

Differential Lifestyle and Metabolic Risk Factor Associations in Early- Versus Late-Onset Alzheimer's Disease in US Women

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BACKGROUND

- Women are disproportionately affected by Alzheimer's disease, accounting for a larger share of cases and often experiencing faster cognitive decline and a greater overall disease burden than men.
- Despite this higher burden, research on women-specific Alzheimer's disease risk factors has focused predominantly on late-onset Alzheimer's disease.
- Early-onset Alzheimer's disease in women remains comparatively understudied, particularly regarding potentially modifiable lifestyle and metabolic risk factors.
- This study used the Epic Cosmos database, a large U.S. electronic health record dataset, to examine risk-factor patterns among women with EOAD and LOAD.
- The study addresses this knowledge gap by identifying lifestyle and metabolic factors associated with EOAD in women and comparing them with patterns observed in LOAD.
- Understanding these distinct risk profiles may improve early identification, support targeted prevention strategies, and help reduce the disproportionate impact of Alzheimer's disease on women.

Study Objective:

To characterize and compare risk-factor and comorbidity profiles associated with early- versus late-onset Alzheimer's disease in women and to assess the robustness of these associations using age-matched controls and sensitivity analyses.

METHODS

Study Design and Data Source

Retrospective study of U.S.-based patients in the Epic Cosmos database. Epic Cosmos includes nearly 300 million patients from more than 1,700 hospital systems and 40,000 clinics across the United States and its territories. The study period was from January 1, 2020, to December 31, 2024.

Patient Selection

- Included patients were U.S. females with Alzheimer's disease, identified using ICD-10 code G30.
- G30 ICD 10 code validation criteria a) more than G30 code, b) Prescribed AD medications
- Controls were randomly selected from U.S. females without an Alzheimer's disease diagnosis.
- Cases and controls were exact matched 1:1 by age.

Exclusion Criteria

- Patients with conditions associated with rare or secondary forms of dementia were excluded.
- Exclusion diagnoses included cerebral palsy, Down syndrome, schizophrenia-spectrum disorders, and intellectual or learning disabilities.

EOAD and LOAD Definitions

- Early-onset Alzheimer's disease was defined as first documented AD before 65 years of age.
- Late-onset Alzheimer's disease was defined as first documented AD at 65 years of age or older.

Demographic Variables

- Age
- Sex
- Social Vulnerability Index

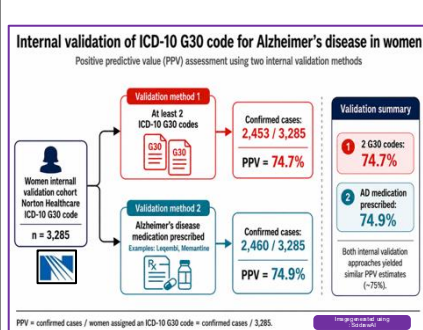
Group Comparisons

- McNemar's tests were used for categorical comparisons between EOAD or LOAD cases and their matched controls.
- Wilcoxon rank-sum tests were used for continuous-variable comparisons.

Regression Analysis

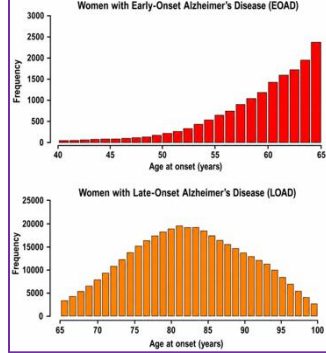
- Multivariable conditional logistic regression was performed separately for EOAD and LOAD cohorts and their matched controls.
- All recorded medical-history variables were included as predictors.
- Results were reported as adjusted odds ratios with 95% confidence intervals.
- Statistical significance was defined as $p < 0.05$.

ICD-10 Code Validation



Internal validation of the G30 ICD-10 code in 3,285 women yielded similar PPVs using two criteria: at least two G30 codes (74.7%) and AD medication use, including Leqembi or Mementine (74.9%). The close agreement between both approaches supports the reliability of the G30-based Alzheimer's disease case definition.

PATIENT CHARACTERISTICS

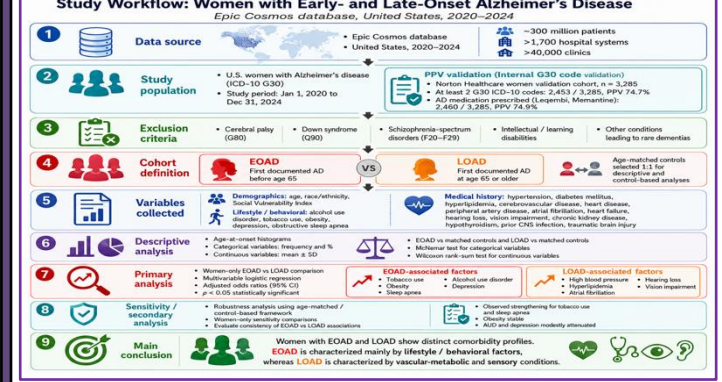


The figure shows the distribution of age at first documented Alzheimer's disease diagnosis in women, separated into early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD).

Patient Characteristics	Early Onset Alzheimer's Disease (EOAD) n=14612	Controls n=14612	p-value	Late Onset Alzheimer's Disease (LOAD) n=408618	Controls n=408618	p-value
White race (%)	98.44 (67.4)	97.93 (67.0)	0.533 (75.9)	30.9960 (7.5)	31.6574 (7.5)	<0.001
African American race (%)	21.79 (14.9)	18.74 (12.8)	<0.001	46.029 (11.3)	40.50 (9.3)	<0.001
Asian race (%)	32.8 (2.2)	70.4 (4.8)	<0.001	10.295 (2.5)	15.767 (3.9)	<0.001
Other race (%)	60.4 (4.1)	10.77 (7.4)	<0.001	12.179 (3.0)	15.767 (3.9)	<0.001
More than one race (%)	16.57 (11.3)	11.64 (8.0)	<0.001	30.155 (7.4)	23.318 (5.7)	<0.001
Hispanic (%)	12.99 (8.9)	17.61 (12.1)	<0.001	24.324 (6.0)	23.624 (5.8)	<0.001
Social Vulnerability Index, mean (SD)	0.56 (0.29)	0.55 (0.29)	0.182 (0.52)	0.53 (0.28)	0.53 (0.28)	<0.001

Table 1: Patient characteristics as shown in EOAD and LOAD. Patient characteristics were broadly similar between EOAD and LOAD cases and their age-matched controls, although several racial and ethnic distributions differed significantly. Differences were modest in absolute size, suggesting generally comparable cohorts.

OVERALL STUDY WORKFLOW



CONCLUSION & SUMMARY

- EOAD and LOAD showed distinct comorbidity profiles in women.
- EOAD was more strongly associated with tobacco use and obesity.
- Sleep apnea, alcohol use disorder, and depression were also more strongly associated with EOAD.
- LOAD showed stronger associations with high blood pressure, hyperlipidemia, atrial fibrillation, hearing loss, and vision impairment.
- Sensitivity analysis strengthened the associations for tobacco use and sleep apnea, while obesity remained stable.
- Alcohol use disorder and depression were modestly attenuated but remained more strongly associated with EOAD than LOAD.
- Conclusion: EOAD in women is characterized predominantly by lifestyle and metabolic associations, whereas LOAD is characterized more strongly by vascular-metabolic and sensory comorbidities.
- The persistence of these contrasting patterns across sensitivity analyses supports the overall robustness of the findings, although the magnitude of some individual associations changed.

LIMITATIONS

- Potential misclassification from ICD-10 coding: Reliance on the G30 Alzheimer's disease code and its subcodes may limit diagnostic specificity, although we have mitigated this limitation by internal PPV led validation.
- Residual confounding and limited clinical detail: The retrospective EHR design cannot fully account for unmeasured factors such as APOE genotype, family history, education, socioeconomic status, medication exposure, disease severity, healthcare utilization, or lifestyle intensity. Associations therefore should not be interpreted as causal.

FUTURE DIRECTIONS

- Validate the findings externally in independent health systems, non-U.S. cohorts, men, and more diverse racial and socioeconomic populations to test generalizability.
- Improve EOAD/LOAD phenotyping by combining G30 subcodes with chart review, cognitive assessments, biomarker data or utilizing LOINC codes.
- Use longitudinal designs to determine whether these risk factors precede EOAD diagnosis or emerge as consequences of prodromal disease.
- Investigate subgroup heterogeneity by race, ethnicity, age, menopause, socioeconomic status to identify vulnerable populations.
- Develop and validate prediction models that combine risk and demographic factors to distinguish EOAD from LOAD in women.

For Contact →

