AALBORG UNIVERSITY
STUDENT REPORT

Prediction of Adherence to Basal Insulin in People with Type 2 Diabetes Initiating Telemonitoring

– Development of a Multivariable Machine Learning Prediction Model

Master's Thesis

Written by:

Kristian Ahlbeck & Melina Bødker Deleuran & Lasse Sigsgaard

February 2024 – June 2024

Titel: Prædiktion af adherence til basal insulin hos personer med type-2-idabetes, der opstarter telemonitorering – udvikling af en multivariabel machine learning prædiktionsmodel

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ECTS: 30 **Vejledere:** Thomas Kronborg, Jonas Dahl Andersen og Jannie Damsgaard Nørlev

Projektgruppe: KVT24gr10508

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Baggrund: Type 2-diabetes udgør en betydelig global sundhedsudfordring med stigende økonomisk byrde. På trods af behandling bidrager dårlig adherence til insulinbehandling til forværring af sygdomsresultatet og øgede omkostninger ved hospitalsindlæggelse. Formålet med dette studie var at udvikle en machine learning model, til tidlig prædiktion af adhernece og identificere features. Som potentielt kan hjælpe sundhedsprofessionelle med at identificere patienter med behov for ekstra pleje.

Metode: Data fra DiaMonT-studiet blev anvendt, hvor patienter insulindoser var telemonitoreret med forbundet insulin smart penne. Baseline information, data fra spørgeskema og blodprøver, fra 149 danske patienter med type 2 diabetes, blev brugt som potentielle features til machine learning modeller. Til forudsigelse af tidlig adherence blev dag 1-21 inkluderet. Sekventiel feature selektion blev anvendt med Logistisk regression klassifikationsmodel. Features scoret efter arealet under kurven med fire-folds krydsvalidering. Logistic regressions modellen blev evalueret på accuracy ved forskellige sensitivitetets niveauer.

Resultater: Studiet forudsagde patienternes adherence til insulin behandling med ni identificerede features. Fire-folds krydsvalidering gav en gennemsnitlig ROC AUC score på 0,69 ± 0,03. Modellen viste et moderat præstationsniveau med den højeste accuracy værende 63.10% med en grænseværdi på 52.10% og positiv prædiktiv værdi på 62.78%.

Konklusion: Det var muligt at udvikle en prædiktionsmodel for tidlig adherence og feature koefficienter. Anvendelsen af tærskelværdien vil afhænge af den relative betydning af sensitivitet og specificitet i den specifikke kliniske anvendelse.

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Background: Type 2 diabetes poses a significant global health challenge, with an increasing economic burden. Despite treatment, poor adherence to insulin therapy contributes to worsening of disease outcome and increased cost in hospitalization. The aim of this study was to develop a machine learning model for early prediction of adherence to basal insulin and identify features, supporting health professionals with identifying patients in need of extra care.

Method: Data from the DiaMonT trial was utilized in which patients' insulin doses were telemonitored with a connected insulin smart pen. Baseline information, questionnaire data, and blood samples from 149 Danish patients with type 2 diabetes were used as potential features for the machine learning model. For prediction of early adherence, days 1-21 were included. Sequential feature selector was used with Logistic regression as the classifier. Features scored by area under the curve with a four-fold-cross validation. The logistic regression model was evaluated using accuracy, based on various sensitivity levels.

Results: This study predicted patients' adherence to insulin with nine identified features. Fourfold cross validation yielded a mean receiving operating characteristic area under the curve of 0.69 ± 0.003. The model showed a moderate level of performance with the highest accuracy at 63.10%, with a threshold of 52.10% and positive predictive value of 62.78%.

Conclusion: It was possible to develop a prediction model for early adherence and feature coefficients. The threshold to be used in a clinical application moving forward will depend on the relative importance of sensitivity and specificity in the specific clinical application.

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Preface

This master's thesis was conducted by three students in their 4th semester from the master's in clinical science and technology at Aalborg university from 1st of February to 31st of May 2024.

This thesis' objective was to examine features associated with adherence in patients with type 2 diabetes, to be used in a clinical setting. This was made possible through preprocessing and analysis of data provided by our supervisor through the DiaMont Project.

Scientific paper

This thesis was reported as a scientific paper. It's written based on the guidelines from the journal of diabetes, science, and technology.

Worksheets

Additional worksheets are placed after the scientific paper to meet current learning objectives from the description of the semester. Additional appendices for further description have been included at the back of the study.

The authors of this project would like to express their deepest gratitude to their supervisor Thomas and co-supervisors Jonas Dahl Andersen and Jannie Damsgaard Nørlev, for their invaluable advice, encouragement, and patience through the process. Especially through the learning of machine learning topics and preprocessing of data, and for always having their door open and answering authors questions regarding the topic. Your expertise and insights were indispensable in helping us navigate through the challenges and refine our research focus.

In this study, adherence is defined as the extent to which a patient's behavior corresponds with agreed recommendations to prescribed medication regiment. Although a patient can be adherent in different aspects, this study focuses solely on medication adherence to insulin therapy and will be referred to as adherent or non-adherent.

The Vancouver citation system has been used in this study.

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Prediction of Adherence to Basal Insulin in People with Type 2 Diabetes Initiating Telemonitoring – Development of a Multivariable Machine Learning Prediction Model

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Abstract

Background: Type 2 diabetes poses a significant global health challenge, with an increasing economic burden. Despite treatment, poor adherence to insulin therapy contributes to worsening of disease outcome and increased cost in hospitalization. The aim of this study was to develop a machine learning model for early prediction of adherence to basal insulin and identify features, supporting health professionals with identifying patients in need of extra care.

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Conclusion: It was possible to develop a prediction model for early adherence and feature coefficients. The threshold to be used in a clinical application moving forward will depend on the relative importance of sensitivity and specificity in the specific clinical application.

Keywords

adherence, machine learning, logistic regression, algorithms, insulin, smart pens, prescribed, type 2 diabetes, sensitivity, accuracy

Introduction

Diabetes is a global challenge to the public health and a major cause of morbidity and mortality worldwide, with estimates of 537 million adults living with diabetes and 240 million undiagnosed (1–3). The prevalence for diabetes has increased over past decades. According to the World Health Organization (WHO), 108 million people lived with diabetes in 1980 (4). A number which quadrupled in 2014 and is predicted to rise by 60% in 2050 (2,5), with type 2 diabetes (T2D) being the most prevalent type affecting more than 95% diabetes patients (4,5).

The economic burden of diabetes on countries, health systems, and individuals living with diabetes are co-increasing. This cost was estimated to 966 billion USD in 2021, which represents a 316% increase over the past 15 years. Moreover, it is estimated to increase to 1.03 trillion USD in 2030 (3).

In early stages with T2D, patients have a lower production of insulin. First-line treatment includes diet-plan with exercises, often combined with Metformin which helps reduce the glucose production in the liver and improves insulin sensitivity in muscles and fat tissues. Second-line treatment includes medications, like Sulfonylureas, DPP-4

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Inhibitors, GLP-1-RA, and SGLT2 inhibitors which helps lowering blood sugar levels. When this no longer is sufficient, most patients with T2D are subjected to insulin treatment (6).

Poor medication adherence to T2D treatment contributes to worsening disease, mortality rates, and increasing healthcare costs (7,8). This is supported by Aroda, et al. (9) which suggest lower rates of healthcare costs and lower direct medical costs for patients with T2D adhering to prescribed insulin doses. Nichols, et al (10) suggest early adherence has a significant effect on glycaemic control, resulting in a lowered glycaemic burden. Hence, early interventions to minimize risks and establish optimal glycaemic control is important (11). Accurately measuring glycaemic control and insulin intake can be difficult due to complexities in tracking and quantifying adherence. Moreover, communication gaps between patients and health professionals may delay detection of non-adherence (7,12). Insulin adherence has often been evaluated through self-reported measures (questionnaires) and quantitative measures (electronic medical records) (13,14). Although, the measurements are associated with varying challenges from accuracy to reliability (15). Therefore, additionally patient engagement and education, combined with a standardized approach to measure insulin adherence is needed (16). Digital technologies, like connected insulin smart pens, could potentially increase the quality measure. Sharing data could help improve clinical care, improve individualized patient care and engagement (17). Measurements from smart pens could provide real time data to quantify injected or missed doses of insulin (18). Recent studies have successfully measured insulin injections via smart pens to determine adherence to insulin therapy (19–23). Additionally, multiple studies (13,14,24–29) found numerous factors associated with adherence to insulin in patients with T2D.

Machine learning (ML) algorithms in a clinical setting have forecasted possibilities to allow clinicians to make predictions and treat patients more accurately (30,31). Identifying patients in need of extra care can be a complex challenge depending on the accuracy of the risk assessments, as well as implementations of risk stratification approaches to detect patients at higher risk (32). Efficiencies might be gained by early identification of adherent/non-adherent patients (showing adherence within 1-3 weeks of initiating medical therapy) to reduce the risk of T2D comorbidities. Yet, no studies have examined factors associated with adherence to insulin therapy using data from insulin smart pan and ML, to be assessed in a clinical setting. Therefore, the aim of this study was to develop a ML model, to classify and identify adherence and find the most relevant features for prediction of early adherence and specify the sensitivity/specificity thresholds for the potential of clinical usage.

Methods

To explore the aim of this study a ML model was developed, and documentation followed the Tripod AI Guidelines (33). All data were pre-processed and analyzed using Python 3.11.5 and relevant modules: *NumPy: v.1.24.3, Pandas: v.2.0.3, Matplotlib: v.3.7.2, Scikit-learn: v.1.3.0, Seaborn: v.0.12.2, MLxtend: v.0.23.1.*

Data source

This study used data provided from the DiaMonT trial (NCT04981808) (34), an open lapel randomized controlled trial whose primary endpoint were to investigate whether telemonitoring can increase change from baseline in CGM time in range. The trial duration was from 18/08/2021 until 24/11/2023 and had a 90-day period where patients monitored their insulin doses, using a NovoPen 6 (Novo Nordisk A/S) received instructions of use prior to the beginning of the trial. The smart pen recorded each insulin administration with time and date of injected doses as well as units dosed. Prescribed basal insulin was registered by trial personnel and continuous adjustments throughout the trial was made by phone conversation for the included group. 331 patients were included in the study which was conducted in two sites in Denmark (Steno Diabetes Center, North Jutland and Steno Diabetes Center, Zealand). The eligible patients were randomized, 1:1 in an intervention group (which received telemonitoring) and a control group (which received usual care). Patients provided baseline information, questionnaire data, and a blood sample containing HbA1c. Patients aged ≥18 and diagnosed with T2D which had received insulin therapy for at least a year were eligible to participate in the study (34).

Definition of adherence

Adherence is defined as the extent to which a patient follows a prescribed medication regimen (35). This definition emphasizes the importance for health professionals to identify patients who have difficulties following their medication plan (not adherent) to provide them with additional support, improving their treatment outcome.

Following previous research by Nørlev et al. (23) and Sokol et al. (36), the present study classified patients as either adherent or non-adherent based on a threshold of 80% adherence. The calculated adherence (see figure 1) was used as the target variable for classification when using ML. Adherence was calculated as a percentage and thereafter defined as binary input for classification based on the 80% threshold.

$$Adherence = \left(\frac{Number\ of\ correctly\ administered\ doses}{Total\ number\ of\ prescribed\ doses\ in\ that\ given\ period} \right) * 100\%$$

Figure 1: *calculation of adherence* (23).

Preprocessing

Due to the risk of imbalance and bias, only data from the intervention group was included.

To enable detection of early adherence, only data from day 1-21 were included. Insulin data was structured into 24-hour periods from 03.00-03.00. This was to make sure no insulin doses overlapped within the same 24 hours. Only basal insulin therapy was investigated in this study. Therefore, bolus insulin injections were excluded as well as all units ≤2, as participants were instructed to do a 2-unit air shot when changing cartridge. Instances where patient did not administrate any insulin within 24 hours was imputed with 0 units.

Features were extracted from baseline data, blood samples, and responses from the questionnaire (Health status (SF12), Diabetes related life quality (DIDP), Hypoglycaemia (Clarke hypoglycaemia awareness survey), The use of telemedicine (TOC) and Self-efficacy and health (SEH)). The dataset had features displaying a missing rate surpassing 25%. They were eliminated from the dataset to prevent an inconsistent representation of data. Nominal and ordinal features were converted, due to ML algorithms, assuming ordinal relationships within attributes.

Feature selection and prediction model

To identify the most informative features, Scikit-learns function *Sequential Feature Selector (SFS)* was utilized. The features were scored by the Area under the receiver operating characteristics curve (ROC AUC). To reduce the risk of overfitting, the feature selection adopted a minimum AUC improvement threshold of 0.005. Logistic regression (LGR) was utilized as a classifier. The model was trained and validated in four-fold cross-validation for the ability to differentiate between people who were adherent and non-adherent to basal insulin therapy and visualized by the mean ROC AUC (37).

Model performance evaluation

The model was evaluated at fixed values of sensitivity of 60, 70, 80, 90, and 95%. This was achieved by calculating sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and the corresponding thresholds of each sensitivity level. The model was evaluated on the highest level of accuracy. The various levels were performed to present different thresholds for potential clinical use to present different acceptance levels of false positives and false negatives.

Results

From a sample size of 331, 149 were included in the study. With the threshold of 80% correctly dosed injections over the first 21 days, 50.34% were registered as adherent, and 49.66% were registered as non-adherent. Further characteristics of the study population was calculated (see table 1).

After preprocessing a total of 85 potential features were selected for feature selection. Identified by the sequential feature selection, nine of the 85 features were selected for model training. Each selected featured had an 0.005 or higher increase on the AUC performance (see figure 2).

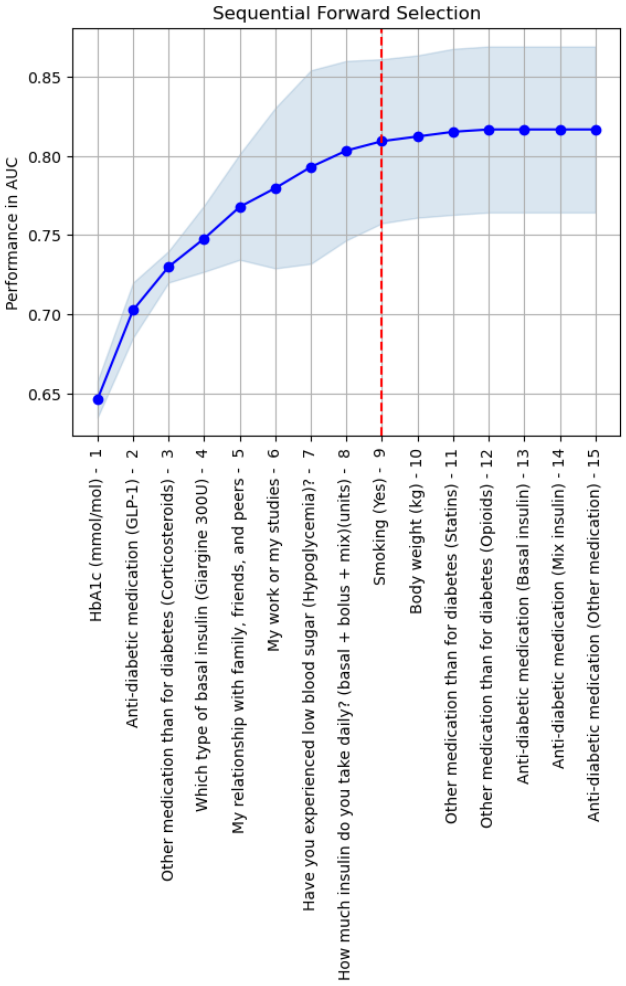

Figure 2: Plot of sequential feature selection, displaying the 15 best performing features, the increase of 0.005 or more ending after feature nine, with the red line indicating the cut-off.

Feature characteristics are illustrated in the selected order by the sequential feature selection, and for the groups, table 2 shows mean, standard deviation and coefficients for the features included in the model. Where "*My work or my studies*" has the highest coefficient at 0.6241 and "*Hypoglycaemia*" has the lowest coefficient at -0.2582.

Following the feature selection, a LGR model was used as the classifier to predict whether patients were adherent to their insulin prescriptions. Four-fold cross validation ranged from ROC AUC of 0.65 - 0.72, resulting in a Mean ROC AUC = 0.69 ± 0.03 (see figure 3). The LGR model achieved varying performance levels when evaluating the different target sensitivity levels (see table 3), resulting in a trade-off between sensitivity and specificity. The table displays mean values based on the four-fold cross validation (CV). The highest accuracy obtained was 63.10% with a threshold of 52.10% and positive predictive value of 62.78%.

Characteristic	Adherence, No. (%)	Non-adherence, No. (%)	Total group, No. (%)
Unique patients	75 (50.34)	74 (49.66)	149 (100)
Age			
20-29 years	0 (0)	1 (0.67)	1 (0.67)
30-39 years	4 (2.68)	2 (1.34)	6 (4.02)
40-49 years	9 (6.04)	4 (2.68)	13 (8.71)
50-59 years	18 (12.08)	20 (13.42)	38 (25.46)
60-69 years	24 (16.11)	28 (18.79)	51 (34.17)
70-79 years	19 (12.75)	17 (11.41)	36 (24.16)
80-89 years	1 (0.67)	2 (1.34)	3 (2.01)
BMI (mean, SD)	32.07 ± 6.51	34.46 ± 6.71	33.26 ± 6.70
HbA1c, %	7.58 ± 3.24	8.15 ± 3.41	7.86 ± 3.36
mmol/mol (mean, SD)	59.39 ± 11.96	65.65 ± 13.79	62.49 ± 13.23
Education level			
No education	1 (0.67)	0 (0)	1 (0,67)
Primary school	9 (6.04)	9 (6.04)	18 (12.08)
High school or similar	7 (4.70)	6 (4.03)	13 (8.72)
Craftsman (electrician, plumber exc.)	20 (13.42)	22 (14.77)	42 (28.18)
Bachelor	31 (20.81)	29 (19.46)	60 (40.26)
Advanced degree	7 (4.70)	8 (5.37)	15 (10.06)
Diabetes duration, years (mean, SD)	18.68 ± 14.57	18.81 ± 10.56	18.74 ± 12.70
Smoking			
Current smoker	10 (7)	7 (5)	17 (11.40)
Previous smoker	36 (24)	41 (28)	77 (51.67)
Never smoked	29 (19)	26 (17)	55 (36.91)
Alcohol			
0-5 items	66 (44.30)	61 (40.94)	127 (85.23)
6-10 items	5 (3.36)	6 (4.03)	11 (7.38)
11-15 items	3 (2.01)	5 (3.36)	8 (5.36)
16-20 items	0 (0)	2 (1.34)	2 (1.34)
More than 20 items	1 (0.67)	0 (0)	1 (0.67)
Marital status			
Domestic partner	22 (14.77)	22 (14.77)	105 (70.46)
Alone	53 (35.57)	52 (34.90)	44 (29.54)
Income			
Low	25 (16.78)	22 (14.77)	47 (31.54)
Middle	46 (30.87)	42 (28.19)	88 (59.09)
High	3 (2.01)	10 (6.71)	14 (9.39)
Didn't answer	1 (0.67)	0 (0)	1 (0.67)
Insulin units (U) pr. day (basal + bolus + mix) (mean, SD)	57.17 ± 50.30	74.82 ± 53.79	65.94 ± 52.64

Table 1: Demographic status for the participants.

Feature	Field attribute	Adherence, Mean, SD	Non-adherence, Mean, SD	Total group, Mean, SD	Coefficients
HbA1c (mmol/mol)	Value	59.39 ± 11.96	65.65 ± 13.79	62.49 ± 13.23	-0,6036
Antidiabetic medicine choice = GLP-1	0 = unchecked 1 = checked	0.52 ± 0.50	0.66 ± 0.48	0.59 ± 0.49	-0.4739
Other medication than for diabetes (choice=Corticosteroids)	0 = unchecked 1 = checked	0 ± 0	0.05 ± 0.23	0.03 ± 0.16	-0.5664
What type of basal insulin 4.0: (Glargine U300)	0 = unchecked 1 = checked	0.09 ± 0.29	0.16 ± 0.37	0.13 ± 0.33	-0.4236
(How has diabetes effected...) My relationship with family, friends, and peers	1 = Very negative 2= negative 3 = slightly negative 4 = doesn't affect 5 = slightly positive 6 = positive 7 = very positive 8 = not relevant	4.89 ± 1.49	5.15 ± 1.55	5.02 ± 1.52	-0.5940
(How has diabetes effected...) My work or my studies	1 = Very negative 2= negative 3 = slightly negative 4 = doesn't affect 5 = slightly positive 6 = positive 7 = very positive 8 = not relevant	5.53 ± 1.95	4.82 ± 2.07	5.18 ± 2.03	0.6241
Have you experienced low blood sugar (hypoglycaemia)?	0 = unchecked 1 = checked	0.72 ± 0.45	0.73 ± 0.45	0.72 ± 0.45	-0.2582
How much insulin do you take daily? (basal + bolus + mix)	Value	57.17 ± 50.30	74.82 ± 53.79	65.94 ± 52.64	-0.4726
Smoking 1.0: Actively smoking	0 = unchecked 1 = checked	0.13 ± 0.34	0.09 ± 0.29	0.11 ± 0.32	0.2792

Table 2: The features in their chronological order. On the far-right shows, coefficients for each feature, along their positive or negative association on adherence.

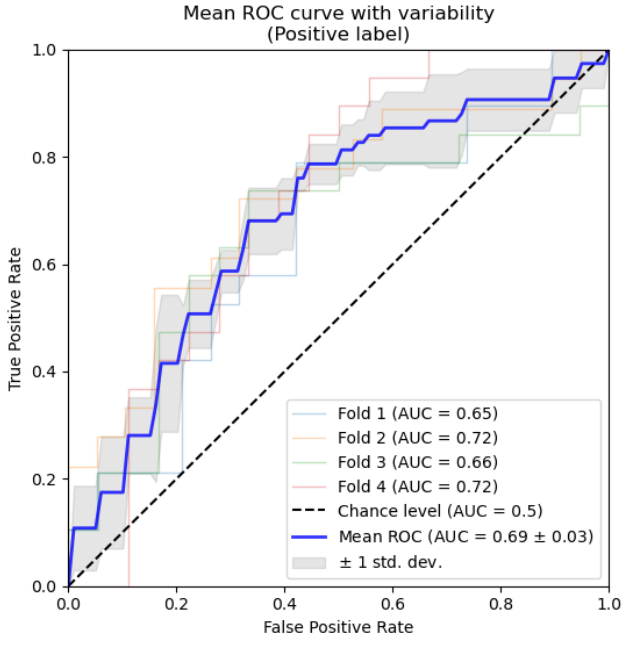

Figure 3: Plot of LGR model, displaying mean ROC AUC for the nine selected features, including the fourfold CV and standard deviation.

Target Sensitivity (%)	Sensitivity (mean, %)	Specificity (mean, %)	Accuracy (mean, %)	Positive Predictive Value (mean, %)	Negative Predictive Value (mean, %)	Threshold (mean, %)
60	49.34	73.17	61.08	65.69	58.77	61.25
70	65.35	60.82	63.10	62.78	63.53	52.10
80	73.25	49.93	61.75	59.92	64.82	41.46
90	85.38	32.09	59.05	56.44	66.43	32.89
95	94.66	10.60	52.99	51.87	51.25	19.16

Table 3: Mean of the four-fold CV model performance at sensitivity levels of 60, 70, 80, 90 and 95%.

Discussion

This study demonstrates the feasibility of predicting adherence using a LGR ML model. Nine features were selected for model use, yielded a mean ROC AUC of 0.69 ± 0.03, for classification of adherence. Based on literature research, three of the nine features were used as features in other ML studies: HbA1c (14,25), type of insulin (27), and use of hypertension drugs and lipid-lowering agents (29).

The study assessed different sensitivity levels (60-95%) to find the optimal threshold for clinical use. However, there's a trade-off of choosing a higher sensitivity for identifying adherent patients to reduce unnecessary interventions thereby reducing healthcare costs. A sensitivity of 60% yielded an accuracy of 63.10%, and a positive predictive value at 62.78%, resulting in approximately 40% of the true positives being classified falsely. Considering available resources and time management, choosing the highest accuracy as evaluation point, was to maximize the total amount of correctly classified patients. Increasing the sensitivity level comes at the expense of increasing the total false positives (table 3), and thereby not, enabling health professionals to focus their attention on patients who require extra care (38). This highlights the importance of considering cost implications when choosing a threshold. The study provides a foundation for selecting the most suitable level based on the specific clinical application and cost minimization goals. Thus, the sensitivity or threshold selection involves an organizational choice between the cost of not identifying an adherent patient versus the cost of wrongly identifying a patient as non-adherent. To gain a better understanding of each feature selected for the model, coefficients were calculated (table 2). HbA1c has a negative coefficient, which suggests that a lower HbA1c value corresponds to greater odds of being adherent. Consistent with other findings, studies have shown a high HbA1c value indicated an elevated risk of being non-adherent (10,39,40). GLP-1 RA therapy has been associated with increased adherence (41,42). Although the feature selection associated GLP1, Corticosteroids, and glargine insulin (U300) with decreased risk of adherence. Non-adherent patients have been associated with having fewer comorbidities, higher HbA1c, blood pressure, all-cause hospitalization risk and mortality rate, compared to the adherent group (43).

An ambiguity emerged where the patient's T2D was affecting their relationship with friends and family positively, associated with a decreased risk of being adherent while a positive association between job or studies and T2D also correlates with adherence. This could be attributed to the scoring of these questions (see table 2) where a maximum score is awarded for “not relevant”, potentially impacting the results. To avoid this, converting these questions as nominal would account for this.

Hypoglycemic events and high insulin intake increased the risk of being non-adherent (44). Unexpectedly, our findings suggest that smoking increased the chance of being adherent, with 17 smokers divided between the adherent and non-adherent group. It was expected that smoking would be associated with non-adherence prior to training the ML model. Given that T2D, and smoking is generally linked to poorer health outcomes and an increased prevalence of lifestyle diseases (45). Studies have associated smoking and T2D with increased risk of low adherence to insulin dosing and managing their condition (46,47). Smoking also increases the risk of developing T2D with 30%–40% (45–47).

Performance bias may have occurred in adherence measurements due to “white coat adherence” (15). This phenomenon is described as the extend in which a patient improves their adherence to treatment around clinic visits giving a false adherence measurement (7,48). This may have influenced the patients being aware of the intervention they receive doing telemonitoring, making them act differently from what they would do before initiating the trial (49), and therefore predicting features to adherence contradicting to known literature and evidence to the fields of example smoking and comorbidities. To validate the

results found, future research should be tested in a clinical setting to determine the relevance for predicting of adherence.

Limitations

Some factors that may limit the generalizability were detected in this study. The dataset used in this study was collected on Danish patients with a different objective, hence the reason for the inability to change data, to questions better suited for classification of adherence to basal insulin, like reasons for missed doses, double doses etc. Despite using precise insulin data from the smart pen, errors, and misunderstandings in dose administration done by the patients, and delays in registered prescribed doses compromised the study's validity of calculating adherence.

These inaccuracies introduced bias, reduced reliability, and may have led to potential misinterpretation of adherence levels, limiting the findings' generalizability and clinical applicability. To address these issues, more detailed training and instructions could have been provided to the participants and using real-time checkups. Additionally, adherence calculations could be adjusted to account for the deviations with the implementation of a tolerance, affecting the overall adherence. Due to a larger variability in the four folds of the CV, a larger sample size would have been desirable. This could potentially strengthen the reliability and generalization of the results for this study. This could also have enhanced the ML model and lowered potential overfitting.

Despite limitations, this study provides useful data in potentially helping enlighten the need for examination of features associated with adherence in patients with T2D and how to apply this knowledge in a clinical setting.

Conclusion

Using the data presented in the DiaMonT trial, it was possible to develop a prediction model, showing a moderate level of performance in evaluation. The nine features selected for adherence prediction were as follow: HbA1c, antidiabetic medicine GLP-1, corticosteroids, glargine U300, how diabetes effected relationship with family, friends, and peers, how diabetes effected work or studies, experienced hypoglycaemia, total daily insulin intake, and being actively smoking. The model may have potential to enhance patient care, helping clinicians identify adherence, and thereby treat individuals more accurately, tailoring care specifically to those who need it most while recognizing those who may not require extra attention.

The results of the model evaluation indicate that the chosen threshold for use in a clinical application moving forward will depend on the relative importance of sensitivity and specificity in the specific clinical application.

Conflicts of interest

The authors do not have any conflicts of interest to declare.

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Reference

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Worksheets

These supplementary worksheets are designed to align with the current semester's learning objectives, addressing points not covered by the scientific paper alone. They offer detailed descriptions of processes and exercises completed, to enhance the understanding of the presented material. Additionally, they include results that were not included in the scientific paper.

Worksheet 1: Background information for the scientific problem within the framework of research

T2D is a chronic condition caused by a partially or completely cease in the production and absorption of insulin. The condition is characterized by high blood sugar, resulting in several frequent symptoms which include increased thirst, frequent urination, fatigue as well as frequent infections (1). The cause of T2D has frequently been linked to overweight/obesity, increasing age, ethnicity, genetics, and environmental triggers (2).

T2D is a progressive disease with several late complications and comorbidities. Comorbidities include microvascular complications, like chronic kidney disease, diabetic retinopathy, neuropathy, and macrovascular complications, like heart failure and atherosclerotic cardiovascular diseases (3,4). Macrovascular complications are the leading cause of morbidity and mortality for patients with T2D (5). Most often people aged >45 develop T2D, with a higher prevalence for people aged ≥65 (6), but the rising prevalence of obesity has resulted an increase in children, adolescents, and young adults developing T2D as well (2,7). Because T2D is a progressive disease, age and diabetes duration positively associates with macrovascular and microvascular complications (8,9). Therefore, it is important to reduce the development of late complications and comorbidities, to prevent a higher morbidity and mortality rate.

Moreover, it is essential for patients with T2D to maintain optimal glycaemic control. This can be done through behavioral modifications, like weight loss or medication (10,11). The initial therapy for T2D is monotherapy with Metformin in combination with lifestyle changes. Usually, the maintaining of glycaemic control with monotherapy is often only possible for a couple of years, resulting in the need for combination therapy (4). When glycaemic control is not achieved through alternative interventions and treatment options, insulin is highlighted as the most effective treatment (1). Insulin has been established as an effective approach for maintaining glycaemic control, especially for patients having T2D for a longer duration of time to reduce late complications and comorbidities (4).

Consequences for patients not meeting treatment goals

Unfortunately, failure to meet glycaemic control for patients treated with basal insulin therapy has been demonstrated to 50-73% (12) while non-adherence to insulin therapy may vary worldwide from France (19.9%), China (33.5%), USA (42.0%) to Finland (44.3%) (13,14). Furthermore, Karter, et al. (15) found that 4% of all patients who just started on antihyperglycemic therapy never dispensed their prescription and 16% never refilled. Approximately 50% of patients with T2D were found to be non-adherent (16,17). Similarities can be found in other studies (18,19), where almost 50% of the patients were non-adherent to their T2D treatment regimens.

A study by Fujihara & Sone (20) found five categories in which ML can be used to treat patients with diabetes; Early retinopathy, continuous glucose monitoring, self-management tool for patients, risk stratification, decision making support tool for clinician. Six categories of factors impacting the level of adherence were found by (21) be summarized as; Demographics, attitudes and beliefs, diabetes management, impact on daily life, disease and medication, and healthcare.

Worksheet 2: Conduction and documentation of the systematic literature review

In the initial phase, unstructured literature searches were carried out in the databases PubMed, Google Scholar, Embase, and Scopus to identify knowledge gaps and formulate the scope of the study. The employment of these databases was justified by their recognition within the health science research area as well as their extensive coverage of health literature.

The structured literature search was conducted in PubMed, as it is one of the largest bibliographic databases managed by the National library of Medicine with over 35 million references to biomedical literature (22). The PubMed search compared to the further chain search was considered adequate in answering the questions regarding the choice of method.

Subject: identification of relevant predictors and applicable ML models to predict adherence in relation to patients with T2D who require insulin therapy.

Focused question: which features are suitable for the predicting of adherence of patients with T2D who require insulin therapy through telemonitoring.

Structured literature search

To concretize the method used in the study based on the existing literature, a structured literature search based on the PICO-framework (population, intervention, comparison, and outcome) was applied. The PICO-framework is a search strategy tool for developing search strategies, and help ensuring relevant components are well defined in the review question and enable a literature search (23). In this study, an experiential PICo was applied with the objective of analyzing human experience (adherence to medicine) and therefore replacing intervention and comparison with the phenomena of interest (24). The search used can be seen in the block table (table 1).

Block 1 P - Population		Block 2 I - Interest		Block 3 Co - Context
Diabetes Mellitus, type 2 [MeSH] OR Diabetes Mellitus type 2 [Text Word] OR Type 2 diabetes [Text Word] OR Diabetes type 2 [Text Word]	AND	Treatment Adherence and Compliance [MeSH] OR Treatment Adherence and Compliance [Text Word] OR Adhere* [Text Word] OR Nonadhere* [Text Word] OR Complian* [Text Word] OR Noncomplian* [Text Word]	AND	Algorithms [MeSH] OR Algorithm* [Text Word] OR Machine learning* [Text Word] OR Predicting [Text Word] OR Predictions [Text Word]

Table 1: Block table.

Population (block 1), Phenomena of interest (block 2) and context (block 3)

The population target for the study is specified to individuals diagnosed with T2D. A combination of Medical Subjects Headings (MeSH) and text word terms was used.

The objective of the study was to predict adherence, therefore MeSH terms and text word terms to cover that specific research field was used.

The MeSH term *"Algorithm"* covers terms like artificial intelligence and ML whereas the text word terms was used as a supplement to cover articles mentioning the chosen terms in case the articles haven't yet registered MeSH terms.

In the table below (table 2) the number of hits on each block is represented. The bottom represents the total number of articles from the search string with all blocks combined.

Block search	Number of hits
Block 1	241,586
Block 2	655,433
Block 3	1,092,958
Total	**298**

Table 2: Block search and number of hits.

The structured literature research in PubMed was carried out on the 14th of March 2024, following the inclusion- and exclusion criteria (see table 3).

Inclusion	Justification for inclusion
Years 2008 - 2024	Based on the technological development, the latest relevant literature within machine learning and coding is desired.
Language: English, Danish, Swedish, or Norwegian	Based on the lingual abilities of the group in being able to read and understand the articles.
Diabetes type 1 and 2	Although the target group of the study was patients with type 2 diabetes, patients with type 1 were included because it was assessed that the study methods in prediction made on type 1 patients was comparable to patients with type 2 diabetes. Therefore, articles with both type 1 and 2 diabetes would be included in the study's structured search.
Machine learning	Another inclusion criteria were that machine learning methods had to be used in the articles as a prediction tool.
Reviews	Reviews summarizing machine learning methods used by articles were be included.
Exclusion	**Justification for exclusion**
Deep Learning	A branch of machine learning, but because of its complexity and high level of abstraction it was excluded.
Articles without explicit formulation of their methods	Articles with failure to explain or describe their used method or results were excluded.
Gestational diabetes	Not relevant as it is only during their pregnancy period.
People < 18 years	Because children have a parent or guardian to manage their medical treatment, the population isn´t comparable with patients >18 years old.
Health professionals' adherence	This study is aimed at patients and their risks of being non-adherent.

Table 3: Criteria for inclusion or exclusion.

Search results and PRISMA

The systematic approach guided by the PICo framework (23), yielded an initial volume of 297 potential articles. The screening tool Rayyan made for undertaking literature and systematic reviews, was used to screen articles blinded for the researchers. All 297 articles were screened by title and abstracts by all members of the group. Conflicts within the group after the blinding process of included and excluded articles were discussed until agreement was reached. This process resulted in a collection of 21 articles for reading through full text where subsequently five articles were excluded due to exclusion criteria. After critical review, 16 articles were included which had scientific relevance for the project. The table below (see figure 1) represents the systematic search and different phases of the review through a PRISMA.

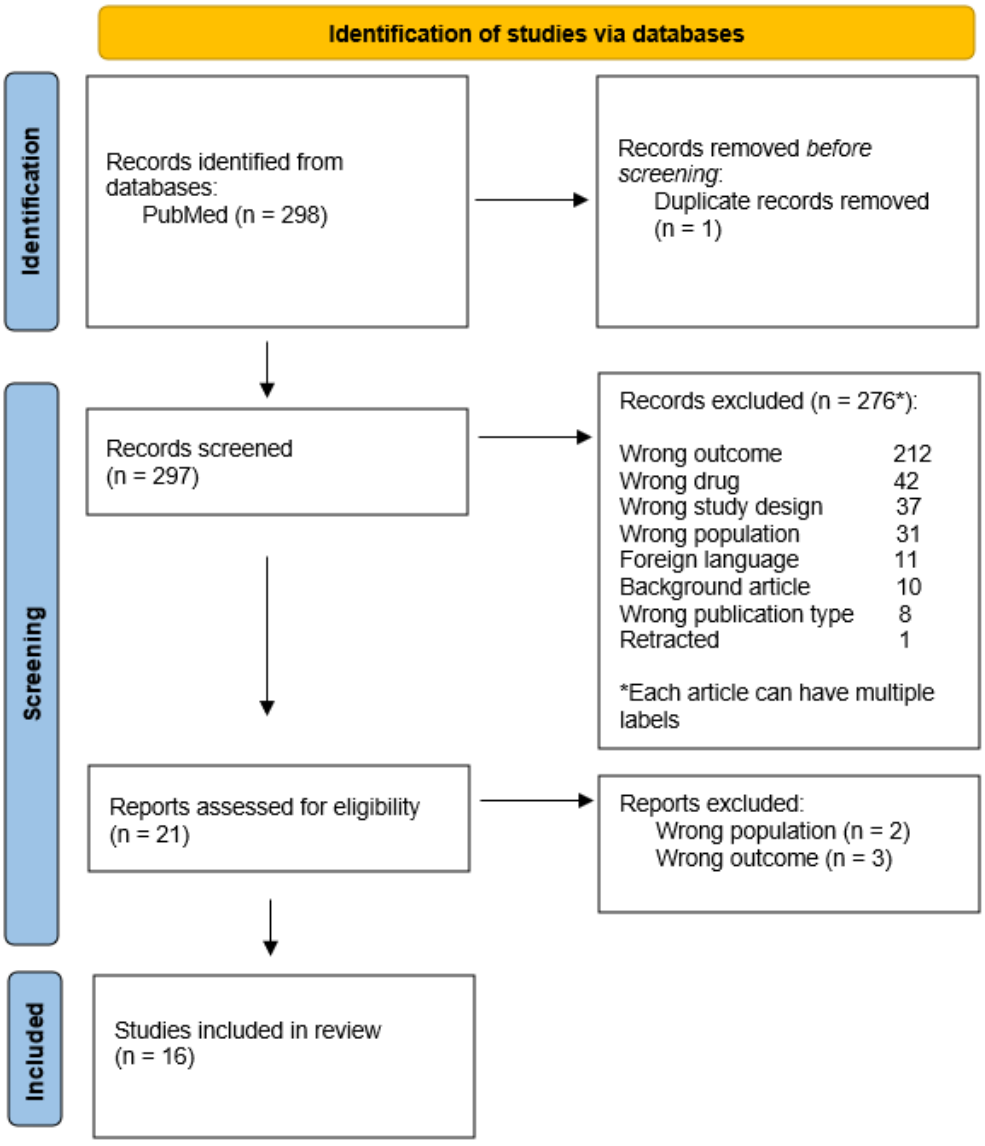


Figure 1: Prisma flowchart.

Worksheet 3: Adherence

Adherence is a term which can be defined in multiple ways (16,25–27). WHO defines adherence in a report based on a critical review as:

> "*The extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.*"((16) p18).

For patients to be adherent, they need to be able to follow and agree with the treatment and the sharing of responsibility between themselves and the health professionals (25). This allows the patient to perform self-care as best as possible and actively carry out self-management, defined as the patient's ability to manage symptoms, treatment, physical and psychosocial consequences, and changes in living with diabetes (25).

It is well reported how diabetes affects the quality of life for patients and their families (26–28). The disease requires lifestyle and behavioral changes that affect large parts of the patients' daily lives and places great demands on their family to adapt to the disease to maintain adherence of the patient (26,27).

Alfian, et al. (26) identified a significant relationship between adherence and diabetes specific Quality of life ($p = 0.009$), where higher adherence contributed to improved Quality of life. The study reported that their results were consistent with several previous studies, suggesting a positive relationship between adherence and Quality of life in patients with diabetes (26).

Skriver, et al. (21) provided in a scoping review an overview of the factors associated with adherence or non-adherence to insulin therapy in patients with T2D. They found that age, healthcare costs, personal beliefs about insulin therapy, social stigma, patient education, the complexity of diabetes treatment, the impact of insulin therapy on daily life, and fear of side effects, were the most prominent factors out of 30 identified, which could be sorted under six themes: Demographics, attitudes and beliefs, diabetes management, impact on daily life, disease and medication, and health.

Cramer (29) highlighted in his systematic review factors such as age, complexity of treatment, duration of illness, depression, and psychosocial problems were identified as contributing to optimal disease management and, by extension, adherence. Insulin adherence in patients with T2D was reported to be 62-64%. It showed adherence to insulin regimens vary across different age groups, with especially younger individuals facing challenges in following their prescribed insulin therapy, leading to more hospitalizations due to diabetes-related complications (29).

Quantification of Adherence

WHO reported that approximately 50% of patients with chronic diseases, such as T2D are non-adherent (16). Nørlev et al. (17) found in their study with 103 participants that 52 (50.5%) were adherent based on an 80% threshold according on Sokol et al. (30). The remaining 51 (49.5%) were considered non-adherent (17).

Skriver et al. (21) addressed the need to determine threshold values for factors found to be associated with adherence, as the lack of quantification challenges the use of these factors in a clinical context as well as the weight of the individual factors and their relationship to adherence.

WHO (16) did not define in its report a specific framework or definition of high or non-adherence but emphasized the importance of developing a so-called golden standard. This is an aspect also highlighted by Osterberg & Blaschke (31), who highlighted the lack of ability of health professionals to track and identify non-adherence. Nørlev et al. (17) aimed to provide a three-step data-driven methodology for assessing different aspects of basal insulin adherence, to provide the right support for the patient.

Nørlev et al. (17) stated that they used an adherence level of ≥80%, based on the results of Sokol et al. (30) had in a retrospective cohort observational study stratified a population of 137,277 patients <65 years into five categories based on their adherence score: 1-19%, 20-39%, 40-59%, 60-79%, or 80-100%. They showed that adherence levels of ≥80% were associated with a lower risk of hospitalization and a lower cost of care for patients with diabetes. This has become a widely recognized tool as a standard for quantification of adherence thresholds.

Defining and calculating of Adherence (y)

In this study, we intend to calculate adherence based on the same method as Nørlev et al. (17). In this context, patients who take ≥80% of their prescribed doses are considered adherent and <80% are considered non-adherent (17). It uses a modified Medication Possession Ratio (MPR) to measure the percentage of adherence. The MPR is defined as the percentage of the number of correctly administered doses, divided by the total number of prescribed doses of the period. This is measured by comparing the basal doses prescribed by trial personnel, with the basal insulin doses recorded by the patient via the connected insulin smart pen for each day.

For example, if a patient is prescribed 20 units of insulin for the day and takes 20 units, their adherence for that day is 1 (100%). If they take 21 units, their adherence would be 0 because exceeding the prescribed dosage is considered not adhering to their insulin therapy.

The calculation looks as follows (figure 2):

$$Adherence = \left(\frac{Number\ of\ correctly\ administered\ doses}{Total\ number\ of\ prescribed\ doses\ in\ that\ given\ period} \right) * 100\%$$

Figure 2: Calculation of adherence.

Critical view of the adherence threshold of 80%

The authors acknowledge the inherent limitations associated with the chosen methodology. While an 80% threshold was used within this study, to identify adherence among patients with T2D, following the protocol based on Sokol et al. (30), the authors recognized the value of incorporating research that critically examines and challenges the validity of this specific cut-off point.

Lim et al. (32) found, based on statistical analysis and LGR, that the optimal adherence cut-off values for patients with T2D ranged from 86.1% to 98.3% for HbA1c ≤7.0%, and 86.1% to 92.8% for HbA1c ≤8.0%. These findings suggest that a stricter adherence criterion may be necessary for better clinical outcomes. These findings are in line with the results of Karve et al. (33) where adherence thresholds >80% was associated with a reduction of hospitalization risk. Similarly, Lo-Ciganic et al. (34) utilizing ML, identified adherence thresholds predictive of hospitalization risk, ranging from 46% to 94% depending on patient health and medication complexity. This variability underscores the complexity of adherence and its association with clinical outcomes, suggesting that a one-size-fits-all approach may not be suitable for all patient populations. Concluding that a uniform threshold of 80% adherence is not optimal for predicting adherence and the risk of hospitalization, and that the threshold may vary depending on the T2D patient group (32–34). Hence, it highlighted that a reasonably cut-off threshold to be clinically meaningful, in distinguish between adherence or non-adherence should be at 90% (32). Baumgartner et al. (35) tried in their systematic review to investigate adherence thresholds in relation to clinical outcomes highlighting studies using an 80% threshold without clinical rationale. Due to lack of quantitative comparability in studies, Baumgartner et al. (35) could neither reject nor confirm the validity of the 80% threshold and questioned it as a general standard. But does not provide a better alternative to be used.

Moving forward, it’s to be considered the implications of a stricter adherence criteria in improving and analyzing clinical outcomes by reevaluating the used adherence thresholds in the management of T2D. Incorporating a personalized adherence threshold based on the precise studied group by using advanced analytical techniques may enhance our understanding of adherence and its impact on clinical outcomes among patients with chronic conditions like T2D.

Worksheet 4: Data source and identifying existing research related to adherence

The data used in the study was data collected from the DiaMonT study (36). The study was an open label, randomized controlled trial aimed at exploring the effect of telemonitoring in patients with T2D using insulin.

DiaMonT had a trial-period of 3 months. The intervention group was patients with T2D on insulin therapy, who were monitored via telemonitoring. The intervention group was contacted by phone at least three times during the trial period - 1 week, 1 month and 2 months after admission to the trial.

The monitoring laboratory technicians/nurses discussed the data with each participant and gave them treatment advice or changed the prescribed insulin doses, if deemed necessary, based on their data. The group was compared with a control group of patients with T2D, who received regular care. The study included 331 participants divided 1:1 between the two groups. During the trial period, participants used NovoPen 6 (Novo Nordisk A/S) and were treated with long-acting and fast-acting insulin, compatible with NovoPen 6. Data recorded from the smart pen displayed the exact unit injected by the patient, the time since last injection as well as the type of insulin injected. Prescribed doses of insulin given to each patient were recorded manually by the nurses giving the prescription along with date and time of prescription.

Apart from insulin data, various baseline data was collected to cover the patient holistically. Baseline information about the participants was collected at the start of the trial. Included in baseline data was a venous blood sample which was taken to identify secondary endpoints for the DiaMonT study. This information included, among others HbA1c taken during the first week of inclusion and at the end of the trial. In this study, only the early HbA1c was included, according to the aim of prediction of adherence in patient with T2D initiating telemedicine.

A comprehensive questionnaire was provided at the start and end of the inclusion period. The questionnaire was divided into the following categories (table 4):

Questionnaire categories
Demography
Health status (SF12)
Diabetes related life quality (DIDP)
Hypoglycaemia (Clarke hypoglycaemia awareness survey)
The use of telemedicine (TOC)
Self-efficacy and health (SEH)
Equipment
Completed

Table 4: Display of each category in the questionnaire.

From these categories, TOC, Equipment, and Completed were deemed unrelated to this study's aim, and based on this, these questions were not included for the feature selection. The Hypoglycemia category was a drop-down menu only asked to patient having had a hypoglycemic event in the past year, resulting in 40 patients omitting this category of question. Due to < 25% of patients not answering this category, it was decided to exclude Hypoglycemic events, as features.

Additional data collected in the DiaMonT data and excluded in this study were activity from a (FitBit) device, which recorded heart rate and steps for the entire inclusion period, and data from continuous glucose monitor.

Comparing DiaMont features with a literature review

Being able to predict adherence in patients with T2D is a crucial aspect of identifying the need for intervention, what to look for from a clinical perspective, to be able to optimize the management of T2D and to improve health outcomes.

This study has explored eight other studies (21,37–43), who identified factors associated with adherence in patients with T2D, by utilizing systematic literature review or ML models in developing predictive algorithms (appendix 1). In our comprehensive review of eight studies, 34 unique top features were identified, with some features consistently appearing across multiple studies. The most appearing features were as followed (table 5):

Feature	Mentioned	References
Age	4	Li et al. (37); Wu et al. (38); Cramer & Pugh (39); Skriver et al. (21)
Cost of medications/ therapy/ healthcare	3	Wu et al. (38); Fan et al. (40); Skriver et al. (21)
Duration of T2D	3	Fan et al. (40); QiMuge et al. (41); Martinez et al. (42)
Gender	3	Wu et al. (38); QiMuge et al. (41); Martinez et al. (42)
Education	3	QiMuge et al. (41); Skriver et al. (21); Martinez et al. (42)
Present Fasting Blood Glycose values	3	Li et al. (37); Wu et al. (38); Martinez et al. (42)
BMI	2	Li et al. (37); Wu et al. (38)
Present HbA1c values	2	Li et al. (37); Cramer & Pugh (39)
Intensity/ Complexity of diabetes management	2	Cramer & Pugh (39); Skriver et al. (21)

Table 5: Number of times each top feature has been utilized in other studies.

By synthesizing findings from multiple studies, valuable insights were gained into the vastness of prediction of adherence and its complexity. Eight studies found 34 unique top features.
Incorporating these features into the predictive model and ensuring their inclusion in the data has the potential to improve the validity of the output. However, it is important to note that these features may not inherently serve as strong predictors within this study's data collection.

Of the 34 unique top features identified through the literature review, it was interesting to investigate which of these features also existed within the data collected from the Diamond study (table 6).

Common features found in the DiaMont study	Reference
Age	Li et al. (37); Wu et al. (38); Cramer & Pugh (39); Skriver et al. (21)
Duration of T2D	Fan et al. (40); QiMuge et al. (41); Martinez et al. (42)
Education	QiMuge et al. (41); Skriver et al. (21); Martinez et al. (42)
Body Mass Index (BMI)	Li et al. (37); Wu et al. (38)
HbA1c (Present Values)	Li et al. (37); Cramer & Pugh (39)
Types of Insulin	Fan et al. (40)
Use of Medications	Chen et al. (43) (Hypertension & Lipid-Lowering)
Insulin Treatment	Cramer & Pugh (39)
Marital Status	Martinez et al. (42)

Table 6: Features found in both DiaMonT and the literature review studies.

The nine features listed above were included in the DiaMonT trial (36). Sharing features indicate that data collected in the DiaMonT trial has relevance for feature selection. The common top features increased the possibility of finding similar traits in this study. The total number of features included in this study was 85. With this number of features, there was a potential to find other features that could previously have been overlooked. By including both common and relative unused features, it was possible to investigate whether other features could be of relevance for prediction of adherence.

Worksheet 5: Preprocessing of data

The preprocessing of data was carried out in Jupyter Notebook (ver. 6.5.4) and Python (ver. 3.11.5).

To identify the target value (y), calculating adherence for each patient during the study period was necessary. Data from the following *sas7bat* files were collected and converted into more easily manipulable formats: *prescribed (adapt_ano_prescribed_insulin_a), insulin (adapt_ano_insulin),* and *stamdata (adapt_ano_redcap_stamdata).* A table of all datafiles, with descriptions can be seen in table 7.

File name	Colums	Number of measurements	File types	Description
Adapt_ano_fitbit_skridt_f.sas7bdat	Id_patient MaalingTidFraInkl AntalSkridt	787214 787214 787214	float64 object float64	Includes data for number of steps each patient took during the inclusion period. This data was collected from Falster.
adaot_ano_insulin.sas7bdat	Id_patient MaalingTidFraInkl InsulinVaerdi DataEnhed InsulinType	80544 80544 80544 80544 80544	float64 object float64 object object	Includes how much insulin each patient has taken during the inclusion period and what type of insulin was injected.
adaot_ano_insulin_f.sas7bdat	Id_patient MaalingTidFraInkl InsulinVaerdi DataEnhed InsulinType	5710 5710 5710 5710 5439	float64 object float64 object object	Includes how much insulin each patient has taken during the inclusion period and what type of insulin was injected. This data was collected from Falster.
adapt_ano_labka_a.sas7bdat	Id_patient MaalingTidFraInkl NPUKode Analysenavn Analysekode ResultatForholdstegn InterntResultatTekst InterntResultatNumerisk ResultatTekst ResultatEnhed	594 594 594 594 594 594 594 594 594 594	float64 object object object object object object float64 object object	Includes various blood samples, text name, first letter in each name, analysis code, numeric values, and results units.
adapt_ano_prescribed_insulin_a.sas7bdat	Id_patient AnbefalingTidFraInkl InsulinVaerdi InsulinType	1002 1002 1002 1002	float64 object float64 object	Includes prescribed insulin value, time of prescription and the type of insulin.
adapt_ano_redcap_spg_afs.sas7bdat	Id_patient Spoergeskema Spoergsmaal SvarKode SvarTekst	12382 12382 12382 9790 9790	float64 object object float64 object	Includes questionnaire category, questions, answer code and text.
adapt_ano_redcap_spg_afs_f.sas7bdat	Id_patient TidFraInkl Spoergeskema Spoergsmaal SvarKode SvarTekst	1218 1218 1218 1218 981 953	float64 object object object float64 object	Includes questionnaire category, time from inclusion, questions, answer code and text. This data was collected from Falster.
adapt_ano_redcap_spg_ink.sas7bdat	Id_patient Spoergeskema Spoergsmaal SvarKode SvarTekst Hojde_cm Vegt_kg BMI	22650 22650 22650 21319 19820 301 301 301	float64 object object float64 object float64 float64 float64	Includes questionnaire category, questions, height, weight, BMI, answer code and text.

adapt_ano_redcap_st amdata.sas7bdat	Id_patient AlderInklusionInterval RandomiseringGruppeKode RandomiseringGruppeTekst AfslutningMaadeKode AfslutningMaadeTekst	302 302 302 302 302 302	float64 object float64 object float64 object	Includes age intervals, randomized group tag as code and text, and how the patient finished the trial.
adapt_ano_redcap_st amdat_f.sas7bdat	Id_patient AlderInklusionInterval RandomiseringGruppeKode RandomiseringGruppeTekst AfslutningMaadeKode AfslutningMaadeTekst	29 29 29 29 29 29	float64 object float64 object float64 object	Includes age intervals, randomized group tag as code and text, and how the patient finished the trial. This data was collected from Falster.

Table 7: Description of each datafile, columns and data type.

By visual inspection of the data, it became clear that some patients used two-unit air shot after replacing the insulin cartridge in their smart pen. Some patients took this test before every insulin injection. To account for potential systematic error and minimize consistency bias introduced by low-dose insulin measurements ≤2 units were excluded in the insulin data analysis. This decision was to ensure the accuracy of measured insulin doses, as there is a 0 margin for error in every insulin dose per day. Even small deviations from prescribed doses (e.g., taking 46 units instead of 45 units as prescribed) would be considered non-adherent in the context of this study's calculation of adherence. The case of the study only explores adherence to long-acting insulin. Therefore, all bolus-insulin administered doses were removed.

Calculation of adherence for all long-acting administered doses was division of total number of prescribed doses taken correctly and number of days included in the trial, resulting in an adherence percentage for the whole study period (for further explanation see worksheet: adherence).

For easy calculation, all time-interval was recalculated to a 24-hour-day format, and the combined insulin was summed up for each day, making it possible to calculate actual insulin dose taken for each patient, as some doses were split between two or more injections, for example when switching cartridge or the insulin dose was too high to be administer in one dose (≥61 units). Using a standard index of 24 hours going from 00:00-00:00 for each day was problematic, as some patients took multiple units around midnight. To calculate a better time index, a histogram showing insulin dose frequencies was created (figure 3). By investigating the histogram, it was possible to determine the best time index for a day. The histogram showed that between 03.00 and 04.00 hours in the morning the lowest number of injections was made. Therefore, three hours were subtracted from each day to ensure that each day ranged from 03.00-03.00.

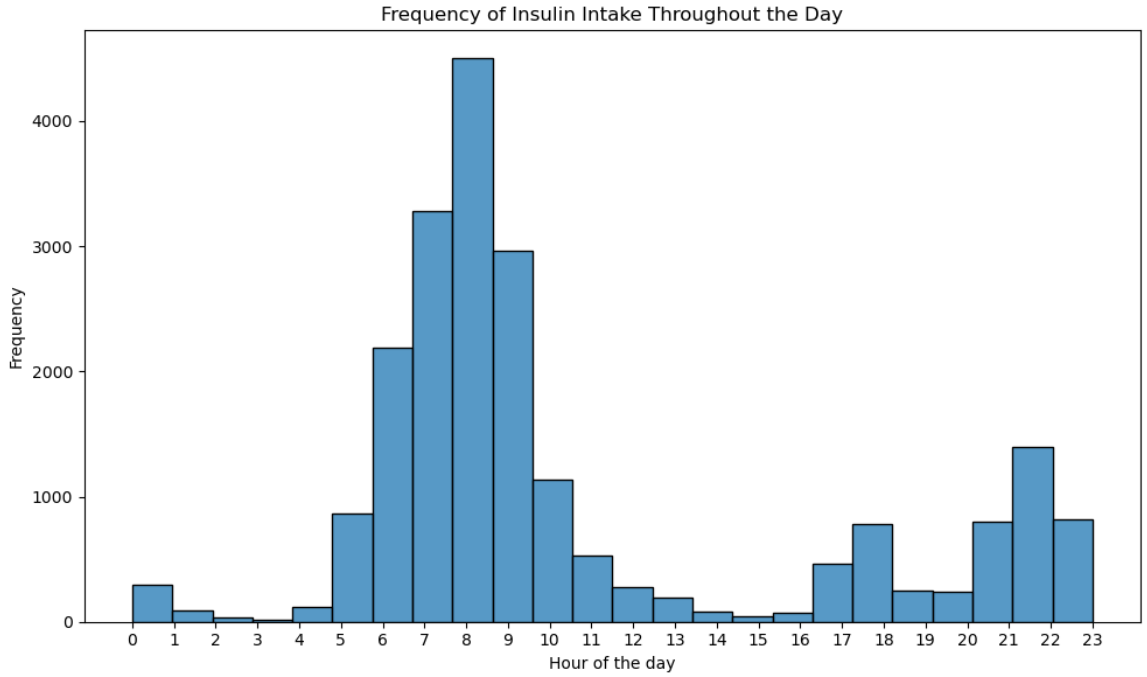


Figure 3: Histogram displaying when each patient takes their insulin doses.

To calculate adherence, the insulin and prescribed insulin data frame were merged, using a left join, and sorted by id_Patient and Day, on the insulin data. Doing this, ensured that the prescribed data that matches *id_Patient* and *Day* was added to those rows with matching insulin data. In prescribed insulin, the collum called *AnbefalingTidFraInkl* which included the time of day when a patient got a new prescribed insulin dose. When this collum had a value, it indicated that the patient had received a new prescribed value. Each new prescribed value was added to the columns and compared with the actual value of insulin, each patient took. To handle missing values in *AnbefalingTidFraInkl,* the function *fillna* was used to fill *NaN* with the previous value, as the prescribed value only changes when the *AnbefalingTidFraInkl* changes which indicates a change in the prescribed insulin dose for that patient. The *stamdata* data frame was merged to remove all patients which was not in the intervention group by using their ID provided in the datasets. The removal of the control group was due to lack of comparability to the intervention group.

Because this study focuses on prediction of early adherence, only the first three weeks (day 0-21) of the trial were included. To do so, a reindexing of groups function was used on each *id_patient*. The function uses an *if* statement to check if *Day* = 0, if not, the function added a new row, with *Day* = 0 and the rest of the row got *NaN* values. Then the reindexes of the group were set to start from *Day* 0. To fix *NaN* in *id_Patient* a check was made on each *NaN* value if the values before and after a *NaN* were the same the *NaN, it* was replaced by that value. If different, the code looked for the next *NaN* value. Some places had multiple *NaN* rows, therefore a *Fillna* with limit=33 ensured even 33 *NaN* in a row would be filled.

Missing values were handled in the insulin and prescribed dataset. The insulin dataset had missing days when patients did not register any insulin dose. To calculate the adherence, *NaN* rows were added on missing days. To get the prescribed data value for the added missing days, the original rows were merged back with the table. The data was copied in and unnecessary rows removed (*AnbefalingTidFraInkl_x, InsulinVaerdi_y, InsulinType_x, InsulinType_y*). To avoid missing data due to a small sample size, special considerations for unique patient ID's were made where a prescribed dose was given before trial start. In one case, the prescribed data was given on day –31, therefore the prescribed data value was manually set in the code for day 0.

To calculate if a patient had taken the correct amount of insulin each day, a new empty collum was created called *difference_pr_day (table 8*), each row in the collum contained a value of subtracting insulin and prescribed insulin dose for each day. Each day with a *zero-difference* indicated 100% adherence, all other days, the patients got registered as non-adherent.

	Day	id_Patient	InsulinVaerdi_x	AnbefalingTidFraInkl_y	InsulinVaerdi	difference_pr_day
0	0	100991.0	45.0	0.000e+00	45.0	0.0
1	1	100991.0	45.0	NaN	45.0	0.0
2	2	100991.0	45.0	NaN	45.0	0.0
3	3	100991.0	0.0	2.592e+05	42.0	-42.0
4	4	100991.0	42.0	NaN	42.0	0.0
5	5	100991.0	42.0	NaN	42.0	0.0
6	6	100991.0	42.0	NaN	42.0	0.0
7	7	100991.0	32.0	6.048e+05	40.0	-8.0
8	8	100991.0	40.0	NaN	40.0	0.0

Table 8: Displaying adherence score for each day.

The target value is presented as *zero_ratio_percentage* (adherence percentage) (Table 9) and is the total adherence for the study period for each id_Patient.

	id_Patient	zero_ratio_percentage
0	100991.0	77.272727
1	106179.0	77.272727
2	108165.0	27.272727
3	109831.0	95.454545
4	122979.0	90.909091
...	...	...
146	476180.0	90.909091
147	477714.0	4.545455
148	483607.0	90.909091
149	496049.0	63.636364
150	498437.0	90.909091

151 rows × 2 columns

Table 9: Displaying adherence score for the study period.

In total, 75 patients were registered as adherent. A histogram displaying the distribution of adherence in percentage (0-100%) for the included patients in the dataset (figure 4).

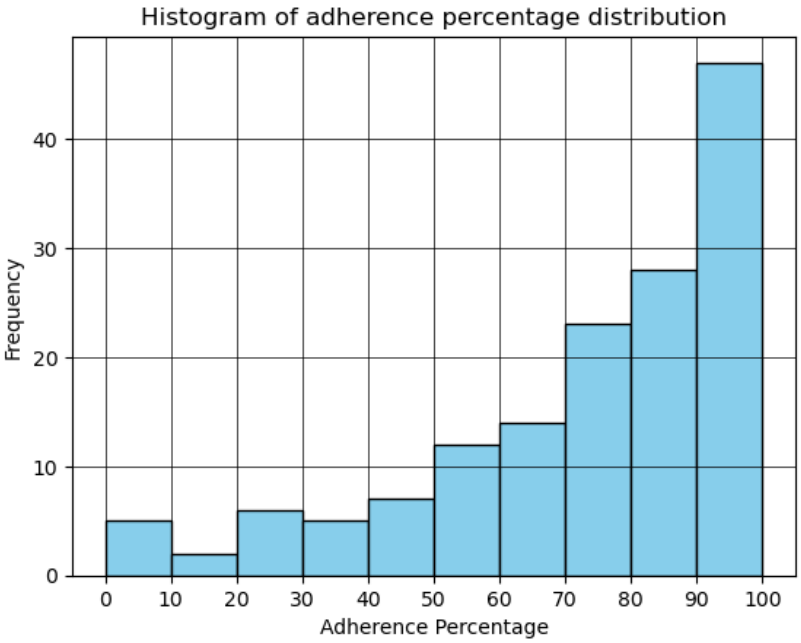


Figure 4: The distribution of percentage adherence for each patient.

The making of a data frame with input variables and the target value

In this section of the code, the aim was to create a data frame consisting of one row for each input feature to apply promising ML models on.

Data from the following *.sas7bat* files were collected and converted into more easily manipulable formats: *hba1c (adapt_ano_labka_a)*, *stamdata (adapt_ano_redcap_stamdata)* and *spg_ink (adapt_ano_redcap_spg_ink)*.

The *HbA1c* and *stamdata* dataframe were merged. Imported data from the *HbA1c* data frame was converted into days, hours, minutes, and seconds.

HbA1c for each patient was measured at the beginning and ending of the DiaMonT trial. Because this study only focuses on the first three weeks, only the first HbA1c measure was included. Due to anonymity, the age of each patient was split into groups in the following way: 20-29, 30-39... 70-79. This means when using the one hot encoding age groups changes to 1...5. Unnecessary columns were removed (NPUKode, Analysenavn, Analysekode, ResultatForholdstegn, InterntResultatTekst, InterntResultatNumerisk, ResultatEnhed, RandomiseringGruppeKode, AfslutningMaadeKode, MaalingTidFraInkl).

Spg_ink was imported, but the questions for each *id_Patient* had to be manually filtered out from the collum and stored in its own collum. To ensure the correct answer was selected, each corresponding answer code had to be added to the collum after mearing each question. The data frame was then merged with the *HbA1c* and *stamdata* data frame.

Missing values were handled in the merged data frame. By visual inspection of the data, two patient IDs ended the trial before time and had to be removed, resulting in 149 patient IDs.

7 questions were removed as features. These questions were from a drop-down category called *“Clarke hypoglycaemia awareness survey”* and where only given to 109/149 participants, therefore these features where not included as available features due to missing values.

Two additional features had an error in the way they were registered in the questionnaire, resulting in the answer code not being transformed, instead the answer text was added. To address this issue, a value code was added manually based on data from the DiaMonT study.

Feature engineering was applied with a decomposing of features from Ordinal and nominal columns because most ML methods assume attributes have an ordinal relationship OneHotEncoding was applied to the data frame.

Because ML algorithms do not perform well on input from numerical data containing different scales, feature scaling was applied on the data frame to standardize the features (44).

All tables with features x0 to x85 and the target value were merged to form a single table (table 10).

Patient ID	*Feature$_{x1}$*	*Feature$_{x2}$*	*Feature$_{x3}$*	.....	*Feature$_{x85}$*	*Feature$_{Y}$*
0						
1						
...						
148						

Table 10: A table displaying the data frame table with all the potential features.

Worksheet 6: Machine learning

ML enables computers to learn from data and make predictions without being programmed. ML can iteratively learn from data, to improve performance over time. Prediction algorithms based on ML can be used to estimate the probability of a patient experiencing a given health outcome. This includes the ability to predict the likelihood of developing a given disease, patient prognosis, or treatment response (45). The latter being the objective of this study regarding prediction of adherence to insulin therapy. There exist numerous different kinds of ML models, which can be divided into supervised, unsupervised, and semi-supervised (44). In this study, supervised ML is used. In supervised learning, the models are trained on labelled data, making it relevant for prediction of adherence in patients with T2D, as it involves making decisions based on known outcome in form of the patient either taking their prescribed insulin dose or not. ML allows for advanced analysis of complex datasets and identification of patterns that traditional methods might overlook, making it an advantage for prediction of adherence.

In a review by Ellahham (46), an overview is formed to which areas within diabetes where ML is thought to be strengthening treatment and patient's own management of their disease. Ellahham (46) presented ML as a paradigm shift in diabetes treatment with a higher focus on targeted data-driven precision care that contributes to efficiency as well as focusing on the individual. In this study, the data provided to the ML model includes demographics, baselines, various lifestyle variables, and self-reported data. This enables the model to make predictions to help personalize interventions and improve patient outcomes. The relevance for using ML in this study was to support health professionals quickly identifying patients being adherent to their T2D treatment. To better tailor intervention to the individual patient, bringing down healthcare costs.

Choosing a model

Selecting the right model for accurate prediction of adherence in patients with T2D is pivotal. Several models were debated, in which LGR and Random Forest RF were the most suited models for this study.

LGR is a statical model for classification tasks. It estimates the probability of outcome based on feature variables. This model assumes a linear relationship between the features and their outcome. The model is most suitable when the relationship between the features and adherence is close to linear (44). The simplicity and interpretability of the model was a highlight for choosing it as a starting point for entering the field of ML. However, it comes with disadvantages including that it might not capture complex nonlinear patterns, it can also be sensitive to outliers. Therefore, it was important to test a more powerful model, like RF before deciding on which model to use.

RF is an ensemble learning model with higher complexity. It works by creating multiple decisions trees during training. Each tree is trained on a random subset of the data which gives an independent prediction. The final prediction is made by accumulating the prediction from each tree. This model is more suitable if there are nonlinear relationships between features and adherence. This model is robust in handling outliers but can be prone to overfitting which makes it difficult to interpret compared to a simple model like LGR (44).

Test and training of the model

ROC AUC curve was chosen as the metric to assess the model's effectiveness prior to training. This would give a visual curve and number of interpretations for the model's accuracy. Another benefit was that it was possible to find an optimal threshold based on the output results. When training the model, it learns patterns and relationship from the data between features and the target value (adherence). Once training is completed the model is then used on the test set (held-out data) and for evaluation, the AUC ROC was used which furthermore could help investigate potential errors, underfitting or overfitting. After the first set of results, it is important to run the model with different settings to investigate what gives the most accurate and clinically relevant results (44).

Setting up machine learning model for Logistic regression

After calculating adherence percentage for each patient, data had to be prepared for ML models. To do this, the first step was to separate each feature in a list whether it was ordinal or nominal. By doing this, it was possible to use one hot encoding to make sure all data from each feature was encoded correctly regarding the specification of LGR.

pd.to_numeric: Made it possible to change features that were not in numeric form to numeric.

!pip install mlxtend" and "*sklearn*": Installed functions to initiate the LGR model from the module libraries. *SequentialFeatureSelector (SFS), LogisticRegression (LGR)* (47) and *train_test_split* was imported.

Stratify = y (adherence): Was used to ensure that the classes distribution remained equal in both training and test set.

*random_state: E*nsured reproducibility of the results if its value remained the same across all runs.

max_iter = 1000 is used to set the max number of iterations in the run equal to 1000.

*forward=True: T*he model starts with an empty set of features and adds features one by one; it evaluates the performance of the model with all possible additional features but only selecting the one that improves the model's performance the most.

floating = False: Restricting the model to only move forward in the feature selection.

Verbose = 2: Determines the number of details for each output during the feature selection process.

roc_auc: AUC was employed as a performance metric to facilitate the comparison of different models. The minimum AUC improvement threshold of 0.005 across cross-validation folds for the feature selection was determined. This criterion ensured that only features showing a measurable enhancement in the model's capacity to distinguish between classes were integrated into the final model.

*cv = 4: R*epresents a four-fold cross validation on data, meaning the dataset was divided into four equal parts and the model was trained and tested on each part iteratively. The benefit of using K-fold CV is the possibility of aggregating results across the different fold which helps reduce variability in the model performance compared to a test and train split (44). Once training was complete, different plots were used to examine and analyze the results.

Combining intervention and control group: Two tests included eligible patient IDs from both control and intervention groups (n = 266). The two groups were considered too different from each other when predicting the same outcome, hence the low AUC's (as seen in appendix 2). After this, only the intervention group was used for prediction.

A combination of different numbers of features were tested to determine the most optimal result for the model. With the best results agreed on, the chosen features were used in combination with *X_test, y_test* and *LGR* to give the optimal test result.

The LGR had varied results with AUC's ranging from 0.83 to 0.69 in training and 0.65 to 0.44 on the test set. LGR was the only model with performance within the 0.15 AUC limit set prior to training. Based on these arguments, LGR was chosen as classification model for prediction. Evaluation of the model was obtained from mean AUC of a four-fold CV on the whole dataset for consideration of varied results.

Testing models: Random Forest

Scikit learn *RandomForestClassifier* (48) was also tested as a classification model for prediction of adherence. Despite modifications to various parameters aimed at improving performance, the model ultimately did not meet the criteria for inclusion as a classification tool. The modifications of parameters were as follows:

Train_test_split: Determination of the sizes of the training and test population taken from the dataset. Test size values ranged from 0.25 to 0.40.

n_estimators (): Determining the number of decision trees utilized, and to avoid overfitting various values up to 25, 50 and 100 were tested.

max_depth (): Maximum depth of each tree refers to the levels of splits. The more splits the more complex patterns. However, deeper trees can be prone to overfitting, especially with a small dataset, 10, 5 and 2 were tested since the dataset was considered small. Train/test population was divided into a 75/25% split.

min_samples_split (): Minimum data points required to split a node. A higher *min_samples_split* can prevent overfitting by avoiding the creation of decision trees that are too specific to small subsets of the data. Values 5 and 10 were tested but did not lower the overfitting of the model as expected.

min_samples_leaf (): Minimum data points required to be at a leaf node in the decision tree. A leaf node is the terminal node that represents a specific prediction in classification (48).
5 and 2 were tested but did not lower the overfitting of the model as expected.

As seen in appendix 2, using *RandomForestClassifier* as a classification model on our dataset delivered mixed results with AUC scores, ranging from 0.91 to 0.86 in training and 0.60 to 0.52 in the test set. A larger difference between test and training than 0.15 in AUC was not desirable to reduce the probability of overfitting and the generalizability of the model. This would affect the model's ability on unseen data. Since none of the AUC's were within the desired range, *RandomForestClassifier* was not utilized as a classification model.

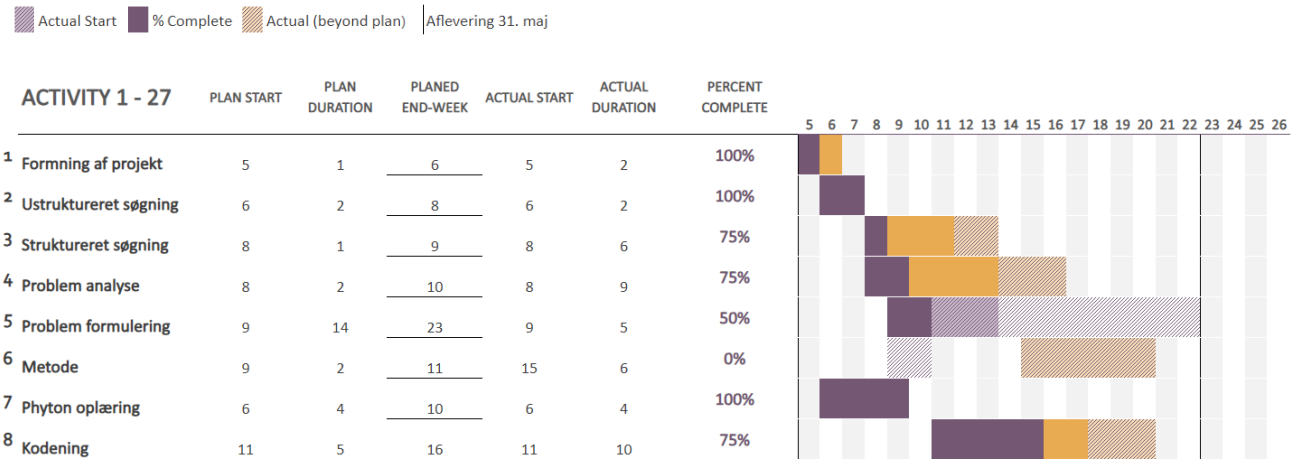
Worksheet 7: Identification and organized based learning

In this worksheet, you will find tables that illustrate how the study was organized.

Table 11: presents a Gantt chart, outlining the estimated duration for each task within the study and evaluating their progress over time. This visual representation helps in understanding the timeline and sequence of activities, ensuring that each phase is clearly defined and monitored as the study progresses.

Table 12: provides a more granular view with a detailed plan for each working day. This table breaks down the daily tasks. This level of detail facilitates precise scheduling and effective time management, ensuring that every day of the study is meticulously planned and executed.

Together, these tables offer a comprehensive overview of the study's organizational structure, enabling efficient tracking and management of tasks to ensure the study's objectives are met within the stipulated timeframe.



ACTIVITY 1 - 27	PLAN START	PLAN DURATION	PLANED END-WEEK	ACTUAL START	ACTUAL DURATION	PERCENT COMPLETE
1 Formning af projekt	5	1	6	5	2	100%
2 Ustruktureret søgning	6	2	8	6	2	100%
3 Struktureret søgning	8	1	9	8	6	75%
4 Problem analyse	8	2	10	8	9	75%
5 Problem formulering	9	14	23	9	5	50%
6 Metode	9	2	11	15	6	0%
7 Phyton oplæring	6	4	10	6	4	100%
8 Kodening	11	5	16	11	10	75%

Table 11: Display of the first 8 activities out of 27 of the Gantt diagram, doing time management.

Uge	Dato	
16	15	Rette artikel del skrevet i sidste uge + Vejledning
	16	Kodning af det sidste
	17	Kodning af det sidste
	18	Evaluering af outcome
	19	Buffer til kodning? Evt. En ekstra model
Uge	Dato	
17	22	Buffer til kodning? Evt. En ekstra model
	23	Peer review
	24	Evaluering + Vejledning
	25	De vigtigste beslutninger bliver taget her – mor er væk
	26	De vigtigste beslutninger bliver taget her – mor er væk
Uge	Dato	
18	29	Analyse og resultater – Fra kodning
	30	Analyse og resultater – Fra kodning
	1	Analyse og resultater
	2	Analyse og resultater + Risikovurdering
	3	Analyse og resultater + Risikovurdering
Uge	Dato	
19	6	Diskussion + Risikovurdering / klinisk relevance
	7	Diskussion + Risikovurdering / klinisk relevance
	8	Diskussion
	9	Diskussion

Table 12: Weekly time management table and schedule for each working day.

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Appendix 1:

Feature table

For a table displaying features found in other articles see table 1.

Study	Aim/Outcome	Method choice for the determination of predictors	AUC	Top predictors
Li et al. (37)	Developing machine learning model to predict high-risk non-adherence in patients	Modified random forest	0.8369	Age Present FBG values Present HbA1c values Present random blood glucose (RBG) values BMI
Wu et al. (38)	Aims to assess multiple machine learning algorithms and screen out a model that can be used to predict patients' non-adherence risks	Ensemble and KNN	0.866±0.082	Age Gender Whether the prior fasting blood glucose was under control Duration of the current treatment regimen Diet adjustment or not Daily cost of medications Fasting blood glucose value Hyperlipidemia BMI
Fan et al. (40)	Predicting risks of complications and poor glycemic control in non-adherent type 2 diabetes	Ensemble (XF) models	0.902-0.825	Duration of T2D Duration of unadjusted hypoglycemic treatment Types of insulin Number of hypoglycemic drugs Total cost of hypoglycemic therapy
Chen et al. (43)	Aims to create classification models to predict insulin adherence among adult T2DM naïve insulin users	Extreme gradient boosting (Xgboost) classifier	Training: 0.782 Test: 0.771	Lower quarterly medication quantities. Use of hypertension drugs and lipid-lowering agents Use of sulfonylurea, thiazolidinediones, and alpha-glucosidase inhibitors Higher number of outpatient visits. Higher number of inpatient visits in the previous year. Lower values of serum creatinine and pre-prandial blood glucose
QiMuge et al. (41)	Development of a predictive nomogram for evaluating medication non-adherence risk in a type 2 diabetes	Multivariate logistic regression analysis.		Being single male, having No formal education Employed Living far from hospital Long disease duration Taking antidiabetics twice or thrice daily
Cramer & Pugh (39)	Relationship between insulin	Ordinary least-squares regression		Race HbA1c levels

	self-management and glycemic control and to identify characteristics associated			Intensity of diabetes management Age Insulin
Skriver et al. (21)	Factors associated with adherence or non-adherence to insulin therapy among adults with type 2 diabetes mellitus: A scoping review	Scoping review		Age Cost of healthcare Personal beliefs towards insulin therapy Social stigma Patient education Complexity of diabetes treatment Impact of insulin therapy on daily life Fear of side effects
Martinez, et al. (42)	Quality of life associated with adherence in patients with T2D	Multiple linear regression analysis		Educational Level Combination of Knowledge and Attitude Gender Hypertension Duration of Diabetes Fasting Glucose Levels Marital Status

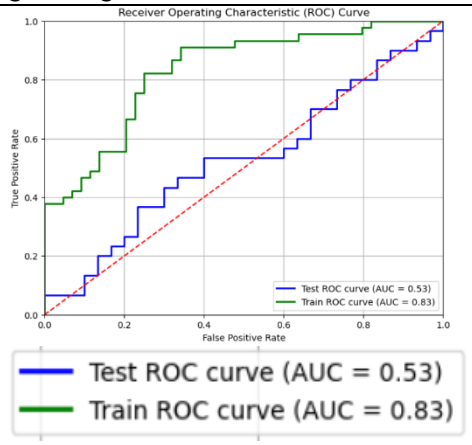
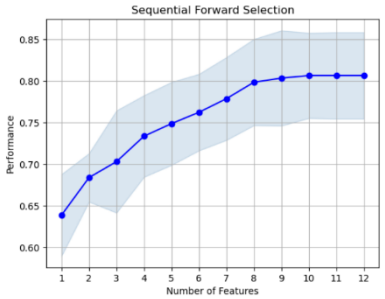
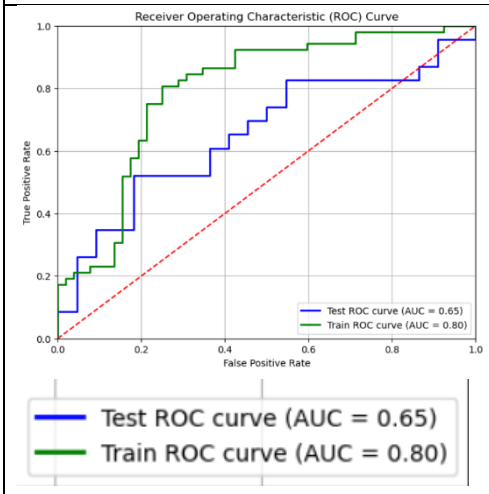
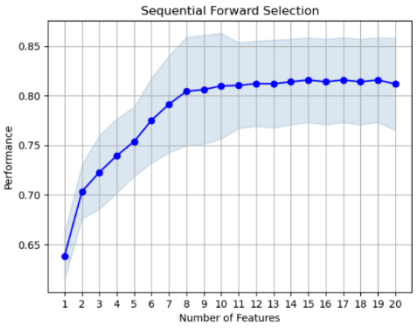
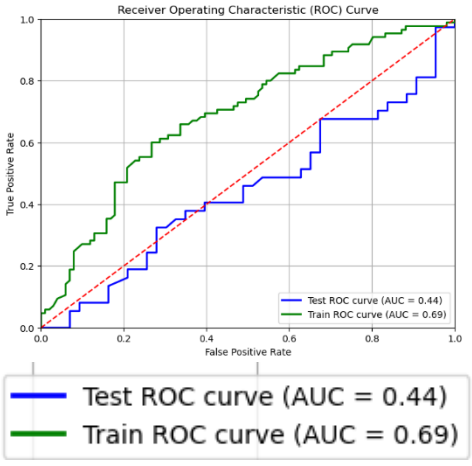
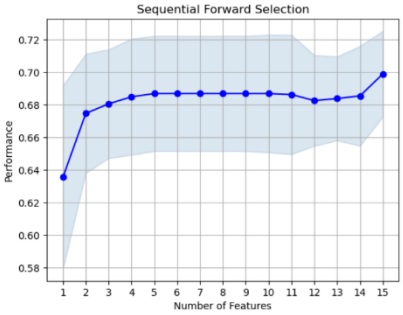
Table 1: Features found in other articles.

Appendix 2:

Result from testing

In this appendix tables for LGR (table 2) and RF (table 3) results can be seen.

Logistic regression

 Test AUC = 0.53 Train AUC = 0.83	*Train/Test: 60/40* Day: 0-21	 Features = [11, 14, 23, 25, 37, 39, 51, 56, 65]
 Test AUC = 0,65 Train AUC = 0,80	*Train/Test: 70/30* Day: 0-21 *Seed = 42*	 Features = [1, 12, 22, 25, 42, 49, 51, 59]
 Test AUC = 0,44 Train AUC = 0,69	*Train/Test: 70/30* Day: 0-21 *Control and intervention group included (n=266)*	 Features = [26, 33, 56, 70]

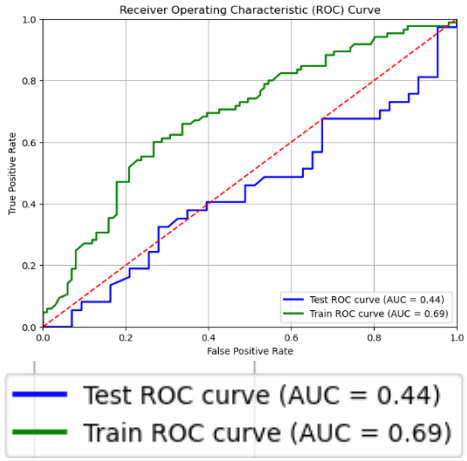
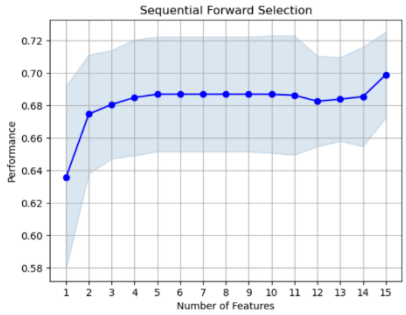
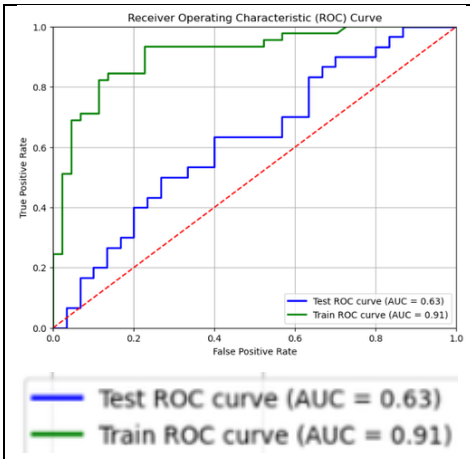
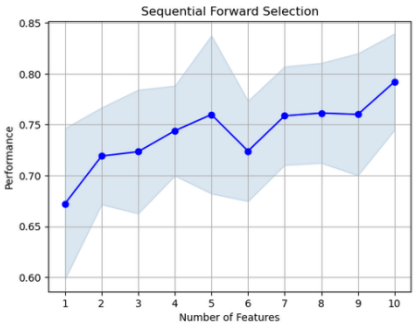
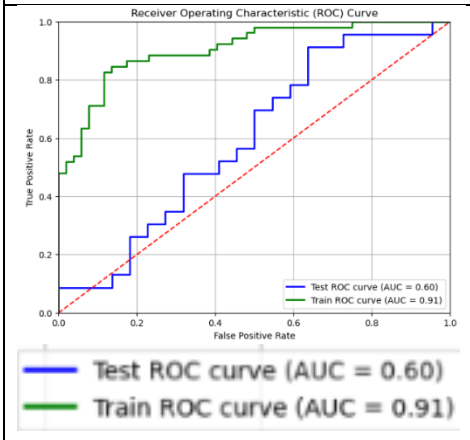
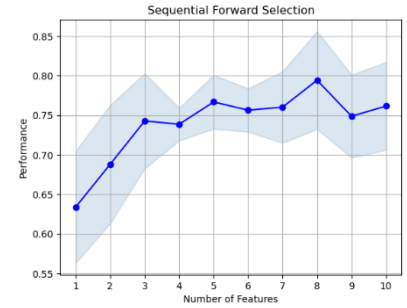
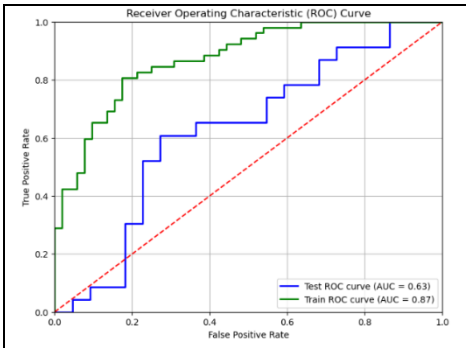
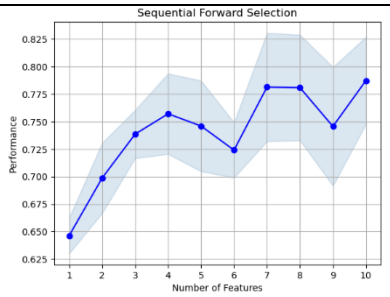
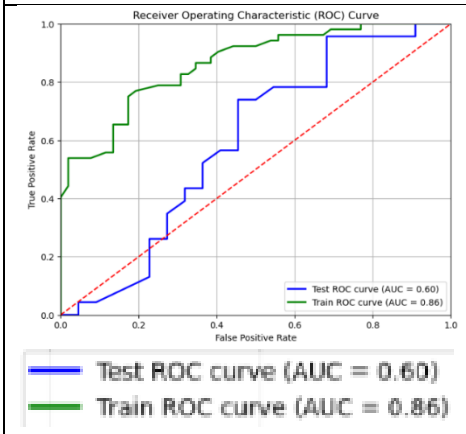
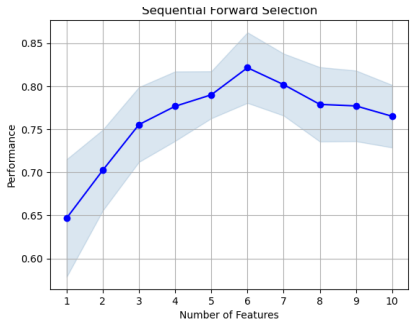
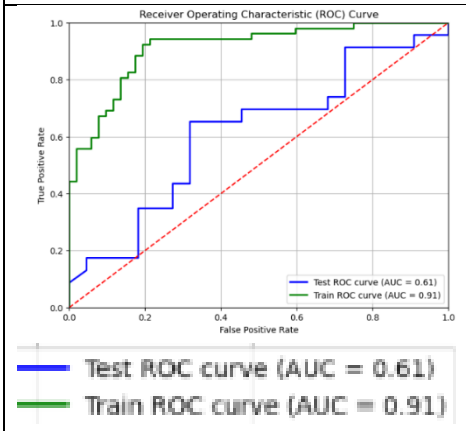
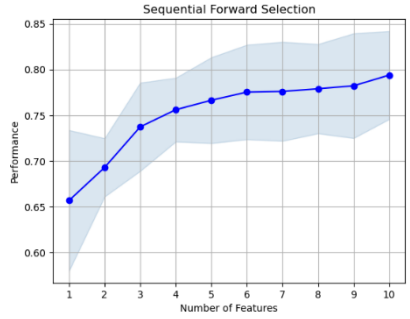
 Test AUC = 0,44 Train AUC = 0,69	*Train/Test: 70/30* Day: 0-21 *Control and intervention group included (n=266)*	 Features = [26, 33, 56, 70]

Table 2: Results from various LGR tests.

Random forest

 Test AUC = 0,63 Train AUC = 0,91	Train test 60/40 RFC(n_estimators=25, max_depth=2, random_state=42, min_samples_leaf=5)	 Features = [1, 7, 20, 48, 51]
 Test AUC = 0,60 Train AUC = 0,91	Train test 70/30 SFS(RFC(n_estimators=25, max_depth=2, random_state=42, min_samples_leaf=5), k_features=10 forward=True, floating=False, cv=5,	 Features = [1, 7, 46, 49, 51]

 Test AUC = 0.63 Train AUC = 0.87	Train test 70/30 SFS(RFC(n_estimators=25, max_depth=2, random_state=42, min_samples_leaf=2) k_features=10, forward=True, floating=False, cv=5	 Features = [2, 3, 25, 51]
 Test AUC = 0,60 Train AUC = 0,86	Train test 70/30 SFS(RFC(n_estimators=25, max_depth=10, min_samples_split=5, min_samples_leaf=5, random_state=42, k_features=10, forward=True, floating=False, cv=5,	 Features = [16, 37, 46, 51, 56, 63]
 Test AUC = 0,61 Train AUC = 0,91	Train test 70/30 SFS(RFC(n_estimators=100, max_depth=5, min_samples_split=10, min_samples_leaf=5, random_state=42), k_features=10, forward=True, floating=False, cv=5	 Features = [1, 7, 48, 49, 51, 54]

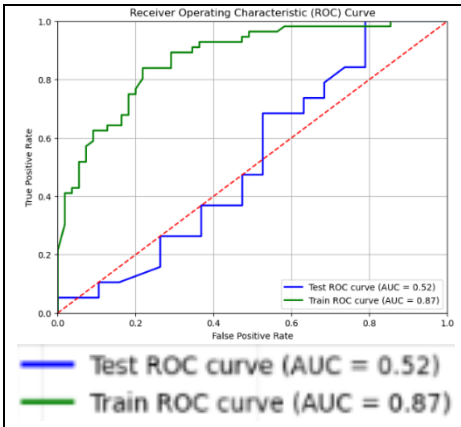
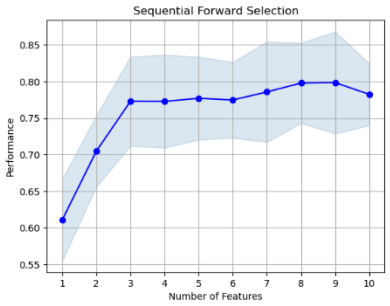
	Train test 75/25 SFS(RFC(n_estimators=25, max_depth=2, random_state=42, min_samples_leaf=5), k_features=10 forward=True, floating=False, cv=5	 Features = [1, 51, 56]

Table 3: Results from various FR tests.