

A risk stratification pipeline to enrich study populations for early dementia detection in the PREDICTOM project

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Introduction

- Dementia is an escalating global health concern, with the number of affected individuals projected to rise sharply in the coming decades. (1)
- The Lancet Commission on dementia prevention, intervention, and care highlighted the importance of identifying high-risk individuals early to enable interventions that may influence the progression of the disease. (2)
- In PREDICTOM we aim to develop an AI driven screening platform for early dementia detection and to extend the clinical pathway to home-based screening, following a two-level recruitment strategy and evaluation. (3)

We have developed a risk stratification pipeline to enrich the PREDICTOM Level 2 population with people with elevated risk using an all-cause dementia risk model and a normative model for cognitive performance.

Methods

All-Cause Dementia Risk Model

- Key risk factors for dementia, as identified by the Lancet Commission, can often be assessed during routine general practitioner (GP) visits. (2)
- We have developed a time-to-event model for all-cause dementia free survival combining these risk factors; trained and validated on data from the UKBiobank. (4)

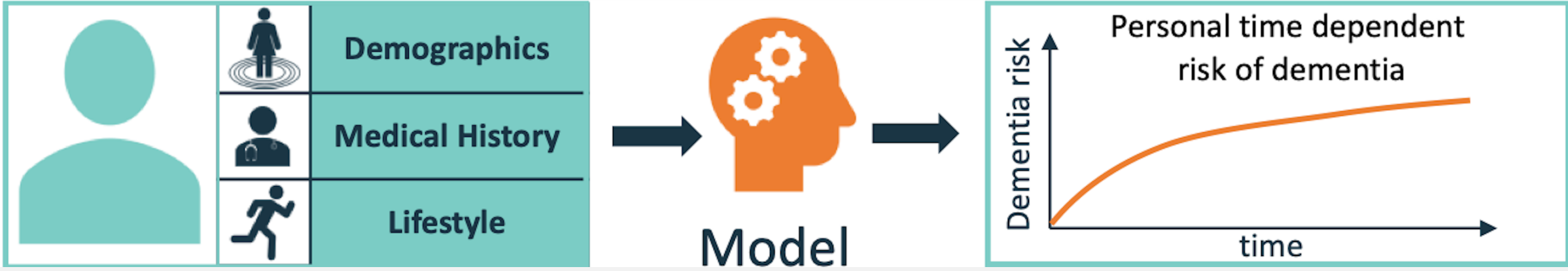


Figure 1. Schematic visualization of individual risk assessment.

Results

Our model outperformed an age & sex only baseline model with a mean AUC and c-index around 80%.

Application in Risk Stratification Pipeline

1. Use an external dataset (PROTECT (5)) and PREDICTOM inclusion criteria (see (3)).
2. Apply the pretrained model on this dataset and compute the cumulative incidence function (CIF) values at a specific time point (e.g., 15 years after baseline).
3. Define thresholds from percentiles of the CIF distribution to match the expected sample sizes.
4. Apply the pretrained model on the PREDICTOM participants and stratify according to the thresholds.

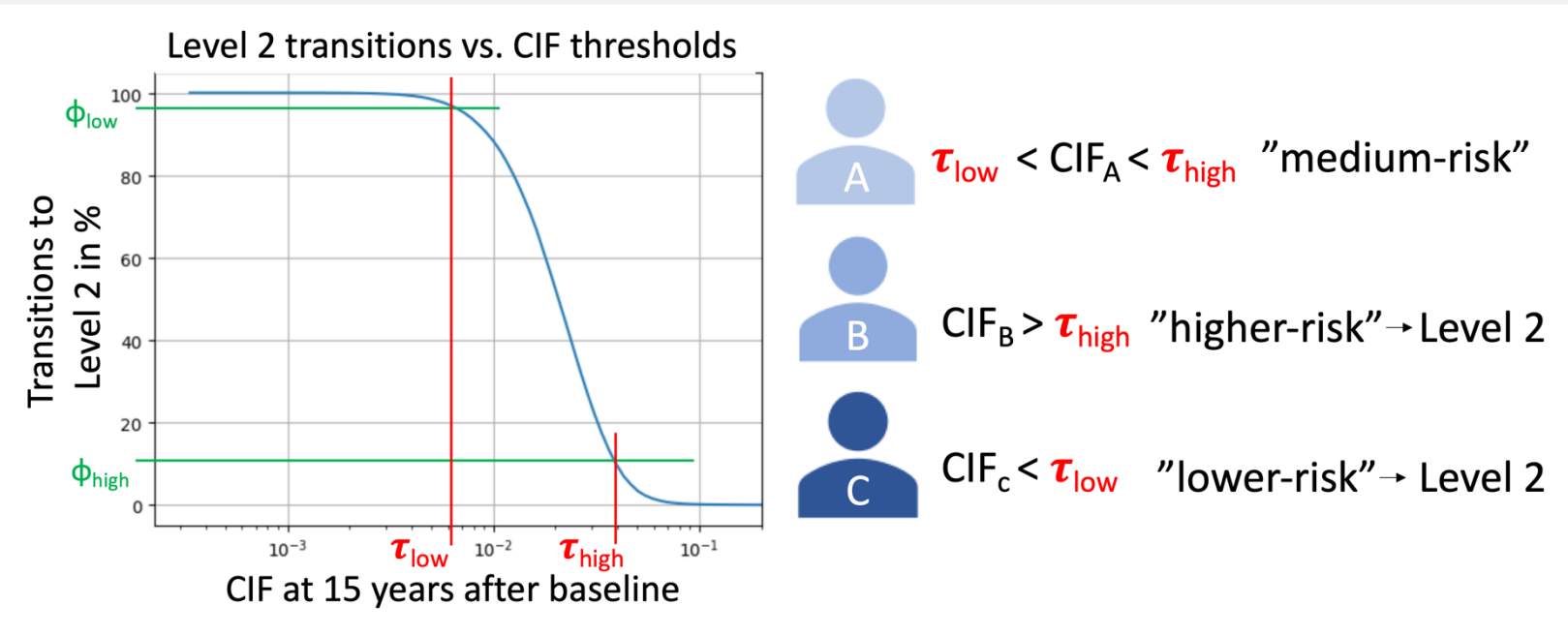


Figure 2. Schematic visualization of risk thresholding.

Note: The lower risk group is used as a control group for following statistical analyses.

Age correction

- The threshold approach would favor participants with higher age, as risk for dementia increases with age; in practice we should correct for this.
- Fit a GAMLSS (6) model to the CIF values of the UKBiobank population at a specific time point vs. age.
- Get the percentiles of the individual CIF value for the respective age group.
- Based on previously defined thresholds (e.g., 10th and 90th percentile) stratify participants to respective risk groups, independent of their age.

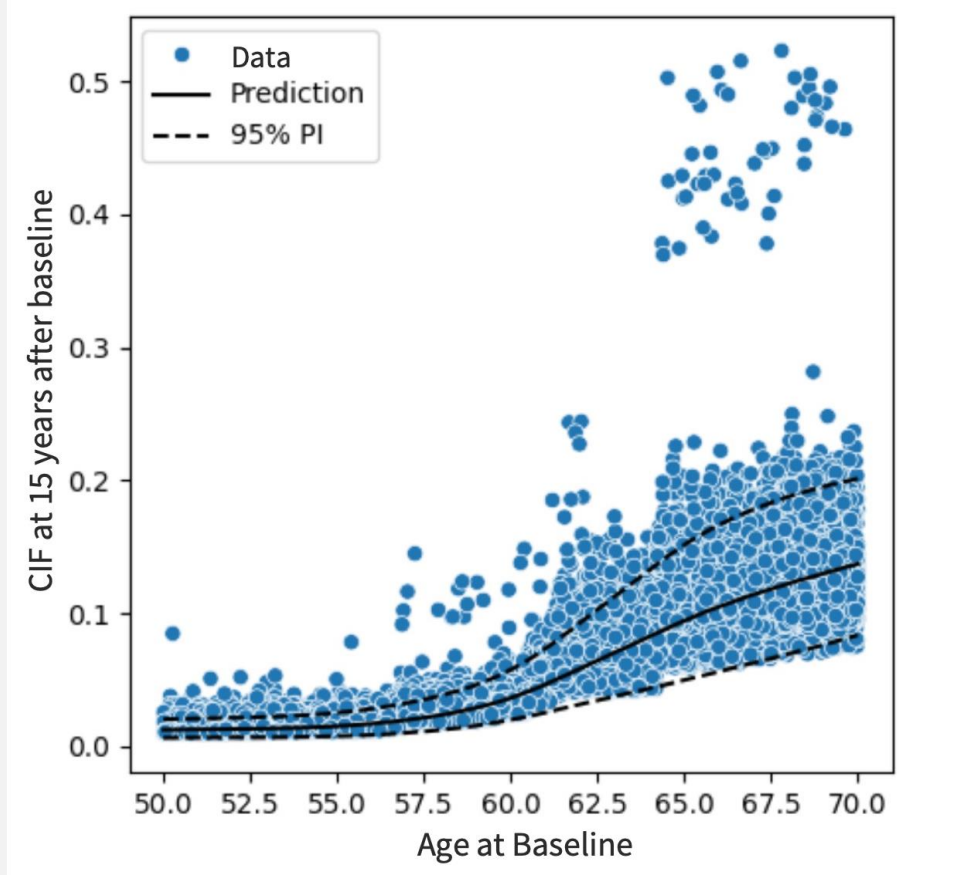


Figure 3. GAMLSS fit on CIF values at 15 years after baseline.

Normative Model for Cognitive Performance (Poster #1702)

- Although, cognitive performance naturally decreases with age, it is often evaluated based on simple cut-offs.
- We have developed a normative model for cognitive performance correcting for age, sex and education based on the FLAME (7) composite score.

Results

- We found well-calibrated models with significant differences in the z-score distributions of CU and SCI.
- Using the derived z-scores leads to an enrichment of 28% of participants with elevated risk (here SCI).

Application in Risk Stratification Pipeline

- Apply the normative model to the FLAME scores of the PREDICTOM participants -> derive z-scores.
- Use $z < -1.64$ as a threshold for identifying someone with abnormal deviation in cognitive performance.
- Exclude them from the lower risk group.

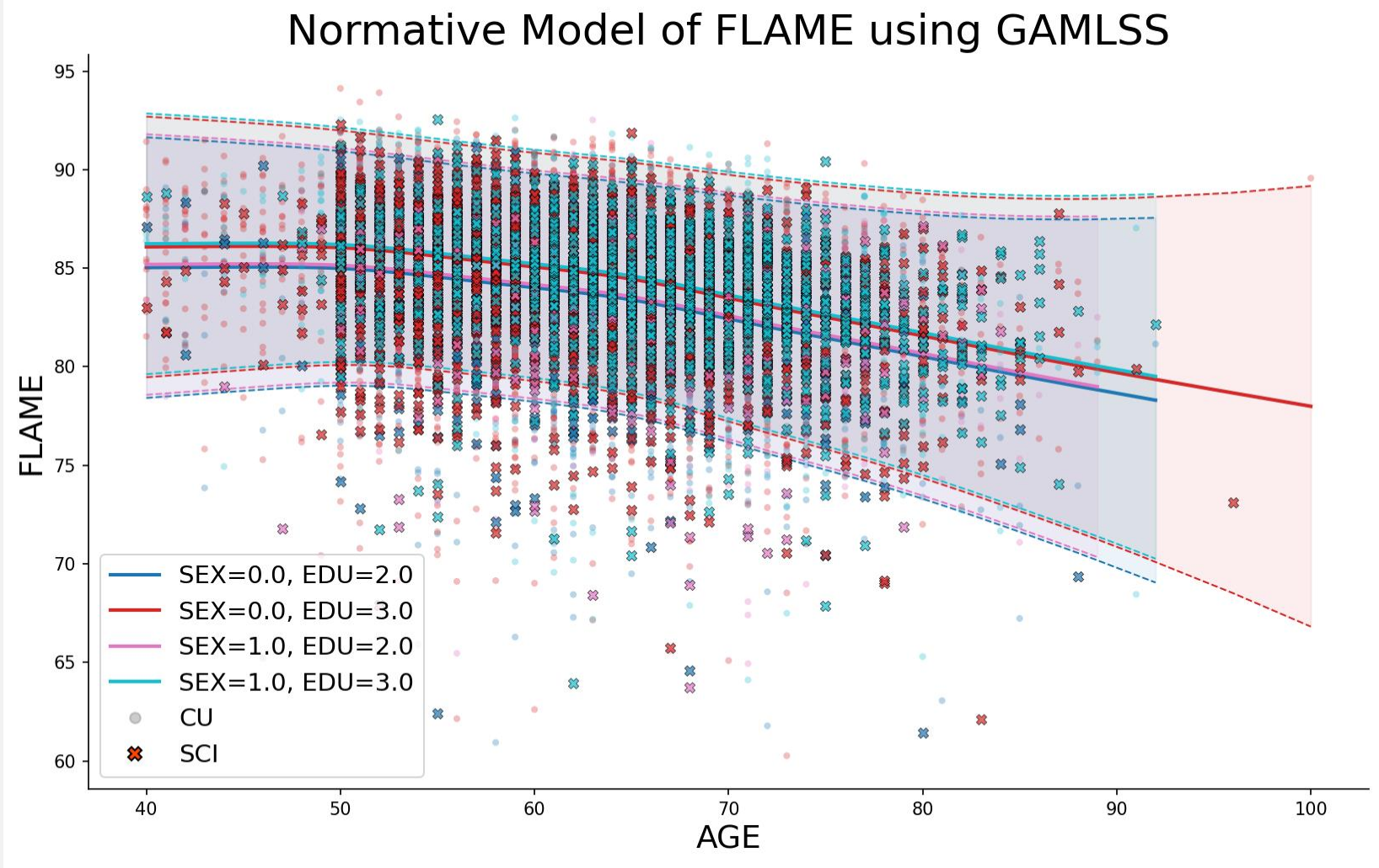


Figure 4. Normative Model of FLAME using GAMLSS. SEX (0:female, 1: male), EDU (2: <=12 years, 3: >12 years)

Results

- The PREDICTOM study and corresponding risk stratification process is currently on-going.
- To date (May 2026) 1180 participants finished Level 1 and have been stratified accordingly.
- By the end of Level 1 (N ~ 4000), we aim to have 415 at higher and 200 at lower risk in Level 2.

	All Sites	UK	Norway	Spain	Switzerland	Germany
Lower Risk	202	26	54	57	58	7
Higher Risk	189	54	60	48	14	13

Table 1. Current status of risk stratification in PREDICTOM.*

* Note: We chose to stratify more higher and lower risk individuals than needed in Level 2 to have more freedom in the recruitment process.

References

- (1) [https://doi.org/10.1016/S2468-2667\(21\)00249-8](https://doi.org/10.1016/S2468-2667(21)00249-8)
- (2) [https://doi.org/10.1016/S0140-6736\(24\)01296-0](https://doi.org/10.1016/S0140-6736(24)01296-0)
- (3) <https://doi.org/10.1016/j.tjpad.2026.100545>
- (4) <https://doi.org/10.1371/journal.pmed.1001779>
- (5) <https://www.protectstudy.org.uk>
- (6) <https://doi.org/10.1201/9780429298547>
- (7) <https://doi.org/10.1002/dad2.12098>

Abbreviations: AUC - Area Under the Curve, A β - Amyloid Beta, c-index - Concordance Index, CIF - Cumulative Incidence Function, CSF - Cerebrospinal Fluid, CU - Cognitively Unimpaired, EDU - Education, FLAME - Factors of Longitudinal Attention Memory and Executive Function, GAMLSS - Generalized Additive Models for Location Scale and Shape, GP - General Practitioner, PET - Positron Emission Tomography, ptau217 - Phosphorylated Tau 217, SCI - Subjective Cognitive Impairment

Discussion & Outlook

- We enabled stratification in an ongoing study, consistent with the inclusion criteria and maximizing the distance of dementia risk in both groups using prior validated risk factors and models.
- We will validate this approach once Level 2 results become available, i.e., blood-based ptau217 and CSF A β .
- Since this approach relies on simple risk factors and at home cognitive tests, it could be applied to large-scale population screening to identify people with elevated risk of future dementia.
- They could then undergo additional tests (e.g., digital biomarkers or body fluids).
- If these tests also reveal elevated risk, high risk individuals could be referred to a specialist for a final evaluation (ptau217, CSF, PET).

A clear patient journey that reduces costs and enables timely detection and intervention.

#1706



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