The Journal of Prevention of Alzheimer's Disease 13 (2026) 100621

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Combined effect of anxiety disorder and insomnia on the risk of incident ADRD diagnosis

SangNam Ahn [a,b,*], Joanne Salas [c], Jinmyoung Cho [d], Jeffrey F. Scherrer [c,d,e,f]

[a] Department of Health Management and Policy, College for Public Health and Social Justice, Saint Louis University, Saint Louis, MO 63103, USA
[b] The Center for Community Health and Aging, School of Public Health, Texas A&M University, College Station, TX 77843, USA
[c] Advanced HEAlth Data (AHEAD) Research Institute, Saint Louis University School of Medicine, 3545 Lafayette Ave, 4th Floor, St. Louis, MO 63104, USA
[d] Department of Family and Community Medicine, Saint Louis University School of Medicine, 1008 S. Spring, St. Louis, MO 63110, USA
[e] Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine, 1438 South Grand Blvd., St. Louis, MO 63104, USA
[f] Department of Health and Clinical Outcomes Research, Saint Louis University School of Medicine, 3545 Lafayette Ave, 4th Floor, St. Louis, MO 63104, USA

ARTICLE INFO

Keywords:
Anxiety disorders
Insomnia
Alzheimer's disease and related dementias
TriNetX
Electronic health records (EHRs)
Entropy balancing
Retrospective cohort study

ABSTRACT

Background: Anxiety disorders and insomnia are common modifiable conditions in older adults, but their independent and combined effects on the risk of incident Alzheimer's disease and related dementias (ADRD) remain unclear.
Objectives: To estimate the independent and combined associations of anxiety disorders and insomnia with the risk of incident ADRD.
Design: Retrospective cohort study using an intention-to-treat approach with a 10-year follow-up period (2014–2023).
Setting: De-identified electronic health record (EHR) data from 70 participating healthcare organizations within the TriNetX Research Network.
Participants: Adults aged ≥50 years without prior dementia who had regular ambulatory care during a three-year baseline period (n = 1,868,790).
Measurements: Anxiety and insomnia were identified using ICD-based algorithms and categorized into four exposure groups: neither condition, anxiety only, insomnia only, and both. Incident ADRD was defined by two or more diagnostic codes within 12 months. Entropy balancing controlled for confounding, and weighted Cox proportional hazards models estimated hazard ratios (HRs).
Results: At baseline, 4.1% had anxiety only, 3.8% had insomnia only, and 1.1% had both. Over follow-up, 2.3% developed ADRD. In weighted models, insomnia alone (HR: 1.12; 95% CI: 1.06–1.19), anxiety alone (HR: 1.49; 95% CI: 1.39–1.60), and co-occurring anxiety and insomnia (HR: 1.31; 95% CI: 1.06–1.62) were each associated with higher ADRD risk compared with neither condition. No significant effect modification by age, sex, or race was observed.
Conclusions: Anxiety and insomnia independently increase ADRD risk, though insomnia's contribution is very modest compared to the primary association demonstrated by anxiety. Co-occurrence does not confer additional risk beyond anxiety alone. Clinically, routine screening and treatment of anxiety and sleep disturbances represent actionable, broadly applicable strategies for ADRD prevention and healthy cognitive aging.

1. Introduction

Alzheimer's disease and related dementias (ADRD) represent one of the most urgent public-health challenges in the United States. Current estimates indicate that about 7.4 million older adults are living with ADRD, a number projected to reach 13.8 million by 2060 in the absence of effective interventions [1–3]. The societal burden is substantial: annual medical and long-term care spending exceeds $409 billion, and unpaid caregiving contributes an additional $446.3 billion in economic value [3–5]. Although two FDA-approved disease-modifying therapies

* Corresponding author at: Department of Health Management and Policy, Saint Louis University College for Public Health and Social Justice, Saint Louis, MO, USA.
E-mail address: sangnam.ahn@slu.edu (S. Ahn).

https://doi.org/10.1016/j.tjpad.2026.100621
Received 13 April 2026; Received in revised form 20 May 2026; Accepted 1 June 2026
Available online 6 June 2026
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are now in clinical use for early-stage Alzheimer's disease, fully curative treatments do not yet exist. Consequently, the Lancet Commission emphasizes that risk-factor modification is the most viable pathway to reducing future dementia incidence, estimating that up to 40% of cases may be preventable [6,7]. Within this prevention framework, mental-health and sleep-related conditions—particularly anxiety disorders and insomnia—have emerged as promising, modifiable targets.

Anxiety and insomnia are especially compelling targets for dementia prevention research because they are highly prevalent, strongly interrelated, and frequently co-occur across adulthood. Population-based and clinical studies consistently show a bidirectional relationship, whereby anxiety disorders substantially increase the risk of persistent insomnia, and chronic insomnia independently predicts subsequent anxiety [8–10]. These conditions share core behavioral and neurophysiological mechanisms, including hyperarousal, dysregulated stress-system activity, and altered sleep–wake regulation, which may reinforce one another and promote chronic symptom trajectories [11]. Individuals with co-occurring anxiety and insomnia experience worse mental and physical health outcomes than those with either condition alone [12]. Despite their frequent co-occurrence and shared mechanisms, anxiety and insomnia are typically examined in isolation in dementia research, leaving their joint contribution to ADRD risk poorly understood.

A growing body of longitudinal research demonstrates that both anxiety disorders and insomnia are independently associated with increased risk of cognitive decline and incident dementia. Multiple meta-analyses show that clinically significant anxiety confers a higher risk of all-cause dementia independent of depression and vascular comorbidities, while large prospective cohorts across Europe, North America, and Asia consistently link anxiety symptoms, persistent anxiety trajectories, and chronic psychological distress to incident dementia over follow-up periods of 5–15 years [13–19]. Parallel evidence indicates that insomnia and sleep disturbances—including chronic insomnia, sleep-maintenance difficulty, fragmented sleep, and short sleep duration—are associated with faster cognitive decline and elevated ADRD risk [20–23]. Longitudinal studies further demonstrate that insomnia symptoms predict incident dementia and accelerated cognitive deterioration in older adults [20,23]. Importantly, both conditions are modifiable: improvements in anxiety through psychotherapy have been associated with reduced long-term dementia risk, [24] and cognitive behavioral therapy for insomnia (CBT-I) improves sleep and cognitive functioning in older adults, [25] underscoring anxiety and insomnia as actionable targets for dementia prevention rather than fixed or purely prodromal markers.

Despite strong evidence that anxiety and insomnia independently elevate dementia risk, almost no large-scale studies have examined their combined effects. Existing research on comorbid sleep and mental-health disorders has largely focused on depression plus insomnia. For example, a recent population-based work demonstrated that co-occurring insomnia and major depressive disorder substantially increased ADRD risk [26]. However, comparable investigations of anxiety plus insomnia—a clinically common and biologically intertwined combination—are lacking. This gap is consequential because anxiety and insomnia may act synergistically or additively to influence neurodegeneration, stress physiology, inflammation, and sleep-dependent brain clearance processes implicated in dementia pathogenesis.

Clarifying how anxiety and insomnia jointly influence ADRD risk also has significant health equity implications. Dementia incidence is disproportionately higher among Black, Hispanic, and low-income older adults, populations that also experience reduced access to mental-health care, sleep medicine services, and preventive interventions [27–29]. Women—who represent nearly two-thirds of dementia cases—report higher rates of anxiety and insomnia, particularly during midlife and older adulthood. Understanding whether the associations of anxiety and insomnia with ADRD risk differ by sex, age, or race/ethnicity is important for informing tailored prevention approaches and resource allocation.

To address these gaps, this study leverages a large, longitudinal electronic health record dataset to examine the combined impact of anxiety and insomnia on the risk of incident ADRD. Specifically, we aim to: (1) characterize the demographic and clinical factors of adults with comorbid anxiety and insomnia, (2) estimate both the independent and combined effects of anxiety and insomnia on ADRD incidence, and (3) evaluate whether these associations vary across racial, gender, and age groups. We hypothesize that individuals with both anxiety and insomnia will exhibit a higher risk of developing ADRD compared with those with either condition alone or neither, after accounting for sociodemographic and health-related confounders. We further anticipate stronger associations among women, racial minority groups, and older adults.

2. Methods

2.1. Data source: TriNetX research network

This retrospective cohort study used de-identified electronic health record (EHR) data from the TriNetX Research Network, downloaded on 8/9/24. The source dataset included 7,351,260 patients from 70 participating healthcare organizations who were aged ≥50 years as of 1/1/14, had at least one ambulatory visit during the baseline period (2011–2013), and had no indication of dementia (e.g., dementia diagnostic codes or dementia-related medications) prior to 1/1/14. Available data elements included demographics, diagnostic codes, visit-type information, prescription orders, procedure orders, and laboratory values. Approximately 70% of patients had clinical facts (e.g., encounters, pharmacy orders, diagnoses and procedures, laboratory results) spanning at least 5 years. This study utilized historical, de-identified electronic health records from the TriNetX Research Network. The Saint Louis University Institutional Review Board (IRB) formally reviewed the study protocol and data source (August 2, 2023) and issued an official determination that the activity does not constitute human subjects research under DHHS regulations, thereby exempting it from formal IRB submission and approval.

2.2. Eligibility

This retrospective cohort analysis used TriNetX EHR data from 2011–2023 and applied an intention-to-treat (ITT) design (see Fig. 1). In this retrospective setting, the ITT approach classifies patients based on exposure status at the start of follow-up (the index/baseline date) and analyzes outcomes accordingly, even if exposure status changes during follow-up. McCoy (2017) notes that this approach may attenuate estimated effects, but it is generally less biased than per-protocol analyses in observational cohorts [30].

The index date was January 1, 2014 (1/1/14), and follow-up extended for 10 years (2014–2023). The baseline period (2011–2013) was used to measure exposures and covariates (see Figure 2). From the 7.3 million patients without dementia at baseline, we required at least one ambulatory visit in each baseline year to identify regular healthcare users (n = 2,206,666). To support biologically plausible exposure accumulation and reduce potential prodromal bias, we additionally required more than 90 days of follow-up (n = 2,106,073). After excluding patients with missing key demographic information (e.g., sex, race, or region), the final analytic sample included 1,868,790 patients.

2.3. Variable definitions

Detailed definitions for all study variables are provided in the Appendix (e-Table 1).

Exposure: Insomnia was defined by the presence of at least one ICD diagnostic code during the baseline period. Anxiety disorders were defined as a composite of panic disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder, posttraumatic stress disorder, and anxiety not otherwise specified. Anxiety was identified by

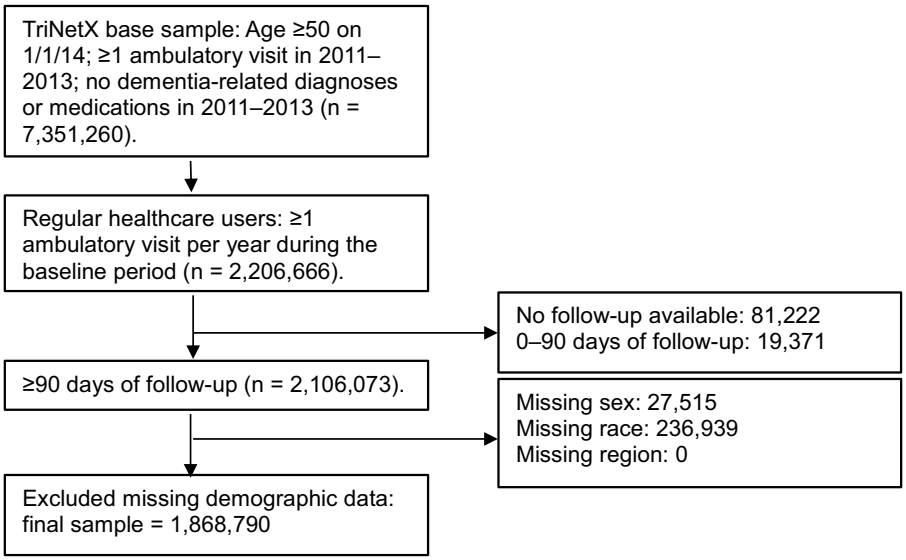


Fig. 1. Sampling Scheme.

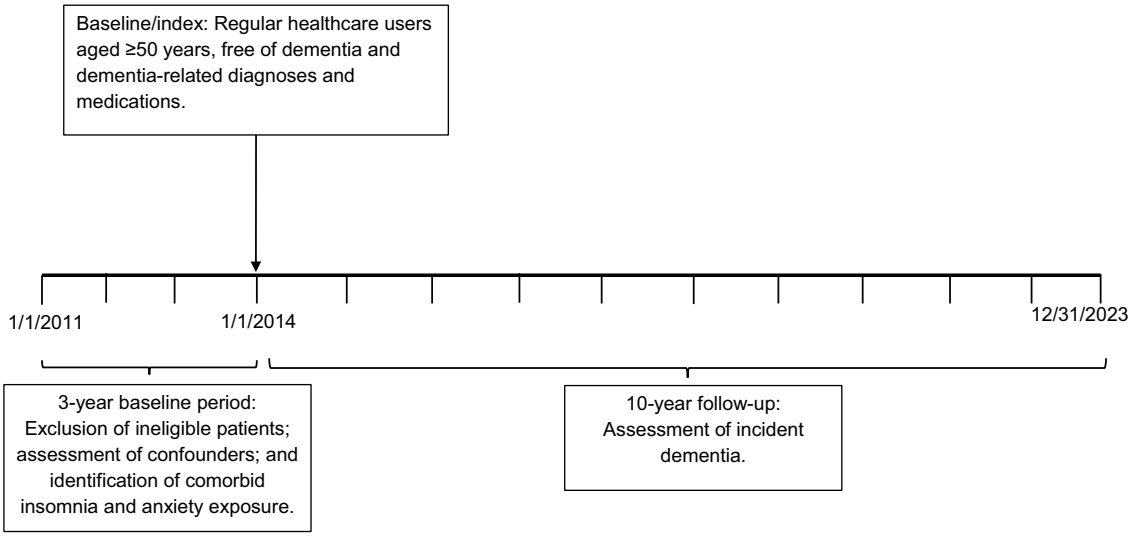


Fig. 2. Study Design – Retrospective cohort.

either at least two diagnostic code occurrences on separate outpatient visit days within a 12-month period or one inpatient hospitalization, a commonly used and validated approach for identifying mental health conditions in administrative and EHR data [31,32]. Based on ICD diagnostic codes present during the baseline period (2011–2013), participants were classified into a four-group exposure variable: (a) neither anxiety nor insomnia (n = 1,701,085; 91.0%); (b) anxiety only (n = 77,062; 4.1%); (c) insomnia only (n = 71,010; 3.8%); and (d) co-occurring anxiety and insomnia (n = 19,633; 1.1%). As a sensitivity analysis reflecting DSM-5 reclassification, anxiety was alternatively defined excluding posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD), and all primary models were re-estimated using this alternative definition.

Outcome: Incident dementia during the 10-year follow-up period was defined by the presence of dementia-related diagnostic codes on at least two separate days within any 12-month period, and the date of the first qualifying diagnostic code was used to define dementia onset. This EHR-based case-finding algorithm demonstrates good agreement with standardized cognitive assessments, including the Mini–Mental State Examination (MMSE) and the Saint Louis University Mental Status (SLUMS) Examination, indicating at least mild dementia [33]. This dementia identification approach has been successfully applied and validated in multiple prior studies using administrative and EHR data [34–39].

Follow-up time: Follow-up time was defined as the number of months from the index date (January 1, 2014) to incident dementia diagnosis or censoring. Participants who did not develop dementia were censored at the date of their last recorded clinical encounter during the follow-up period, ensuring that follow-up reflected active observation within the healthcare system.

Covariates: Covariates were selected a priori based on established dementia risk-factor frameworks and disparities literature, as well as known correlates of anxiety and insomnia that could confound associations in EHR-based cohorts [6,7]. Demographic covariates included age at baseline/index (50–64, 65–74, ≥75), sex (male, female), race (White, Black, Asian, other), and U.S. Census–based region (Midwest, Northeast, South, West, Outside the U.S.), because dementia risk, healthcare access, and diagnostic pathways vary systematically across these strata and contribute to documented inequities in detection and outcomes [6,7,28]. To mitigate potential detection (ascertainment) bias inherent in

real-world EHR data—where greater healthcare contact increases opportunities for symptom documentation and diagnosis—we adjusted for baseline healthcare utilization by dichotomizing the mean number of outpatient/ambulatory visits per month during 2011–2013 into high (>75th percentile) versus low utilization.

All remaining covariates were measured during the 3-year baseline period (2011–2013) and were defined by the presence of diagnostic codes, prescription orders, or procedure codes, unless otherwise specified. Physical comorbidities included type 2 diabetes, obesity, hypertension, stroke, ischemic heart disease, congestive heart failure, atrial fibrillation, asthma, chronic obstructive pulmonary disease (COPD), sleep apnea, traumatic brain injury, vitamin B12 deficiency, and cancer. Psychiatric comorbidities included depression—identified using an algorithm analogous to anxiety—as well as bipolar disorder and schizophrenia. We also controlled for psychotherapy utilization, identified using CPT (Current Procedural Terminology) codes. Substance use disorders included alcohol abuse or dependence, drug abuse or dependence, and nicotine dependence. Finally, we adjusted for sustained medication use (defined as ≥2 prescription orders within any 6-month period) of non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensives, statins, steroids, antivirals, metformin, sulfonylureas, antidepressants, atypical antipsychotics, and benzodiazepines. These medication classes were included to reduce confounding by indication, as they proxy underlying cardiometabolic and inflammatory disease burden and psychiatric symptom severity—factors independently associated with cognitive outcomes and dementia risk—and because several have been linked to ADRD-related outcomes in prior pharmacoepidemiologic and clinical studies [40–43].

Analytic approach. Entropy balancing (e-balance) was used to control for confounding across the four anxiety/insomnia exposure groups [44]. Entropy balancing is a data-driven, multivariate reweighting procedure applied during data preprocessing that assigns a weight to each individual such that prespecified balance constraints are satisfied while minimizing information loss. Specifically, the method generates weights so that selected covariate moments (e.g., means, variances, or full distributions) are equalized across exposure groups, and the entropy distance between the resulting weights and uniform weights (the inverse of the sample size) is minimized. When these balance constraints are achieved, systematic differences between groups attributable to measured covariates are effectively eliminated, and the weighted sample approximates the covariate balance expected under successful randomization. Compared with commonly used approaches such as propensity score matching or inverse probability of exposure weighting, entropy balancing often achieves superior and more stable covariate balance because it does not rely on correct specification of a propensity score model or iterative balance diagnostics [44]. After application of entropy-balancing weights, subsequent analyses compare exposure groups as if they were drawn from a pseudo-population with balanced baseline characteristics. We used the WeightIt package in R version 4.2.2 to generate entropy-balancing weights. Covariate balance before and after weighting was assessed using the standardized mean difference percent (SMD% = 100 × SMD), an effect-size measure that is independent of sample size. Adequate balance was defined a priori as an SMD% <10% for all covariates and all pairwise exposure-group comparisons [45]. The maximum SMD% across any pairwise comparison was used to summarize overall balance.

All primary statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC), with a two-tailed alpha level of 0.05. Baseline differences in covariates across exposure groups were evaluated using chi-square tests. Descriptive incidence estimates in unweighted data were reported as cumulative incidence over the 10-year follow-up period and as incidence rates per 10,000 person-years (PY). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals for the association between anxiety/insomnia exposure group and incident dementia, both before and after application of entropy-balancing weights. Weighted models employed robust sandwich variance estimators to obtain valid standard errors and confidence intervals under weighting [45]. The proportional hazards assumption was evaluated in all models using the ZPH option in PROC PHREG and was satisfied for all analyses ($p > 0.05$).

To assess potential effect modification, weighted Cox models were stratified by race (White, Black, Asian), sex (male, female), and age group (50–64, 65–74, ≥75 years). Entropy balancing was repeated within each stratum to ensure covariate balance in stratified analyses. In addition, effect heterogeneity was formally tested by including interaction terms between each demographic variable and the four-level anxiety/insomnia exposure variable in separate overall weighted models; a two-sided p-value <0.05 was considered evidence of statistically significant effect modification. Several sensitivity analyses were conducted to evaluate the robustness of findings. First, analyses were repeated after excluding the 48,862 individuals whose care was recorded as occurring outside the United States, and overall weighted effect estimates were re-estimated. Second, anxiety was redefined excluding PTSD and OCD to reflect DSM-5 reclassification, and both crude and entropy-balanced Cox models were re-estimated using this alternative exposure definition.

3. Results

As shown in Table 1, the cohort was predominantly younger than 65 years (58.3%), female (58.9%), and White (81.6%), with most patients receiving care in the Northeastern United States (37.0%); only 2.6% were from healthcare organizations outside the U.S. Baseline characteristics differed substantially across anxiety/insomnia exposure groups. Compared with patients with neither condition, those with anxiety, insomnia, or both were more likely to be aged 50–64 years and female (maximum SMD% = 20.1% and 25.6%, respectively). High healthcare utilization was markedly more common among the comorbid anxiety–insomnia group (59.0%; SMD% = 76.3%), followed by anxiety only and insomnia only groups.

Nearly all physical comorbidities—including cardiometabolic, respiratory, neurologic, and sleep-related conditions—were more prevalent among patients with anxiety and/or insomnia than among those with neither condition (SMD% range = 14.2%–49.4%), with the largest differences observed for hypertension, obesity, sleep apnea, asthma, and COPD. Psychiatric comorbidities showed the greatest imbalance across groups, particularly depression (SMD% = 94.6%), bipolar disorder (32.1%), and substance use disorders, which were most prevalent among patients with co-occurring anxiety and insomnia. Patterns of medication use mirrored these clinical differences: sustained use of psychotropic and cardiometabolic medications—including antidepressants, benzodiazepines, antihypertensives, and steroids—was highest in the anxiety+insomnia group, indicating substantially greater baseline clinical complexity.

Overall median follow-up time (time to incident dementia or censoring) was 110 months (IQR, 79–119). Median follow-up was similar across exposure groups: 109 months (IQR, 79–119) for those with neither anxiety nor insomnia, 113 months (IQR, 80–120) for anxiety only, 114 months (IQR, 85–120) for insomnia only, and 113 months (IQR, 78–120) for comorbid anxiety and insomnia. During 10 years of follow-up, 42,234 participants (2.3%) developed incident dementia, corresponding to an overall incidence rate of 28.8 per 10,000 PY. Dementia incidence was lowest among individuals with neither anxiety nor insomnia (27.6 per 10,000 PY), higher among those with insomnia only (36.7 per 10,000 PY), and highest among those with anxiety only (44.9 per 10,000 PY) and comorbid anxiety and insomnia (43.6 per 10,000 PY). Similar gradients were observed across race, sex, and age strata (Table 2).

Table 3 presents overall associations before and after entropy-balancing to control for confounding. In crude (unweighted) models, compared with patients without anxiety or insomnia, insomnia alone was associated with a 32% higher risk of dementia (HR = 1.32; 95% CI =

Table 1
Demographic and baseline characteristics overall and by anxiety[a] and insomnia status at baseline (n = 1,868,790)*.

Covariates, n(%)	Overall (n = 1,868,790)	No Anxiety -insomnia (n = 1,701,085)	Anxiety only (n = 77,062)	Insomnia only (n = 71,010)	Anxiety + insomnia (n = 19,633)	Max SMD%
Age category						
50-64	1090151 (58.3)	982402 (57.8)	50807 (65.9)	43711 (61.6)	13231 (67.4)	20.1
65-74	573235 (30.7)	527871 (31.0)	20109 (26.1)	20377 (28.7)	4878 (24.8)	13.8
≥ 75	205404 (11.0)	190812 (11.2)	6146 (8.0)	6922 (9.7)	1524 (7.8)	12.0
Female gender	1100443 (58.9)	988322 (58.1)	52875 (68.6)	45462 (64.0)	13784 (70.2)	25.6
Race						
White	1524479 (81.6)	1387193 (81.5)	63869 (82.9)	56990 (80.3)	16427 (83.7)	8.9
Black	200703 (10.7)	183912 (10.8)	7191 (9.3)	7833 (11.0)	1767 (9.0)	6.8
Asian	91078 (4.9)	81338 (4.8)	4314 (5.6)	4452 (6.3)	974 (5.0)	6.6
Other	52530 (2.8)	48642 (2.9)	1688 (2.2)	1735 (2.4)	465 (2.4)	4.3
Region						
Outside US	48862 (2.6)	41693 (2.5)	3492 (4.5)	2941 (4.1)	736 (3.7)	11.0
Midwest	475603 (25.5)	430180 (25.3)	20728 (26.9)	19528 (27.5)	5167 (26.3)	5.0
Northeast	692446 (37.0)	644726 (37.9)	22895 (29.7)	19648 (27.7)	5177 (26.4)	25.2
South	517747 (27.7)	461171 (27.1)	26326 (34.2)	23102 (32.5)	7148 (36.4)	19.9
West	134132 (7.2)	123315 (7.2)	3621 (4.7)	5791 (8.2)	1405 (7.2)	13.7
High healthcare utilization	463512 (24.8)	382742 (22.5)	37382 (48.5)	31814 (44.8)	11574 (59.0)	76.3
Type II Diabetes	259704 (13.9)	225853 (13.3)	15517 (20.1)	14324 (20.2)	4010 (20.4)	18.5
Obesity	193560 (10.4)	160115 (9.4)	16010 (20.8)	12879 (18.1)	4556 (23.2)	36.3
Hypertension	758981 (40.6)	658002 (38.7)	47535 (61.7)	41118 (57.9)	12326 (62.8)	49.4
Stroke	33131 (1.8)	27470 (1.6)	2745 (3.6)	2119 (3.0)	797 (4.1)	14.2
Ischemic heart disease	211417 (11.3)	184672 (10.9)	13207 (17.1)	10024 (14.1)	3514 (17.9)	19.8
Congestive heart failure	73189 (3.9)	61695 (3.6)	5687 (7.4)	4165 (5.9)	1642 (8.4)	19.5
Atrial fibrillation	95555 (5.1)	84927 (5.0)	5177 (6.7)	4112 (5.8)	1339 (6.8)	7.6
Asthma	115558 (6.2)	92786 (5.5)	11114 (14.4)	8302 (11.7)	3356 (17.1)	35.9
COPD	87136 (4.7)	68557 (4.0)	9643 (12.5)	6091 (8.6)	2845 (14.5)	35.3
Sleep apnea	119043 (6.4)	94413 (5.6)	9676 (12.6)	11468 (16.1)	3486 (17.8)	36.6
Traumatic brain injury	24831 (1.3)	19257 (1.1)	2916 (3.8)	1751 (2.5)	907 (4.6)	20.5
Vitamin B12 deficiency	26795 (1.4)	21023 (1.2)	2464 (3.2)	2470 (3.5)	1018 (5.2)	22.3
Cancer	278058 (14.9)	248503 (14.6)	13356 (17.3)	12622 (17.8)	3577 (18.2)	9.6
Depression	109137 (5.8)	64674 (3.8)	24600 (31.9)	11723 (16.5)	8140 (41.5)	94.6
Bipolar disorder	22870 (1.2)	15163 (0.9)	4513 (5.9)	1778 (2.5)	1416 (7.2)	32.1
Schizophrenia	9239 (0.5)	7162 (0.4)	1301 (1.7)	488 (0.7)	288 (1.5)	12.4
Psychotherapy use	14943 (0.8)	6562 (0.4)	5839 (7.6)	914 (1.3)	1628 (8.3)	39.2
Nicotine dependence	170441 (9.1)	134483 (7.9)	18750 (24.3)	11744 (16.5)	5464 (27.8)	51.6
Alcohol abuse/ dependence	29213 (1.6)	20733 (1.2)	4684 (6.1)	2371 (3.3)	1425 (7.3)	29.4
Drug abuse/dependence	22108 (1.2)	13829 (0.8)	4542 (5.9)	2064 (2.9)	1673 (8.5)	37.4
NSAIDs[b]	206273 (11.0)	167606 (9.9)	18230 (23.7)	14752 (20.8)	5685 (29.0)	47.8
Antihypertensives[b]	573360 (30.7)	496615 (29.2)	36617 (47.5)	30405 (42.8)	9723 (49.5)	41.7
Statins[b]	311882 (16.7)	269108 (15.8)	20019 (26.0)	17403 (24.5)	5352 (27.3)	27.2
Steroids[b]	234801 (12.6)	194092 (11.4)	18853 (24.5)	15912 (22.4)	5944 (30.3)	46.1
Antivirals[b]	39365 (2.1)	31598 (1.9)	3324 (4.3)	3230 (4.5)	1213 (6.2)	21.5
Metformin[b]	91285 (4.9)	78914 (4.6)	5624 (7.3)	5258 (7.4)	1489 (7.6)	11.8
Sulfonylurea[b]	48916 (2.6)	42586 (2.5)	2826 (3.7)	2812 (4.0)	692 (3.5)	8.0
Antidepressant medications[b]	197060 (10.5)	133842 (7.9)	32859 (42.6)	19846 (27.9)	10513 (53.5)	104.3
Atypical antipsychotics[b]	19615 (1.1)	11781 (0.7)	4731 (6.1)	1528 (2.2)	1575 (8.0)	36.7
Benzodiazepines[b]	145794 (7.8)	91630 (5.4)	30236 (39.2)	13954 (19.7)	9974 (50.8)	108.8

Notes: SMD (%) = standardized mean difference (percent).

* All comparisons were statistically significant ($p < 0.0001$).

[a] Anxiety disorders included panic disorder, obsessive–compulsive disorder (OCD), social phobia, generalized anxiety disorder (GAD), anxiety disorder not otherwise specified (NOS), and post-traumatic stress disorder (PTSD).

[b] Medications were defined as sustained use prior to the index date (≥2 prescription orders within any 6-month period).

1.26–1.38), while anxiety alone (HR = 1.62; 95% CI = 1.56–1.68) and co-occurring anxiety and insomnia (HR = 1.57; 95% CI = 1.46–1.70) were each associated with approximately 60% higher risk. After entropy-balancing, effect estimates were attenuated but remained statistically significant. In weighted models, insomnia alone was associated with a 12% higher dementia risk (HR = 1.12; 95% CI = 1.06–1.19), anxiety alone with a 49% higher risk (HR = 1.49; 95% CI = 1.39–1.60), and co-occurring anxiety and insomnia with a 31% higher risk (HR = 1.31; 95% CI = 1.06–1.62), compared with individuals with neither condition.

E-tables 3 to 5 show results stratified by race, sex and age. Results showed no heterogeneity of effects among any demographic variable (all interaction p-values > 0.05). Finally, e-table 6 shows overall weighted models among the 1,819,928 patients in the sample from only US healthcare organizations; hazard ratio estimates were nearly identical to the overall sample. Finally, e-Table 7 presents crude and entropy-balance–weighted hazard ratios estimating the association of insomnia and anxiety with incident ADRD after excluding PTSD and OCD from the anxiety definition. Findings were consistent with the primary model, with modest attenuation for the anxiety-only group (weighted HR = 1.43; 95% CI = 1.32–1.55) and the co-occurring anxiety and insomnia group (weighted HR = 1.24; 95% CI = 1.01–1.55).

4. Discussions

In this large cohort, anxiety and insomnia were each independently associated with increased ADRD risk. Patients with both anxiety and insomnia experience the greatest clinical and healthcare burden,

Table 2
Dementia events - cumulative incidence % and incidence rate per 10,000 person-years (PY), patients ≥ 50 years old (n = 1,868,790).

Group	Total n	Dementia events	Cumulative incidence %	Incidence rate per 10,000PY
Overall	*1868790*	*42234*	*2.3%*	*28.8/10,000PY*
No anxiety or insomnia	1701085	36719	2.2%	27.6/10,000PY
Anxiety only	77062	2740	3.6%	44.9/10,000PY
Insomnia only	71010	2103	3.0%	36.7/10,000PY
Anxiety + Insomnia	19633	672	3.4%	43.6/10,000PY
White race	*1524479*	*32749*	*2.2%*	*27.3/10,000PY*
No anxiety or insomnia	1387193	28546	2.1%	26.2/10,000PY
Anxiety only	63869	2148	3.4%	42.5/10,000PY
Insomnia only	56990	1532	2.7%	33.3/10,000PY
Anxiety + Insomnia	16427	523	3.2%	40.6/10,000PY
Black race	*200703*	*5639*	*2.8%*	*36.1/10,000PY*
No anxiety or insomnia	183912	5005	2.7%	35.0/10,000PY
Anxiety only	7191	274	3.8%	47.7/10,000PY
Insomnia only	7833	292	3.7%	45.9/10,000PY
Anxiety + Insomnia	1767	68	3.8%	48.4/10,000PY
Asian race	*91078*	*2855*	*3.1%*	*39.1/10,000PY*
No anxiety or insomnia	81338	2271	2.8%	34.8/10,000PY
Anxiety only	4314	274	6.3%	81.0/10,000PY
Insomnia only	4452	235	5.3%	66.5/10,000PY
Anxiety + Insomnia	974	75	7.7%	97.3/10,000PY
Male gender	*768347*	*16925*	*2.2%*	*28.8/10,000PY*
No anxiety or insomnia	712763	15234	2.1%	28.0/10,000PY
Anxiety only	24187	762	3.2%	40.7/10,000PY
Insomnia only	25548	733	2.9%	36.6/10,000PY
Anxiety + Insomnia	5849	196	3.4%	44.1/10,000PY
Female gender	*1100443*	*25309*	*2.3%*	*28.8/10,000PY*
No anxiety or insomnia	988322	21485	2.2%	27.2/10,000PY
Anxiety only	52875	1978	3.7%	46.7/10,000PY
Insomnia only	45462	1370	3.0%	36.8/10,000PY
Anxiety + Insomnia	13784	476	3.5%	43.3/10,000PY
Age 50-64	*1090151*	*7665*	*0.7%*	*8.6/10,000PY*
No anxiety or insomnia	982402	6388	0.7%	8.0/10,000PY
Anxiety only	50807	678	1.3%	16.4/10,000PY
Insomnia only	43711	434	1.0%	12.0/10,000PY
Anxiety + Insomnia	13231	165	1.3%	15.5/10,000PY
Age 65-74	*573235*	*19344*	*3.4%*	*43.9/10,000PY*
No anxiety or insomnia	527871	16845	3.2%	41.6/10,000PY
Anxiety only	1235	1235	6.1%	79.6/10,000PY
Insomnia only	955	955	4.7%	59.1/10,000PY
Anxiety + Insomnia	309	309	6.3%	83.1/10,000PY
Age ≥75	*205404*	*15225*	*7.4%*	*109.7/10,000PY*
No anxiety or insomnia	190812	13486	7.1%	104.8/ 10,000PY
Anxiety only	6146	827	13.5%	198.6/ 10,000PY
Insomnia only	6922	714	10.3%	146.4/ 10,000PY
Anxiety + Insomnia	1524	198	13.0%	189.5/ 10,000PY

Note: PY = person-years.

Table 3
Results from cox proportional hazard models estimating the association of anxiety and insomnia on incident dementia (n = 1,868,790).

Group	Model 1 – Crude/unweighted Crude HR (95%CI)	Model 2 – Weighted Weighted HR (95%CI)
No anxiety or insomnia	1.00	1.00
Anxiety only	1.62 (1.56-1.68)	1.49 (1.39-1.60)
Insomnia only	1.32 (1.26-1.38)	1.12 (1.06-1.19)
Anxiety + insomnia	1.57 (1.46-1.70)	1.31 (1.06-1.62)

Note: HR = hazard ratio; CI = confidence interval.

demonstrated by substantially higher healthcare utilization (59%) and elevated rates of depression, cardiometabolic and respiratory conditions, traumatic brain injury, substance-use disorders, and extensive psychotropic and medical treatment use compared with those with only anxiety or only insomnia. This comorbid group represents the most medically and psychiatrically complex subgroup, requiring disproportionately greater clinical resources and care intensity across the healthcare system. To our knowledge, only one prior study has examined the combined effect of anxiety and insomnia, showing worse cognitive function but not ADRD risk, underscoring the gap our study addresses [46]. A comparable large-scale study on ADRD risk has only examined the combined effect of insomnia and major depressive disorder, [26] making our focus on insomnia and anxiety a distinct and novel contribution.

Contrary to our hypothesis, the co-occurrence of anxiety and insomnia did not confer a higher risk of ADRD than anxiety alone, despite this subgroup exhibiting the greatest clinical and psychiatric burden. Anxiety demonstrated a substantially stronger independent association with neurodegenerative risk pathways than insomnia, which may explain this pattern. Anxiety has been closely linked to HPA-axis dysregulation, glucocorticoid-related hippocampal vulnerability, and chronic stress–induced neuroinflammation, mechanisms consistently implicated in Alzheimer's disease [47–49]. Insomnia contributes to ADRD risk primarily through impaired glymphatic clearance of neurotoxic proteins—including β-amyloid and tau—and through sleep--fragmentation–related inflammation [50–52]. Because these biological pathways overlap substantially, the presence of insomnia may not add measurable risk beyond that already captured by anxiety-related mechanisms. Additionally, although patients with co-occurring anxiety and insomnia exhibited higher baseline comorbidity, psychotropic medication use, and healthcare utilization, entropy balancing effectively eliminated these differences across exposure groups. As a result, residual differences in clinical burden were unlikely to explain variation in ADRD risk in weighted models. This pattern is consistent with our prior population-based study of comorbid insomnia and major depressive disorder, in which depression emerged as the dominant driver of ADRD risk and the addition of insomnia did not meaningfully alter effect estimates beyond the primary psychiatric condition [26]. Finally, the relatively small size of the comorbid subgroup (1.1% of the cohort) limited statistical power to detect modest interaction effects. Together, these biological overlap and methodological considerations likely contributed to the absence of a detectable combined effect.

Notably, the association for insomnia was more modest than that reported in several prior studies. This attenuation is plausibly explained by underascertainment of insomnia in EHRs when relying on billing codes, which can preferentially capture more severe or clinically recognized cases and bias estimates toward the null. In addition, our baseline-only exposure definition and weighting approach may have reduced residual differences in clinical burden across groups, limiting the ability to detect incremental risk attributable to insomnia when anxiety was already present.

These findings underscore the importance of treating anxiety and insomnia as independent prevention targets for ADRD. In weighted analyses, anxiety alone was associated with a 49% higher risk of ADRD, while insomnia alone conferred a 12% higher risk compared with individuals with neither condition. Although individuals with both anxiety and insomnia exhibited substantial clinical complexity, their ADRD risk did not exceed that of the anxiety-only group, suggesting that each condition contributes distinct but not multiplicative associations with ADRD risk. An alternative interpretation is that insomnia may partially lie along the causal pathway linking anxiety to neurodegeneration, such that its contribution is partly captured within the anxiety–ADRD association rather than producing an independent incremental effect in the comorbid group. This interpretation is consistent with accumulating evidence that anxiety and sleep disturbances in mid- to late life are linked to overlapping neurobiological processes, including HPA-axis dysregulation, neuroinflammation, and impaired glymphatic clearance [48–50,52]. Importantly, studies indicate that effective treatment of anxiety and insomnia may improve cognitive trajectories or reduce dementia risk, providing further rationale for early intervention [25,53–55]. Evidence-based strategies—including psychotherapy and pharmacologic treatment for anxiety and cognitive behavioral therapy for insomnia (CBT-I)—have demonstrated benefits for cognitive performance in older adults. Thus, even if insomnia functions partly as a mediator rather than an independent risk factor, clinical management of both conditions remains a promising and actionable avenue for dementia prevention.

Importantly, we did not observe meaningful variation in the associations of anxiety or insomnia with ADRD risk across age, sex, or race. This consistency suggests that these conditions act as broadly relevant risk indicators rather than factors whose effects differ by demographic subgroup. Prior research similarly shows that the cognitive consequences of anxiety and sleep disturbance are observed across diverse populations, with limited evidence of demographic modification in their longitudinal associations with cognitive decline [13,52,55,56]. Although ADRD prevalence and progression vary substantially by demographic group due to social, structural, and life-course factors, [27–29,57] our findings imply that the relative impact of anxiety and insomnia on dementia risk is comparable across populations. Accordingly, equitable identification and treatment of these conditions—regardless of demographic characteristics—remain important components of dementia prevention efforts.

Several limitations should be considered. First, reliance on ICD-9/ICD-10 diagnostic codes to identify insomnia likely resulted in exposure misclassification, as insomnia is substantially underdetected in routine clinical documentation. In a large EHR validation study, only 17% of patients with physician-documented insomnia symptoms carried an insomnia billing code [58]. We nonetheless relied on diagnostic codes because validated insomnia case-finding algorithms that incorporate structured symptom measures, sleep questionnaires, or actigraphy are not consistently available across large, multi-system EHR networks, and diagnostic codes represent the most feasible and reproducible approach for population-level surveillance studies. Importantly, this underascertainment likely biases estimates toward the null, suggesting our findings may underestimate true associations.

Second, the comorbid anxiety–insomnia subgroup represented only 1.1% of the cohort, limiting statistical power to detect synergistic or interaction effects despite the large sample size. Third, although our intention-to-treat design and baseline exposure assessment—along with exclusion of patients with dementia at baseline and a minimum follow-up requirement—were intended to reduce bias from prodromal neurodegeneration, some degree of misclassification may remain. Anxiety symptoms have been shown to precede overt cognitive decline and may represent early behavioral manifestations of emerging dementia, [13] and sleep–wake disturbances are well-established early features of Alzheimer-related neurophysiology that can occur years before clinical diagnosis [59]. Thus, while our design likely mitigates reverse causation, residual prodromal effects cannot be fully excluded and may attenuate causal inference.

Fourth, although entropy balancing minimized measured confounding—including the baseline use of critical psychotropic medications such as antidepressants, atypical antipsychotics, and benzodiazepines—residual confounding from unmeasured factors persists. Most notably, the TriNetX dataset does not capture genetic markers such as the APOE ε4 genotype, a primary risk factor for Alzheimer's disease. Furthermore, a detailed longitudinal evaluation of incident medication use (including the specific type, dosage, and length of use of anxiolytics and hypnotics) initiated after the baseline period to treat these disorders was beyond the scope of this study. Future research should evaluate how sustained pharmacological management alters these risk trajectories.

Fifth, our reliance on retrospective EHR diagnostic codes limits the precision of our outcome measure. The validated case-finding algorithm we employed effectively captures all-cause ADRD but does not reliably differentiate between specific dementia subtypes, such as Alzheimer's disease versus vascular dementia. This is primarily due to the high prevalence of 'unspecified dementia' diagnostic coding in routine, real-world clinical practice and the inherent validity challenges of isolating pure vascular etiologies within administrative health networks. Because anxiety and insomnia may exert differential effects on distinct neurodegenerative and microvascular pathways, our combined ADRD outcome may mask subtype-specific associations. For instance, if anxiety is a more potent driver of tau pathology than vascular burden, utilizing a combined ADRD outcome may underestimate the specific impact of anxiety on Alzheimer-type pathology while potentially overestimating its link to vascular dementia. Conversely, because chronic sleep and psychiatric disturbances are intimately tied to microvascular risk trajectories through sustained metabolic and autonomic strain, an all-cause ADRD outcome is clinically defensive as it inherently captures dementia cases mediated by mood-driven vascular pathologies. Future prospective studies with comprehensive biomarker phenotyping and standardized neurocognitive staging are essential to disentangle these mechanisms. Furthermore, we did not evaluate Mild Cognitive Impairment (MCI) as an independent outcome or precursor. While MCI has a high conversion rate to ADRD, it is frequently under-coded or inconsistently documented in routine clinical EHR data. Consequently, our findings specifically reflect the risk of progressing to overt clinical dementia.

In conclusion, this large, multi–health-system cohort study demonstrates that mid- to late-life anxiety disorders and insomnia are each associated with an elevated risk of incident ADRD, with anxiety conferring nearly a 50% increase in risk and insomnia a more modest but meaningful 12% increase compared with those with neither condition. These findings align with prior longitudinal research showing that anxiety and sleep disturbances each predict faster cognitive decline and higher dementia risk across diverse populations [13,52]. Although individuals with comorbid anxiety and insomnia exhibited the highest overall clinical and psychiatric burden, their ADRD risk did not exceed that of those with anxiety alone, and no evidence of effect modification by age, sex, or race emerged—patterns similar to large meta-analytic findings reporting broadly consistent associations across demographic groups [47,59]. Collectively, these results suggest that while anxiety operates as a strong, widely relevant indicator of dementia vulnerability, insomnia plays a much more modest, independent role. From a public-health and clinical perspective, routine assessment and timely treatment of anxiety—alongside the management of sleep disturbances—remain promising strategies for supporting healthy cognitive aging [25,53]. Future research should evaluate whether effective, sustained management of these conditions can meaningfully alter long-term dementia trajectories and further clarify the modifiable components of these associations.

Funding

This research was supported by a 2024 Health Research Grant from Saint Louis University.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to proofread and edit the manuscript for readability and language, as well as to assist in identifying more recent and appropriate references for the study. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Ethical statement

Studies on Human and/or Animal subjects: The Saint Louis University Institutional Review Board (IRB) formally evaluated this project on August 2, 2023. The IRB issued an official written determination that the use of this de-identified TriNetX dataset does not involve human subjects under DHHS regulations. Therefore, formal IRB submission and approval were not required.

Informed consent: Because the research utilized fully de-identified, pre-existing data and was officially determined not to constitute human subjects research, the requirement for informed patient consent was not applicable.

Approval / registration number: Not applicable (Official IRB Determination of Non-Human Subjects Research granted August 2, 2023).

Data availability statement

The data that support the findings of this study are derived from historical, de-identified electronic health records housed within the TriNetX Research Network. Due to licensing, privacy, and data use agreements, the authors are not permitted to share or distribute the raw dataset publicly. Researchers interested in accessing the underlying data can contact TriNetX directly (https://trinetx.com) to inquire about establishing their own institutional access and data use agreement.

CRediT authorship contribution statement

SangNam Ahn: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Joanne Salas:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Jinmyoung Cho:** Writing – review & editing, Validation, Investigation, Conceptualization. **Jeffrey F. Scherrer:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Author Contributions: SA conceptualized the study and drafted the manuscript. JS led the data analysis and contributed to the Methods and Results sections. JC contributed to study design and critical revisions. JS provided senior oversight and substantive revisions.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100621.

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