring a series of successively complex models using rich and diverse data. We found that when taking into account all possible demographic, clinical, neurocognitive characteristics, and CGM measures, the characteristics associated with a history of SH compared with those who have not had SH were hypoglycemia unawareness, hypoglycemia fear, glycemic variability as measured by CGM (coefficient of variation), the percent of time with blood glucose below 70 mg/dL, and trail making test B score. These results add to the limited literature for older adults with type 1 diabetes and provide a glimpse into the interactions and relative importance of the range of characteristics that are known to contribute to the risk of SH in this age group. Our results point to the important role of hypoglycemia unawareness in the cycle of SH, as well as how shorter-term measures of glycemia and glucose dynamics can be prioritized as part of the set of characteristics associated with long-term risk for SH. Our analysis also underscores the potential utility of incorporating more comprehensive information, including behavioral, neurocognitive, and CGM data, to discern older adult individuals who are at risk for hypoglycemia.

Table 2 Random forest model classification performance*

	Sensitivity†	Specificity‡	Precision§
Model 1: demographics and clinical characteristics	0.69	0.69	0.71
Model 2: model 1+behavioral and lifestyle characteristics	0.75	0.66	0.71
Model 3: model 2+neurocognitive characteristics	0.74	0.60	0.67
Model 4: model 3+CGM measures	0.77	0.60	0.68

*Reported performance metrics have been averaged across the models fit to the training sets; range=0–1.
†The proportion of times the model classifies an individual as a case subject given that the individual truly is a case subject.
‡The proportion of times the model classifies an individual as a control subject given that the individual truly is a control subject.
§The proportion of participants classified as a case that was truly a case.
CGM, continuous glucose monitoring.

It has been shown that older adults with type 1 diabetes have double the risk of SH compared with their younger counterparts.[3] This is especially true for older adults who have had diabetes for many decades, as the incidence of SH in 1 year increases with longer diabetes duration.[2] As a result, understanding what characteristics put this particularly vulnerable population at increased risk in may help to guide interventions to prevent the potentially devastating impact that SH can have on the health and quality of life of this population. Yet it remains unclear how to make use of diverse input information as part of stratifying older adults with type 1 diabetes based on their risk for SH.[1]

To address this gap, our study used the rich demographic and clinical risk characteristics investigated in the study by Weinstock *et al*[4] to explore potentially complex relationships between those risk characteristics and SH through machine learning modeling. This type of modeling allows for not only the identification of risk characteristics in a more flexible manner than traditional regression style approaches but also to identify the relative importance of those characteristics for SH compared with each other, effectively allowing for prioritization of risk characteristics. The rich data set allowed for the inclusion of characteristics beyond demographic and clinical data to explore behavioral, lifestyle, and neurocognitive risk characteristics associated with SH. Examination of the relative importance of variables in each of the successively rich models illustrates that SH risk is the interplay of characteristics across a multiplicity of domains. Rather than observing characteristics from a single domain, such as clinical characteristics, dominating in importance across models, figure 2 shows that consistently across models the most important characteristics came from a mix of domains. Model sensitivity increased as more characteristic types were included, and the best-performing model in terms of sensitivity was model 4, which incorporated demographic, clinical, behavioral and lifestyle, neurocognitive, and lifestyle characteristics, along with CGM measures, thereby providing a more holistic and detailed view of which characteristics can contribute to SH. Model 4 is important to consider since the complexity of older adults is incompletely captured by their demographic information and basic clinical and laboratory information.

As expected and consistent with Weinstock *et al*, hypoglycemia unawareness was an important risk characteristic for SH in the random forest modeling.[4] Based on recent studies of the Clark questionnaire,[11 12] we intentionally calculated a score to reflect the construct of hypoglycemia unawareness rather than history of SH. Interestingly, this characteristic remained the most important characteristic associated with SH across all four models and was thus robust to the addition of other information. Physiological changes related to aging such as hormonal response to hypoglycemia can make older adults particularly vulnerable to hypoglycemia unawareness.[28] Weinstock *et al*[4] also found that fear of hypoglycemia was

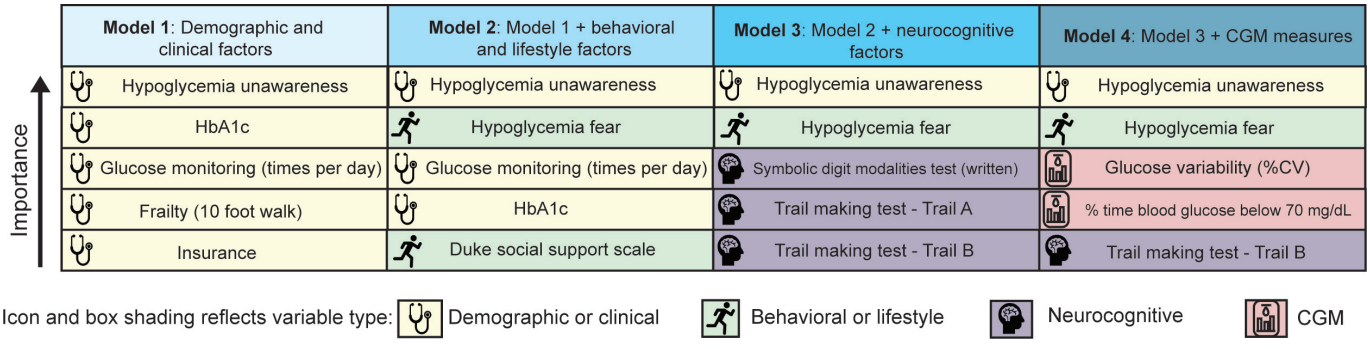

Figure 2 Top five characteristics from each model. These are the individual-level characteristics that emerged as most important for discerning between older adults with and without a history of severe hypoglycemia. CGM, continuous glucose monitoring; CV, coefficient of variation; HbA1c, hemoglobin A1c.

increased in those with recent SH; this characteristic emerged as a significant characteristic that remained robust across models 2–4, although the temporality of the relationship between this variable and the outcome of SH remains unclear in the case–control design. It is probably that older adults who recently experienced SH reported higher fear as a result of their event.

The vast majority of evidence detailing cognitive function in older adults with diabetes primarily involves those with type 2 diabetes.[8 29] One aspect of the original data set that is particularly interesting was the use of multiple neurocognitive assessments given the significant impact that SH can have on cognition in this population.[5 6] Weinstock *et al*[4] used the Montreal Cognitive Assessment, the Symbol Digit Modalities Test, the trail making test, and the grooved pegboard test to assess cognition and functioning. There were significant differences among case and control participants related to certain cognitive and functional tests, but it was not possible to elucidate in that study which tests are most predictive in differentiating those at higher risk for SH. The trail making test for executive functioning was a significant characteristic in the original study, and our modeling similarly indicated that trail B was a more significant characteristic compared with the trail A test for executive functioning for case participants. This test for executive functioning has been used in other studies of older adults with type 1 diabetes and those with recent SH did perform worse on that test.[6] Our results advance an understanding of the relative importance of this measure of executive functioning in the context of other potential risk characteristics, underscoring that these characteristics are likely informative in this age group.

Machine learning methods have been used in other studies for a variety of applications for people with type 1 diabetes including for predicting hypoglycemia. Those studies often used CGM data to predict the risk of hypoglycemia in the shorter term.[30–32] Additionally, these usually involved individuals who were younger with shorter diabetes duration and aimed to understand the risk of hypoglycemia in the immediate future based on CGM data. Since the risk of SH increases with increased diabetes duration, it is important to apply these methods to this group as well. While a number of machine learning methods were available for this analysis, we preferred the random forest algorithm because of its ability to naturally select important variables over a method like support vector machines and its ability to handle categorical features better than a method like L1-regularized logistic regression.

Given that the data from this study came from a case–control study, where the case status was based on a retrospective hypoglycemic event, the results provide insight into the characteristics that are robustly associated with SH, rather than true "risk factors" that are associated with acute events in the future. Prospective studies are needed to empirically test the predictive performance of these characteristics, including combinations thereof. A further limitation of this analysis is that participants who regularly use CGM were excluded, which limits generalizability to contemporary populations as CGM or closed-loop systems are becoming more common in older adults. Moreover, those who use CGM may have a different relationship with SH and other risk characteristics that cannot be accurately predicted using this model. In addition, the study used data from 191 participants from the T1D Exchange Clinical Network, a relatively small cohort consisting of a majority of non-Hispanic white participants.[4] As a result, models based on a more diverse population may have different risk characteristics that have contributed more to past SH or show differences in future SH events as in a prospective study. Because of the modest sample size, the number of CGM metrics included in the analysis were limited to those known to be associated with SH risk. Moreover, the variables of age, diabetes duration, or diabetes-related complications were not available in the data set. Including these variables may change the top five key characteristics across all models. Assessments of the social determinants of health were also not included despite the known importance of these variables in diabetes outcomes.[33]

The strengths of the study include the use of novel machine learning methods and the ability to compare our findings with prior work to assess for clinical validity of the machine learning models and elucidate how these methods complement traditional regression approaches. There are many possible risk characteristics for SH, and traditional statistical methods, which can help identify whether a characteristic is a risk characteristic or not, may be complemented by machine learning methods that can, for example, provide perspective on the relative importance of those characteristics. The models in this analysis allow for prioritization of potential risk characteristics so clinicians can more efficiently use their appointments to provide more personalized, yet data-driven advice for patients who have similar characteristics to those who have experienced SH. Future work in this space can be used to create risk stratification tools for clinician use. The data set that was used was also an important strength of this analysis because we were able to go beyond simple demographic or clinical measures and explore neurocognitive functioning in addition to CGM measures, thus providing a more holistic picture of the participants involved. Together, these results provide a glimpse into how varying levels of individual-level data can be prioritized in clinical settings to inform discussions with their older adult patients.

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Contributors NLBF and ARK conceived the study. NLBF, MVW, and ARK designed the analysis plan. NLBF conducted the statistical analyses. All authors contributed to the interpretation of the results. RM, NLBF, and ARK prepared the manuscript with contributions from MVW and RW. NLBF is the guarantor of this work.

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Competing interests RW participated in multicenter clinical trials through her institution, sponsored by Insulet, Medtronic, Eli Lilly, Novo Nordisk, and Boehringer Ingelheim, and has used donated DexCom CGMs and Tandem insulin pumps in projects sponsored by the NIH and the Leona M and Harry B Helmsley Charitable Trust.

Patient consent for publication Not required.

Ethics approval This study involves human participants. This study analyzed publicly available, deidentified data from a research study that was previously completed. Participants gave informed consent to participate before taking part in the original study. The University of North Carolina at Chapel Hill Institutional Review Board reviewed and approved the study (IRB 23-3227). It was deemed exempt due to being a category 4 study (secondary data/specimens).

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