College of Human Medicine
MICHIGAN STATE UNIVERSITY

LUMBRITA

Stanford MEDICINE

Screening and Validating Drug Efficacy in MCI-to-AD Progression through EHR-Based Analysis

Nabasmita Talukdar, MS[1]; Zeshui Yu, PharmD[2], Xiaodan Zhang, MA[3], Zheng Zeng, MISM[4], Ying Lu, PhD[5], Hui Wang, PhD[4], Bin Chen, PhD*[1,3]
[1] Department of Biostatistics and Epidemiology, Michigan State University, [2] Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy,
[3] Department of Pediatrics and Human Development, Michigan State University, [4] Lumbrita LLC, [5] Department of Biomedical Data Science, Stanford University School of Medicine

INTRODUCTION

Alzheimer's disease (AD) affects over 6.9 million U.S. adults aged ≥65, with annual costs exceeding $360 billion[1]. Individuals with mild cognitive impairment (MCI) progress to AD at rates far higher than the general population, making them ideal for studying early therapeutic effects[2]. Despite over 570 proposed repurposed drugs (2012–2022), none identified through EHR-based studies have achieved clinical approval[3]. We applied an analytic framework to assess associations between medication use and MCI-to-AD progression, finding that many drugs appeared significant, highlighting the need for more rigorous, confounding-aware analyses to validate true therapeutic potential.

METHODS

Data Source: TRUVETA EHR Network with 351K MCI Total Population

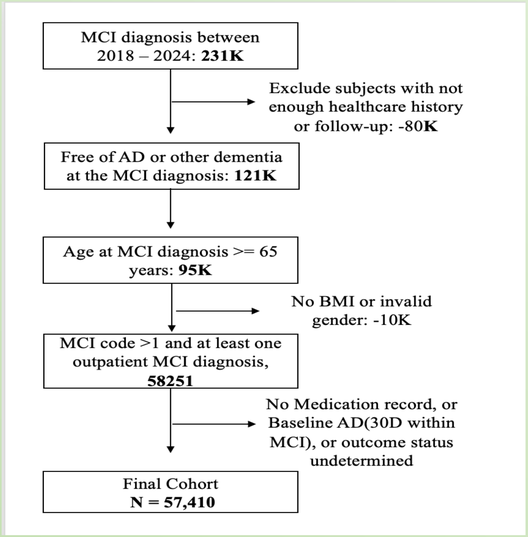
Drug selection: Candidates from review of EHR/RWE AD studies (2020-2024)[4]; combined by class; retained with adequate counts.

Outcome: Incident AD (ICD-10 G30 / ICD-9 331.0) after index; at least ≥ 2 code or ≥ 1 and exposure to approved drug

Covariates: Assessed within 1 year pre-index

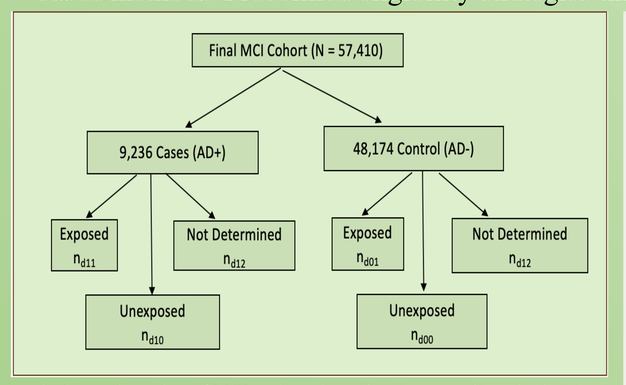
Exposure algorithms (per drug/class): Dispense/Request ≥ 2, or ≥1 & ≥15 total days supply; unexposed = no exposure anytime.

Design & Validation: Parallel **new-user** and **prevalent-user**. Temporal split into Discovery vs Validation by index year to mimic a real-world scenario.

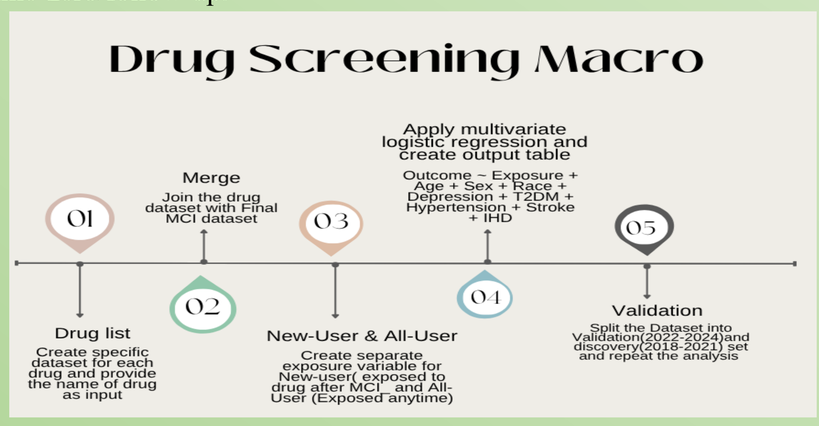


MCI Patient Selection Flowchart

- **Phase 1:** Identify and screen candidate drugs using logistic regression with temporal validation. Multivariate logistic regression; report OR and p-values in full, discovery, and validation sets.
- **Phase 2(Future Work):** Validate significant candidates using target trial emulation with propensity score-based methods. Predefined eligibility/strategies/time-zero/follow-up.

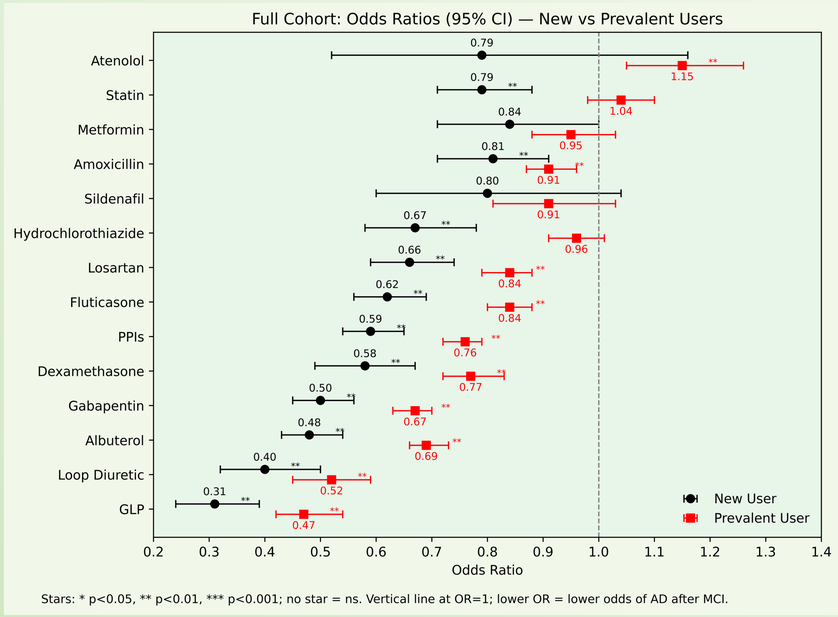


n_{dij} is the total number of MCI patients in each category; where d= drug1, drug2…, i =0/1 (Control/Case), j = 0/1/2 (Exposure status)



PRELIMINARY RESULTS

We analyzed 57,410 individuals with incident MCI (9,236 cases vs 48,174 controls; 57% female; 34% age 65-74, 46% 75-84). In Phase-1 screening, several drugs were significantly associated with lower odds of AD and replicated in the temporal split. Signals that agree across designs (new-user and prevalent-user) include albuterol, amoxicillin, dexamethasone, fluticasone, gabapentin, glucagon-like peptide agents, loop diuretics, losartan, and proton pump inhibitors; statin, and hydrochlorothiazide showed non-significance in prevalent-user. Statins, atenolol, metformin, and sildenafil were inconsistent.



The Discovery and Validation plots can be accessed using the QR code:

CONCLUSIONS

Our results are consistent with prior real-world studies but should be interpreted as preliminary screening signals rather than causal estimates. The widespread significance observed, raises concerns about false discoveries, underscoring the need for more rigorous analyses. Next, we will conduct target trial emulation with propensity score methods and balance diagnostics to adjust for confounding, quantify false discovery rates, and better characterize the association landscape for the promising candidates in phase 1.

REFERENCES

[1] 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024 May;20(5):3708-3821. doi: 10.1002/alz.13809. Epub 2024 Apr 30. PMID: 38689398; PMCID: PMC11095490.
[2] Boyle PA, Wilson RS, Aggarwal NT, et. al. Mild cognitive impairment: Risk of Alzheimer disease and rate of cognitive decline. *Neurology.* 2006;67(3):441-445. doi:10.1212/01.wnl.0000228244.10416.20
[3] Grabowska ME, Huang A, Wen Z, et. al. Drug repurposing for Alzheimer's disease from 2012–2022—a 10-year literature review. *Front Pharmacol.* 2023;14:1257700. doi:10.3389/fphar.2023.1257700
[4] Nabasmita T, Xiaodan Z, Shreya P, et. al., A survey of using EHR as real-world evidence for discovering and validating new drug indications. arXiv:2505.24767