**OHDSI: Prediction of dementia among patients with chronic disease – Patient-level prediction study**

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# List of Abbreviations

| AUC | Area Under the Receiver Operating Characteristic Curve |
| --- | --- |
| CDM | Common Data Model |
| O | Outcome Cohort |
| OHDSI | Observational Health Data Sciences & Informatics |
| OMOP  PROGRESS  ROC | Observational Medical Outcomes Partnership  Receiver operating characteristic |
| T | Target Cohort |
| TAR  T2DM  TRIPOD  MCI | Time at Risk  Type 2 diabetes  Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis  Mild Cognitive Impairment |
| AD  DM | Alzheimer's disease  Diabetes mellitus |

# Responsible Parties

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Investigators:

Reviewers:

# Abstract

Abstract

Background: The possible association between chronic or cardio-metabolic diseases (diabetes mellitus, hypertension, depression, stroke, etc.) and dementia has raised concerns, given the observed coincidental occurrences.

Objective: This study aims to develop a personalized predictive model, utilizing artificial intelligence, to assess the 5-year and 10-year dementia risk among patients with chronic diseases who are prescribed medications.

Methods: This retrospective observational multicenter study comprises electronic medical records. This study applied eight machine learning algorithms to develop prediction models, including logistic regression (LR), linear discriminant analysis (LDA), gradient boosting machine (GBM), lightGBM (LBGM), AdaBoost, random forest, extreme gradient boosting (XGBoost), and artificial neural network (ANN). These models incorporated a range of variables, encompassing patient characteristics, comorbidities, medication usage, and examination data.

# Rational & Background

* The incidence of dementia is mixed globally, but is still an important global public health issue (1, 2).
* Evidence from meta-analytic reviews of seven potentially modifiable risk factors for Alzheimer’s disease that were identified as having consistent evidence for an association in a 2010 US National Institutes of Health independent state-of-the-science report: diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment.(3, 4)
* Type 2 Diabetes is an important risk factor for the development of dementia (5, 6). Diabetes medications, in addition to serving as diagnostic tools for determining the presence of diabetes in individuals, have also been the subject of research indicating a potential correlation with the progression of dementia and Alzheimer's disease. Furthermore, these medications have been suggested to possibly offer therapeutic benefits in the treatment of Alzheimer's disease (6-8) .
* Previous studies have examined the association between cardiovascular health and cognitive outcomes, and most were based on older adults who were followed for cognitive outcomes for less than 10 years. These studies reported better cardiovascular health to be associated with lower risk of cognitive impairment (9), cognitive decline(10) and dementia.(3)
* Persistent midlife hypertension is associated with increased risk of a late life dementia. meta-analyses of blood pressure medications to lower high blood pressure with six studies overlap have provided combined estimates of effects. All meta-analyses suggest reduced dementia in those in the interventions arms for outcomes of any dementia as well as clinically diagnosed Alzheimer’s disease (11).
* Depression is associated with dementia incidence, with a variety of possible psychological or physiological mechanisms. It is also part of the prodrome and early stages of dementia. Reverse causation is possible whereby depressive symptoms result from dementia neuropathology that occurs years before clinical dementia onset (11).

# Objective

We aims to develop a personalized predictive model, utilizing artificial intelligence, to assess the 5-year and 10-year dementia risk among patients with chronic diseases who are prescribed medications.

The objective is to validate our simple score patient-level prediction model for the following prediction problems:

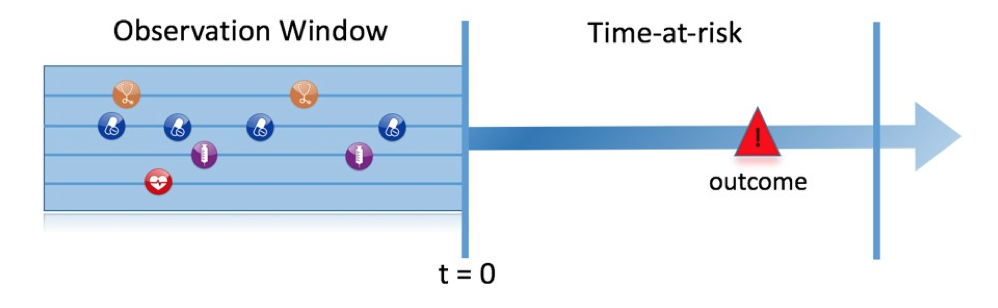
| Target Cohorts | Outcome Cohorts | Time at Risk |
| --- | --- | --- |
| **T2DM**  Subgroup: insulin, metformin, SU, DPP4, SGLT2i, etc. | 1. All types Dementia 2. Subtype: Alzheimer, Vascular Dementia | Risk Window Start: 1;  Add Exposure Days to Start: 1;  Risk Window End: 365 (x5, x10);  Add Exposure Days to End: FALSE |
| **Hypertension**  Subgroup: thiazides, ACEi, ARB, CCBs, etc. | 1. All types Dementia 2. Subtype: Alzheimer, Vascular Dementia | Risk Window Start: 1;  Add Exposure Days to Start: 1;  Risk Window End: 365 (x5, x10);  Add Exposure Days to End: FALSE |
| **Depression**  Subgroup:SSRI, non-SSRI | 1. All types Dementia 2. Subtype: Alzheimer, Vascular Dementia | Risk Window Start: 1;  Add Exposure Days to Start: 1;  Risk Window End: 365 (x5, x10);  Add Exposure Days to End: FALSE |
| **Stroke**  Subgroup: Ischemic, Hemorrhagic | 1. All types Dementia 2. Subtype: Alzheimer, Vascular Dementia | Risk Window Start: 1;  Add Exposure Days to Start: 1;  Risk Window End: 365 (x5, x10);  Add Exposure Days to End: FALSE |
| **Combine group: T2DM + Hypertension + Depression** | 1. All types Dementia 2. Subtype: Alzheimer, Vascular Dementia | Risk Window Start: 1;  Add Exposure Days to Start: 1;  Risk Window End: 365 (x5, x10);  Add Exposure Days to End: FALSE |

# Methods

## Study Design

This study will employ a retrospective, observational, patient-level prediction approach. In a 'retrospective' context, the study utilizes pre-existing data collected before the study commencement. In an 'observational' context, no interventions or treatment assignments are introduced by the study. 'Patient-level prediction' involves a modeling process where the outcome is predicted within a time period at risk relative to the target cohort's start and/or end date. This prediction relies on a set of covariates derived from data collected before the initiation of the target cohort.

Figure 1, illustrates the prediction model we will establish. In a population at risk, our goal is to predict which patients, at a specified moment in time (t = 0), will encounter a particular outcome within a defined time-at-risk window. This prediction is based solely on information available about the patients within an observation window preceding that specific moment in time.



***Figure 1: The prediction problem***

We follow the PROGRESS best practice recommendations for model development and the TRIPOD guidance for transparent reporting of the model results.

## Data Source(s)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Database Name | Version | Start date | End date | Description |
| TMUCRD | V5\_V2 | 2008 | 2021 |  |
| ….. |  |  |  |  |
|  |  |  |  |  |

## Study Populations

### Target Cohort(s) [T]

1. **T2DM**

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for type 2 diabetes)

* Aged at least 18 years old
* A diagnosis of T2DM on or preceding the index date
* Exposure to one of the treatments of interest
* No prior T1DM or Secondary DM

Limit qualifying cohort to **all event per person**

|  |  |  |
| --- | --- | --- |
| Diagnosis | ICD 10 | SNOMED-CT |
| Type 2 Diabetes Mellitus | E11.x | 44054006, 313436004, 127013003, 421326000, 422014003, 422166005, 421750000, 609567009, 190389009, 368101000119109, 1481000119100, 237599002, 199230006, 237627000, 359642000, 81531005, 703138006 |
| Type 1 Diabetes Mellitus | E10.x | 46635009, 421468001, 421893009, 421365002, 420868002 |
| Secondary DM | E12.x, E13.x, E14.x | 8801005, 5368009 |

|  |  |  |
| --- | --- | --- |
| Drug Name | ATC Code | RxNorm Ingredient Code |
| Biguanides | A10BAxx | 6809, 8129, |
| Sulfonylureas | A10BBxx | 2404, 10635, 25789, 4821, 25793, 4815, 10633, 4816, |
| Alpha Glucosidase Inhibitors | A10BFxx | 16681, 30009, |
| Thiazolidindiones | A10BGxx | 33738, 84108, 72610 |
| DPP4 inhibitors | A10BHxx | 1100699, 596554, 593411, 1368001, 857974 |
| GLP-1 receptor analogues | A10BJxx | 475968, 1551291, 60548, 1534763, 1440051, 1991302 |
| SGLT2 Inhibitors | A10BKxx | 1488564, 1373458, 1545653, 1992672 |
| Others anti-DM | A10BXxx | 73044, 274332, 26344, 139953 |
| Insulin | A10Axxx | 253182, 274783, 86009, 236646, 139825, 400008, 1740938, 1670007, 1605101, |

1. **Hypertension**

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for hypertension)

* Aged at least 18 years old
* A diagnosis of Essential Hypertension on or preceding the index date
* Exposure to one of the treatments of interest

Limit qualifying cohort to **all event per person**

|  |  |  |
| --- | --- | --- |
| Diagnosis | ICD 10 | SNOMED-CT |
| Essential Hypertension | I10 | 59621000, 1201005, 78975002 |

|  |  |  |
| --- | --- | --- |
| Drug Name | ATC Code | RxNorm Ingredient Code |
| Thiazides | C03AA06, C03AA03 | 10772, 5487 |
| ACE Inhibitors | C09Axxx | 1998, 29046, 3827, 54552, 18867, 35208, 60245, 35296, 50166, 30131, 3829, 38454, 21102, 36908, 39990 |
| Angiotensin II receptor blockers | C09CAxx | 69749, 214354, 321064, 83818, 52175, 73494, 1091643, 83515 |
| Calcium Channel Blockers | C08CXxx | 17767, 7417, 7396, 4316, 135056, 7426, 39879, 28382, 7435, 7441, 233603, 33910, 29275, 83213, 53692 |

1. **Depression**

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for depression)

* Aged at least 18 years old
* A diagnosis of Depression on or preceding the index date
* Exposure to one of the treatments of interest
* No prior episodes of Bipolar Disorders

Limit qualifying cohort to **all event per person**

|  |  |  |
| --- | --- | --- |
| Diagnosis | ICD 10 | SNOMED-CT |
| Depression | F32.x, F33.x | 310495003, 310496002, 310497006, 36923009, 66344007, 79298009, 191613003, 191610000, 15639000, 430852001, 40379007, 18818009, 191616006, 191659001, 191611001, 36474008, 76441001, 46244001, 19527009, 68019004, 33135002, 191676002, 70747007, 84760002, 442057004 |
| Bipolar Disorders | F31.x | 765176007, 191634005, 13746004 |

|  |  |  |
| --- | --- | --- |
| Drug Name | ATC Code | RxNorm Ingredient Code |
| Selective serotonin reuptake inhibitors | N06ABxx | 36437, 321988, 42355, 4493, 32937, 2556 |
| Monoamine oxidase A inhibitors | N06AGxx | 30121, 38382 |
| [Non-selective monoamine reuptake inhibitors](http://10.164.1.154:8080/Atlas/#/concept/21604687) | N06AA | 5691, 446248, 3638, 2597, 8886, 7531, 10834, 3332, 19895, 5979, 6465, 704, 6646, 722, 7674, 17698, 35242, 3247, 3634 |
| [Monoamine oxidase inhibitors, non-selective](http://10.164.1.154:8080/Atlas/#/concept/21604719) | N06AF | 8123, 6011, 7394, 10734 |
| [Other antidepressants](http://10.164.1.154:8080/Atlas/#/concept/21604729) | N06AX | 10737, 15996, 39786, 72625, 72625, 588250, 10898, 2119365, 1455099, 1307704, 1309228, 1086769, 734064, 29434, 30031, 6929, 11196, 38252, 60842, 47111, 31565 |

1. **Stroke**

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment for depression)

* Aged at least 18 years old
* A diagnosis of Hemorrhagic or Ischaemic Stroke on or preceding the index date

Limit qualifying cohort to **all event per person**

|  |  |  |
| --- | --- | --- |
| Diagnosis | ICD 10 | SNOMED-CT |
| Hemorrhagic stroke | I61.x | 274100004, 291571000119106, 270907008, 21454007 |
| Ischaemic stroke | I63.x | 432504007, 230692004, 230698000, 230699008, 230700009 |

### Outcome Cohorts(s) [O]

* General Dementia

Initial Event cohort) People having any of the following:

* a condition occurrence of all type Dementia

for the first time in the person's history

* + - * with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to **earliest** **event per person**
      * with using one of Dementia medication

|  |  |  |
| --- | --- | --- |
| Diagnosis | ICD 10 | SNOMED-CT |
| Dementia | F02.x, F03.x, G31.8 | 52448006, 56267009, 15662003, 230270009, 12348006, 230288001, 762707000, 79341000119107 |
| Alzheimer | F00.x G30.x | 26929004 |
| Vascular Dementia | F01.x | 429998004 |

|  |  |  |
| --- | --- | --- |
| ATC Name | ATC Code | RxNorm Ingredient Code |
| Donepezil | N06DA02 | 135447 |
| Rivastigmine | N06DA03 | 183379 |
| Galantamine | N06DA04 | 4637 |
| Memantine | N06DX01 | 6719 |
| Ginko folium | N06DX02 | 1356135 |

### Time at Risk

| Time at Risk |
| --- |
| [Time at Risk Settings #1] Risk Window Start: 1, Add Exposure Days to Start: FALSE, Risk Window End: 365, Add Exposure Days to End: FALSE |

### Additional Population Settings

***Population Settings #1***

| Item | Settings |
| --- | --- |
| minTimeAtRisk | 364 (x1, x3, x5) |
| requireTimeAtRisk | TRUE |
| addExposureDaysToStart | FALSE |
| riskWindowStart | 1 |
| washoutPeriod | 365 |
| addExposureDaysToEnd | FALSE |
| includeAllOutcomes | TRUE |
| priorOutcomeLookback | 99999 |
| binary | TRUE |
| removeSubjectsWithPriorOutcome | FALSE |
| riskWindowEnd | 365 (x1, x3, x5) |
| firstExposureOnly | FALSE |

## Statistical Analysis Method(s)

### Algorithms

In this study we will apply multiple algorithms (such as: Lasso Logistic regression, Random Forest, LightGBM, xGboost, Multilayer Perceptron, etc.) under Patient-level prediction package developed by OHDSI: <https://github.com/OHDSI/PatientLevelPrediction.git>

### Model Evaluation

The following evaluations will be performed on the model:

| Evaluation | Description |
| --- | --- |
| Box Plots | The prediction distribution boxplots are box plots for the predicted risks of the people in the test set with the outcome (class 1: blue) and without the outcome (class 0: red). |
| Calibration Plot | The calibration plot shows how close the predicted risk is to the observed risk. The diagonal dashed line thus indicates a perfectly calibrated model. The ten (or fewer) dots represent the mean predicted values for each quantile plotted against the observed fraction of people in that quantile who had the outcome (observed fraction). The straight black line is the linear regression using these 10 plotted quantile mean predicted vs observed fraction points. The two blue straight lines represented the 95% lower and upper confidence intervals of the slope of the fitted line. |
| Demographic Summary Plot | This plot shows for females and males the expected and observed risk in different age groups together with a confidence area. |
| Precision Recall Plot | The precision-recall curve is valuable for dataset with a high imbalance between the size of the positive and negative class. It shows the tradeoff between precision and recall for different thresholds. High precision relates to a low false positive rate, and high recall relates to a low false negative rate. High scores for both show that the classifier is returning accurate results (high precision), as well as returning a majority of all positive results (high recall). A high area under the curve represents both high recall and high precision. |
| Prediction Distribution Plots | The preference distribution plots are the preference score distributions corresponding to i) people in the test set with the outcome (red) and ii) people in the test set without the outcome (blue). |
| ROC Plot | The ROC plot plots the sensitivity against 1-specificity on the test set. The plot shows how well the model is able to discriminate between the people with the outcome and those without. The dashed diagonal line is the performance of a model that randomly assigns predictions. The higher the area under the ROC plot the better the discrimination of the model. |
| Smooth Calibration Plot | Similar to the traditional calibration shown above, the Smooth Calibration plot shows the relationship between predicted and observed risk. The major difference is that the smooth fit allows for a more fine grained examination of this. Whereas the traditional plot will be heavily influenced by the areas with the highest density of data the smooth plot will provide the same information for this region as well as a more accurate interpretation of areas with lower density. the plot also contains information on the distribution of the outcomes relative to predicted risk. However the increased information game comes at a computational cost. It is recommended to use the traditional plot for examination and then to produce the smooth plot for final versions. |
| Test-Train Similarity Plot | The test-train similarity is presented by plotting the mean covariate values in the train set against those in the test set for people with and without the outcome. |
| Variable Scatter Plot | The variable scatter plot shows the mean covariate value for the people with the outcome against the mean covariate value for the people without the outcome. The size and color of the dots correspond to the importance of the covariates in the trained model (size of beta) and its direction (sign of beta with green meaning positive and red meaning negative), respectively. |

## Quality Control

The PatientLevelPrediction package itself, as well as other OHDSI packages on which PatientLevelPrediction depends, use unit tests for validation. More information can be found in the Book of OHDSI at: https://ohdsi.github.io/TheBookOfOhdsi/SoftwareValidity.html

## Tools

To create the study package, ATLAS will be used to specify the cohorts, time-at-risk, covariate and population settings as well as which models will be analyzed. Information on this is available in the Book of OHDSI at: https://ohdsi.github.io/TheBookOfOhdsi/OhdsiAnalyticsTools.html#atlas

The package developed in ATLAS will utilize the Patient-Level Prediction R package to run the analysis. More information on this is available at: https://ohdsi.github.io/TheBookOfOhdsi/PatientLevelPrediction.html

This study will be designed using OHDSI tools and run with R (17). More information about the tools can be found in the Appendix 'Study Generation Version Information'.

# Diagnostics

Reviewing the incidence rates of the outcomes in the target population prior to performing the analysis will allow us to assess its feasibility. The full table can be found in the 'Table and Figures' section under 'Incidence Rate of Target & Outcome'.

Additionally, reviewing the characteristics of the cohorts provides insight into the cohorts being reviewed. The full table can be found below in the 'Table and Figures' section under 'Characterization'.

# Data Analysis Plan

## Algorithm Settings

LassoLogisticRegressionSettings

|  |  |
| --- | --- |
| Covariates | Settings |
| seed |  |
| variance | 0.01 |

## Model Evaluation

We will use the area under the receiver operating characteristic curve (AUC) to evaluate the discriminative performance of the models and plot the predicted risk against the observed fraction to visualize the calibration. See 'Model Evaluation' section for more detailed information about additional model evaluation metrics.

## Analysis Execution Settings

There are 1 target cohorts evaluated for 1 outcome over 1 model over 1 covariate settings and over 1 population settings. In total there is 1 analysis performed. For a full list refer to appendix 'Complete Analysis List'.

# Strengths & Limitations

Strengths

* The model is simple to implement
* We are validating the models across a diverse set of patients
* Model validation is possible due to the OHDSI standardizations

Limitation

* Not all medical events are recorded into the observational datasets and some recordings can be incorrect. This could potentially lead to outcome misclassification.

# Protection of Human Subjects

Confidentiality of patient records will be maintained always. All study reports will contain aggregate data only and will not identify individual patients or physicians. At no time during the study will the sponsor receive patient identifying information except when it is required by regulations in case of reporting adverse events.

# Plans for Disseminating & Communicating Study Results

This work will be submitted to a high impact journal in the field of neurology

# Tables & Figures

## Incidence Rate of Target & Outcome

*<< add incidence here. >>*

## Characterization

*<< add characterization table here. >>*

*<< add results here. >>*

# Appendices

## Study Generation Version Information

Skeleton Version: PatientLevelPredictionStudy - v0.0.1

Identifier / Organization: Janssen Research and Development

## Code List

***Concept Set #1 – T2DM***

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

Cohorts that use this Concept Set:

Cardiovascular Beta Blockers

***Concept Set #2 – T2DM medication***

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

Cohorts that use this Concept Set:

Cardiovascular Beta Blockers

***Concept Set #3 - Dementia***

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

***Concept Set #4 - Alzheimer***

Cohorts that use this Concept Set:

Cardiovascular Beta Blockers

***Concept Set #5 – Vascular dementia***

Cohorts that use this Concept Set:

Cardiovascular Beta Blockers

***Concept Set #6 – Dementia medication***

Cohorts that use this Concept Set:

Major Depressive Disorder

## Complete Analysis List

Below is a complete list of analysis that will be performed. Definitions for the column 'Covariate Settings ID' can be found above in the 'Covariate Settings' section. Definitions for the 'Population Settings Id' can be found above in the 'Additional Population Settings' section.

| ID | Target Cohort Name | Outcome Cohort Name | Model Settings Id | Model Settings Description | Covariate Settings ID | Population Settings ID |
| --- | --- | --- | --- | --- | --- | --- |
| 1 |  |  | 1 | Lasso Logistic Regression | 1 | 1 |
| 2 |  |  | 2 | GBM | 1 | 1 |
| 3 |  |  | 3 | DPLP |  |  |

*<< add models here >>*

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