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Interpretable and multimodal fusion methodology to predict severe hypoglycemia in adults with type 1 diabetes

Francisco J. Lara-Abelenda [a], David Chushig-Muzo [a], Ana M. Wägner [b], Maryam Tayefi [c], Cristina Soguero-Ruiz [a]

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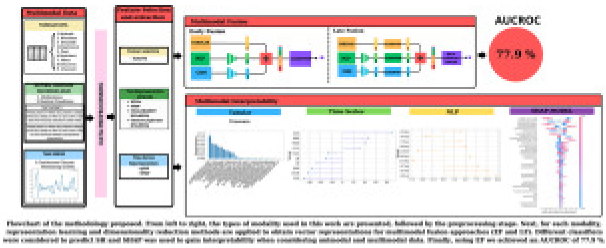
Highlights

- Multimodal fusion approaches improve the prediction of severe hypoglycemia.
- Interpretability techniques lead to identifying key factors for severe hypoglycemia.
- People with severe hypoglycemia show a high frequency of cardiovascular diseases.
- Impaired hypoglycemia awareness elevates severe hypoglycemia risk.

Abstract

Type 1 diabetes (T1D) causes insulin deficiency and exogenous therapy is required for maintaining targeted glucose levels. Hypoglycemia is the most frequent side effect of insulin, being severe hypoglycemia (SH) one of the most critical hazards with a range of life-threatening consequences. Artificial intelligence (AI) and multimodal fusion have boosted predictive performance in different domains. This study aims to evaluate the effectiveness of early fusion (EF) and late fusion (LF) approaches for predicting SH, to create a methodology capable of achieving robust results in datasets with a low number of samples for predicting SH and to characterize the risk factors involved in the SH onset using explainable AI (XAI). Data from a case-control study comprising adults over 60 years with T1D and with diabetes duration of 20 years were used and three types of modalities were considered: (1) continuous glucose monitoring data (time series); (2) clinical codes (text); and (3) surveys related to fear, unawareness, depression, and cognitive tests (tabular data). The results revealed that EF outperformed models trained with single-modality data by 5.8%, with an area under the receiver operating characteristic curve of 0.779. XAI techniques helped to discover that features related to fear and unawareness are mainly associated with SH. Our study introduced an interpretable and multimodal methodology capable of predicting the occurrence of SH in adults with T1D in the next year. Our interpretable methodology contributes to predicting SH and identifying related key factors, thus preventing SH complications and improving patient's quality of life.

Graphical abstract



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Introduction

Noncommunicable diseases (NCDs) are one of the major health issues affecting millions of people worldwide. According to the World Health Organization, NCDs accounted for 80% of the global disease burden in 2020, being one of the main causes of death (Wang and Wang, 2020). Type 1 diabetes (T1D) mellitus is one of the most prevalent NCDs, with a total of 8.75 million people worldwide in 2022 (Mobasseri et al., 2020). From the total of 8.75 million, 1.52 million (17.4%) were aged less than 20 years, 5.56 million (63.5%) were aged between 20 and 59 years, and 1.67 million (19.1%) were aged 60 years or older (International Diabetes Federation, 2022). It shows that although this disease is frequently diagnosed at a young age, its prevalence in adults has increased over the past two decades (International Diabetes Federation, 2022). T1D is characterized by an increase in blood glucose concentration caused by the destruction of pancreatic beta cells, which leads to a decrease in the production of insulin McCrimmon and Sherwin (2010). To treat and control the disease, T1D patients require exogenous insulin therapy and special attention to glucose monitoring and meal planning (Patton, 2011).

Hypoglycemia is the most frequent side effect of insulin therapy and occurs when the glucose level is below 70 mg/dL or 3.0 mmol/L (Lucidi et al., 2018). Episodes of hypoglycemia are classified as severe when the individual needs assistance from another person to restore glucose levels to the safe range (by administering carbohydrates or glucagon) because of altered consciousness or confusion (Lucidi et al., 2018). Severe hypoglycemia (SH) occurs approximately 2–3 times more frequently in T1D patients than type 2 diabetes (T2D) patients (Liu et al., 2020) and affects up to 50% of those with long-standing T1D every year (Flatt et al., 2020). For younger individuals with T1D, drug therapy mainly seeks to control glycemic levels. In contrast, for older adults with T1D, the focus shifts to minimizing hypoglycemic episodes and acute health events that these can cause in this age group (Davis et al., 2021). The occurrence of SH episodes can result in serious health complications, including neurological damage, seizures, trauma from falls, and, in acute cases, death (Ralston et al., 2024). Thus, psychoeducational interventions and individual self-management are protocols designed to prevent the appearance of SH in older adults (Ralston et al., 2024). It is also worth mentioning that T1D is a disease commonly diagnosed at an early age (Mobasseri et al., 2020), and consequently, most research related to hypoglycemia has been conducted on young individuals (Chiang et al., 2018, Patterson et al., 2019). Therefore, there is a need to study the associated risk factors in the development of SH events in adult and older individuals with T1D (Sherr et al., 2024), which makes this work an important contribution to the current literature.

Recently, artificial intelligence (AI) has emerged as a promising technology, with machine learning (ML) playing an important role. ML involves the development of models that allow computers to learn from data and make predictions (Feng et al., 2023b). The application of ML is widely spread across multiple domains (Feng et al., 2023c, Feng et al., 2023a). In particular, several studies have successfully applied AI to medical datasets for detecting health-related risks (Muksimova et al., 2024, Lesley and Kuratomi Hernández, 2024). In the context of hypoglycemia prediction, various AI-based models have been developed to anticipate its occurrence in individuals with diabetes (Tsichlaki et al., 2022). The use of an extreme gradient boosting (XGBoost), natural language processing (NLP) or recurrent neural network (RNN), among other models, have been developed over electronic health records or continuous glucose monitoring (CGM) to predict the hypoglycemic events (Tsichlaki et al., 2022). Nevertheless, the prediction of SH in adults with diabetes remains a relatively under-researched area, which has gained increased attention as a hot topic in the medical field (Misra-Hebert et al., 2020, Freeman et al., 2024). Recently, some methodologies have been proposed in the literature to predict SH in different prediction horizons (PH) for adults diagnosed with T1D and T2D (Misra-Hebert et al., 2020, Freeman et al., 2024, Schroeder et al., 2017). These methodologies primarily rely on a single data modality, such as tabular data or time series, and use a large number of samples to train the models. Despite the reasonable results obtained, the inherent nature of the data introduces significant limitations to the models. Specifically, data from a single modality may be insufficient to fully capture the multifactorial nature of health conditions like T1D, where a wide range of factors can influence the occurrence of SH episodes. Therefore, including data from diverse modalities enables the analysis from multiple perspectives and enhances access to comprehensive information, highlighting the need to explore the potential of a multimodal fusion approach (Baltrusaitis et al., 2018).

However, working with multimodal data is challenging due to its heterogeneity, which involves diverse structures and representations (Zhang et al., 2020). This complexity has made representation learning methods a relevant topic in ML, drawing significant attention for multimodal applications (Mai et al., 2023). In the literature, several representation learning methods have been proposed to obtain effective representations from raw data, including the data modalities of time series and text (Asudani et al., 2023, Khattak et al., 2019). In this paper, three types of modalities were considered to predict SH in adults with T1D, encompassing time series (CGM measurements), text, and tabular data.

The integration of explainability into AI has given rise to a new sub-field known as explainable AI (XAI) (Gunning et al., 2019). XAI methods are designed to understand how the model predictions are reached, thus providing interpretability to *black-box models* and creating transparent and trustworthy AI-based models (Gilpin et al., 2018). In the literature (Gunning et al., 2019, Gilpin et al., 2018), various methods have been proposed to add interpretability; in particular, in our study, we applied two types: feature selection (FS) and post-hoc interpretability models (Bommert et al., 2020, Mothilal et al., 2020). Specifically, this literature review highlights the clear need for a multimodal approach that preserves interpretability at every stage, from the generation of interpretable embeddings to the application of post-hoc XAI methods (Schroeder et al., 2017, Freeman et al., 2024, Fralick et al., 2021). Additionally, the methodology should be capable of achieving accurate results when predicting SH in people with T1D, even when working with datasets that present a scarce number of samples. This approach is essential to addressing the current research gap in the prediction of SH.

The aim of this paper was three-fold. First, we evaluated the effectiveness of multimodal fusion methods, including various early fusion (EF) and late fusion (LF) approaches, for predicting SH in adults with a long history of T1D. Second, we developed a methodology capable of achieving robust results using datasets with a limited number of samples. Third, through post-hoc XAI methods, we identified risk factors contributing to the onset of SH in T1D adults. Towards that end, we employed data from a case-control study comprising adults over 60 years with a 20-year history of T1D. Three types of data modalities are considered: CGM data (represented by time series), text-based clinical descriptions of diseases and medications, and tabular data representing the answers to multiple surveys filled by the participants in the study. These surveys included questions on cognitive and functional tests, depression, hypoglycemia unawareness, and various attitudes and fears associated with hypoglycemia and SH. Several techniques were explored to transform both the raw text and time series into vector representations. In particular, we used: *(i) for text,* word embeddings based on frequency-based methods (the term frequency–inverse document frequency (TF–IDF) Yu, 2008), artificial neural network (ANN)-based models (Word2Vec (Mikolov, 2013)), and two bidirectional encoder representations from transformers (BERT)-models (Clinical BioBERT (Alsentzer et al., 2019) and Clinical-Longformer Li et al., 2022); and *(ii) for time series,* the symbolic aggregate approximation (SAX) (Lin et al., 2007). To gain interpretability and identify risk factors involved in the onset of SH, we considered the FS method Relief (Urbanowicz et al., 2018) and two post-hoc XAI methods, including the Shapley additive explanations (SHAP) (Lundberg, 2017) and the diverse counterfactual explanations (DiCE) (Lesley and Kuratomi Hernández, 2024).

The rest of the paper is organized as follows. The literature review is presented in Section 2. The dataset description, the preprocessing stage as well as the methods considered in this work are detailed in Section 3. Section 4 presents the experimental setup, classification results with single-modality and multimodality data, and analysis of risk factors involved in SH using interpretability methods. Finally, Section 5 and Section 6 present the discussion and conclusions of this study, respectively.

Section snippets

Related work

The use of ML models to predict hypoglycemia has been widely explored in the literature, particularly when trained with CGM data (Tsichlaki et al., 2022), achieving impressive results. For instance, deep learning models trained exclusively with CGM reached an AUCROC of 0.94 (Thomsen et al., 2023), whereas ensemble learning methods obtained an AUCROC of 0.98 (Fleischer et al., 2022). Despite these advances, data-driven approaches designed to predict SH have received less attention. It is only …

Materials and methods

In this section, we present the dataset description and the preprocessing stage. We then introduce the foundations of representation learning methods for text and time series. The multimodal fusion models and XAI methods considered in this work are further described. …

Experimental results

In this section, we present the predictive results of unimodal and multimodal approaches for predicting SH. First, the results obtained using unimodal datasets containing tabular, text, and TS data are presented. Second, the predictive results considering different multimodal data fusions are shown. Finally, we highlight the key insights derived from the interpretable methods. For more details, refer readers to the workflow presented in Fig. 2. The data and source code for the reproducibility …

Discussion

In this work, we evaluated the effectiveness of data-driven and multimodal fusion approaches, EF and LF, to predict SH in adults with a long history of T1D. To quantitatively compare the results, we used as baseline the AUCROC obtained by the top-performing model trained with single-modality data, *i.e.*, the model that achieved an AUCROC of 0.721 ± 0.055 using the data from the *Fear* dataset. The experimental results demonstrated superior performance of the EF approaches compared to the LF …

Conclusion

Our study introduces a multimodal methodology designed to predict the occurrence of SH in adults with T1D in a one-year period while maintaining interpretability throughout the entire process. The proposed methodology maintains the interpretability from the creation of embeddings to the application of post-hoc XAI methods. We applied this approach to datasets from the *Jaeb Center for Health Research*, encompassing a variety of types of surveys, medications, medical conditions, and CGM data. Our …

CRediT authorship contribution statement

Francisco J. Lara-Abelenda: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **David Chushig-Muzo:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ana M. Wägner:** Writing – review & editing, Validation. **Maryam Tayefi:** Writing – review & editing, Validation. **Cristina Soguero-Ruiz:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. …

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Cristina Soguero-Ruiz reports financial support was provided by European Commission. Cristina Soguero-Ruiz reports financial support was provided by Government of Spain. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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