



Electrocardiogram-derived Digital Biomarkers for Early Detection of Dementia in Real-world Clinical Data

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1. Background

Dementia burden

- Rapidly growing global health burden
- Cases projected to nearly triple by 2050¹

Heart-brain axis

- Cardiovascular disease linked to dementia risk²
- Growing mechanistic and epidemiologic evidence

Unmet need

- Scalable, interpretable cardiac markers related to dementia is still limited

ECG opportunity

- Low-cost, routinely collected cardiac signal
- May capture subclinical heart-brain vulnerability³

2. Objective

We aimed to identify dementia-associated ECG phenotypes by analyzing pre-index trajectories of foundation model ECG label probabilities.

3. Methods

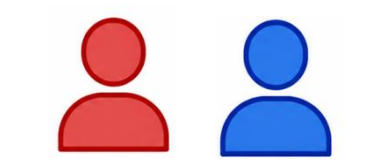
A. Cohort selection



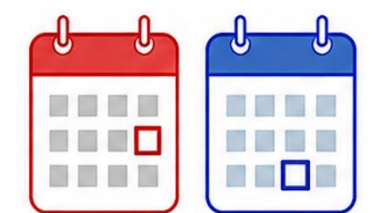
- **12-lead ECGs** from Severance Hospital and Yonsei Severance Hospital



- **Case:** dementia diagnosis (ICD-10)
- **Control:** no dementia diagnosis

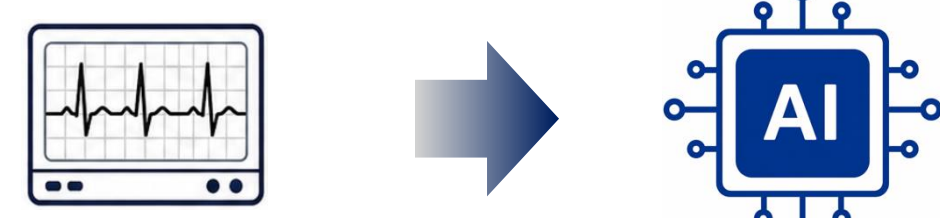


- 1:1 matching by age at ECG



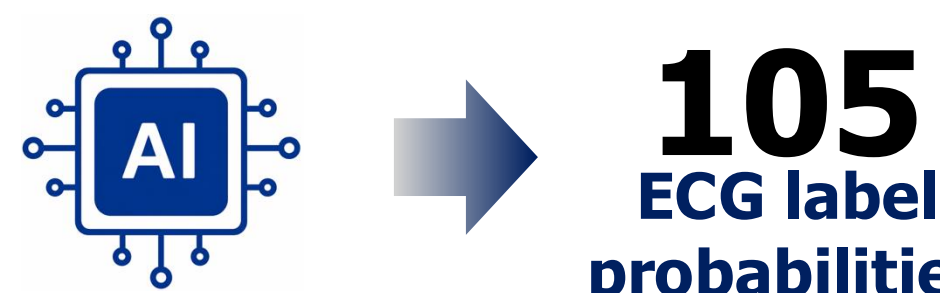
- Index date: dementia diagnosis date (cases); date at the median age (controls)

B. Preprocessing and model application



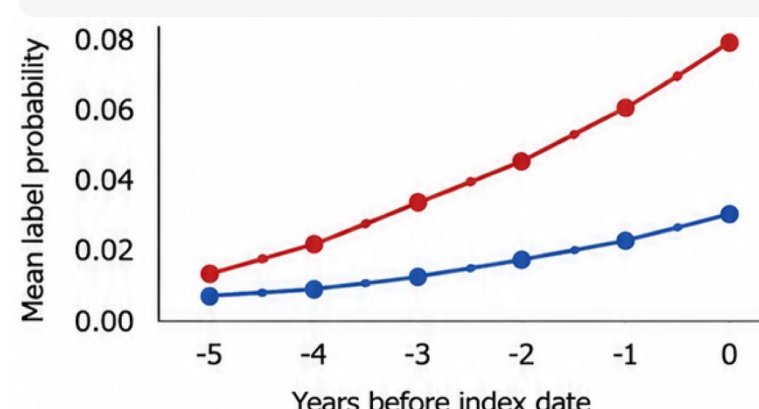
- Filtering ECG noise and resampling each signal to 100 Hz
- Applying the knowledge-enhanced ECG diagnosis foundation model (KED)

C. ECG label probability extraction



- Extracting probabilities for 105 predefined ECG phenotype labels
- Covering rhythm and conduction, ischemia, repolarization, hypertrophy, and overall interpretation

D. Trajectory analysis



- Visualizing trajectories as mean curves with 95% CI in 1-year bins
- Prioritizing labels with a steeper increase and $\geq 20\%$ relative acceleration vs controls
- Controlling the false discovery rate (FDR) across labels

4. Results

Baseline characteristics

	Severance hospital		YSH	
	Case	Control	Case	Control
No. of ECGs	24,874	24,874	2,261	2,261
Age (mean $\pm$ SD)	66.1 $\pm$ 12.1	66.1 $\pm$ 12.1	70.8 $\pm$ 10.4	70.8 $\pm$ 10.4
Sex-Female	13,130	14,134	1,432	1,280

Significant ECG phenotype labels

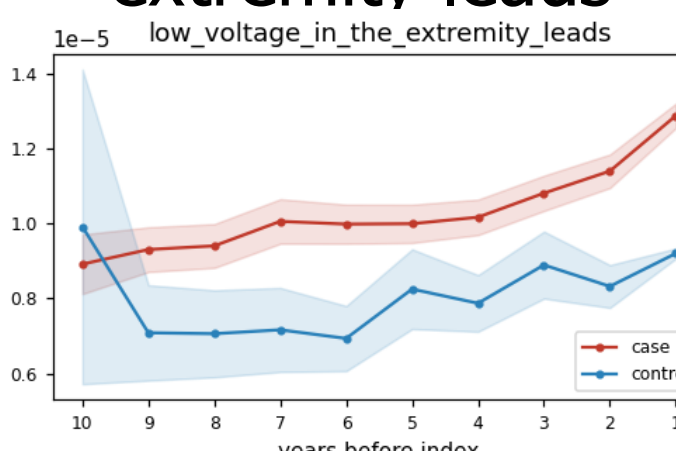
- Identifying 22 ECG phenotype labels significant under both FDR and Bonferroni correction

ECG Category	n
Repolarization and ischemic abnormalities (acute myocardial infarction, non-specific ST segment junctional depression, early repolarization, and so on)	11
Rhythm and conduction abnormalities (atrial fibrillation, ectopic atrial rhythm, accelerated junctional rhythm, atrial premature complex, short PR)	5
Structural or chamber abnormality (left, and right atrial abnormality, low voltage in the precordial leads)	3
Global ECG interpretation (abnormal, and borderline ECG, normal ECG except for rate)	3

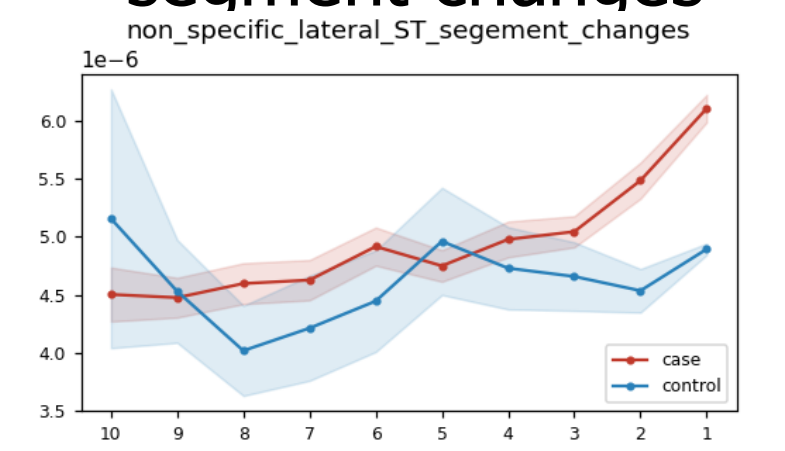
Representative trajectories of significant ECG labels

(x: days before the index date, y: feature probability, red: case, blue: control)

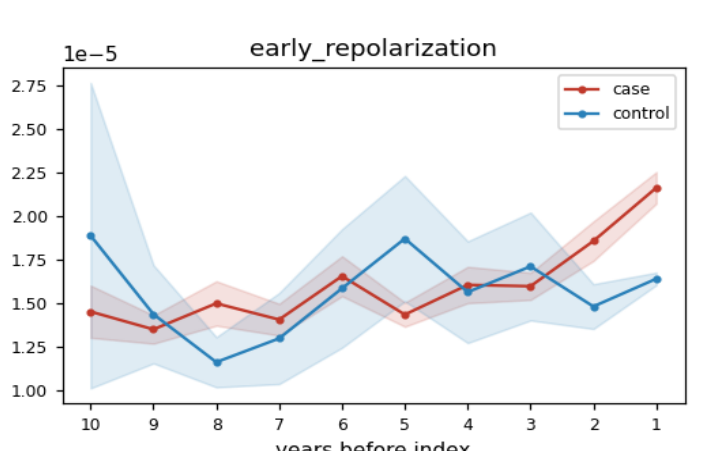
Low voltage in the extremity leads



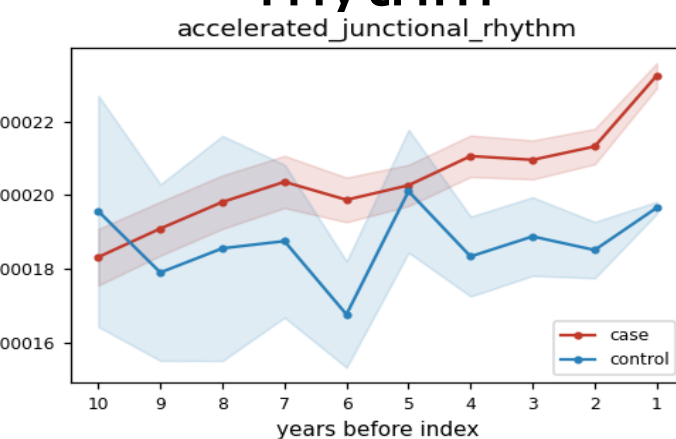
Non-specific lateral ST segment changes



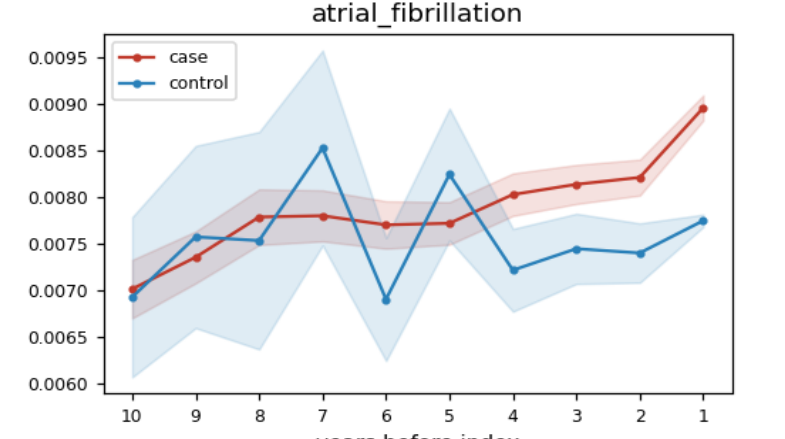
Early repolarization



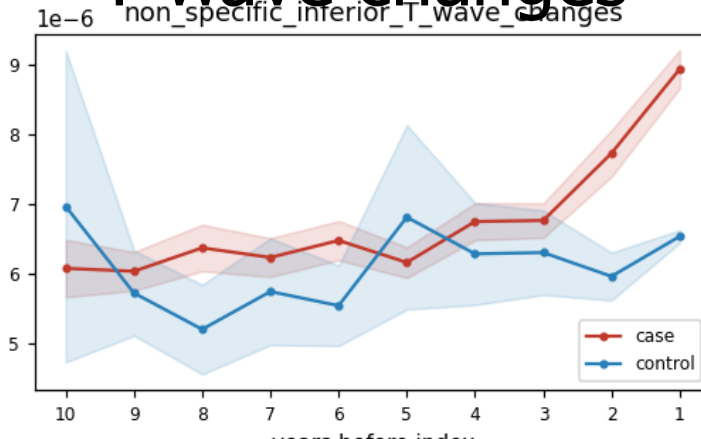
Accelerated junctional rhythm



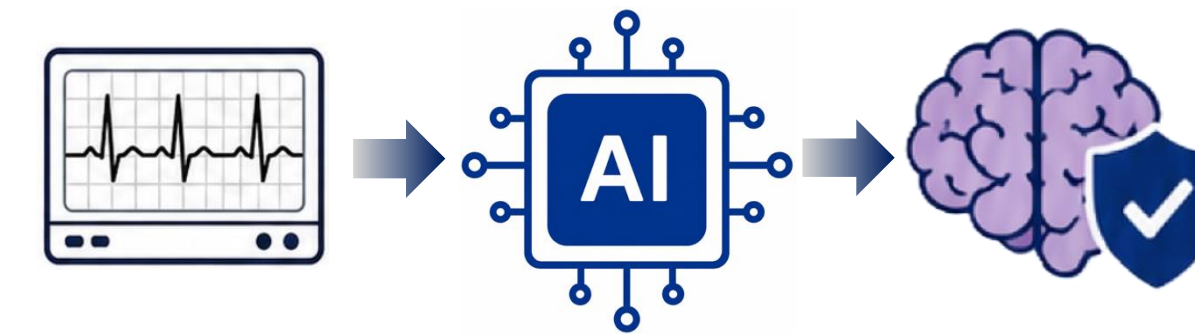
Atrial fibrillation



Non-specific inferior T wave changes



5. Conclusion



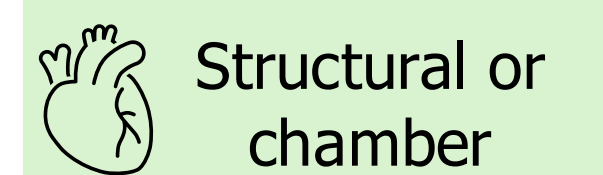
We identified **22** significant dementia-associated ECG phenotype labels, highlighting the **potential of ECG as an interpretable digital biomarker** for dementia.



Repolarization & ischemic



Rhythm & conduction



Structural or chamber



Global interpretation

Key signals were categorized into 1. repolarization and ischemic abnormalities, 2. rhythm and conduction abnormalities, 3. structural abnormalities, and 4. global ECG interpretation.

Reference

1. GBD 2019 Dementia Forecasting Collaborators (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet. Public health, 7(2), e105-e125.
2. Toyli, A., Shaik, A., Zhao, C., Chen, Q. H., Sha, Q., & Zhou, W. (2025). The heart-brain axis: unraveling the interconnections between cardiovascular and Alzheimer's diseases. Frontiers in cardiovascular medicine, 12, 1685461.
3. Imahori, Y., Vetrano, D. L., Ljungman, P., & Qiu, C. (2021). Electrocardiographic Predictors of Cognitive Decline and Dementia: A Systematic Review. Journal of Alzheimer's disease : JAD, 84(3), 1303-1322.

Acknowledgement

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