



Regular Research Article

Prevalence of Comorbid Depression and Insomnia Among Veterans Hospitalized for Heart Failure with Alzheimer Disease and Related Disorders

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ARTICLE INFO

Article history:

Received October, 25 2022

Revised January, 23 2023

Accepted January, 24 2023

Key Words:

Insomnia
depression
dementia
heart failure
veterans

ABSTRACT

Objective: To examine prevalence of Alzheimer Disease and related dementias (ADRD) and patient characteristics as a function of comorbid insomnia and/or depression among heart failure (HF) patients discharged from hospitals. **Design:** Retrospective cohort descriptive epidemiology study. **Setting:** VA Hospitals. **Participants:** N = 373,897 Veterans hospitalized with heart failure from October 1, 2011 until September 30, 2020. **Measurements:** We examined VA and Center for Medicare & Medicaid Services (CMS) coding in the year prior to admission using published ICD-9/10 codes for dementia, insomnia, and depression. The primary outcome was the prevalence of ADRD and the secondary outcomes were 30-day and 365-day mortality. **Results:** The cohort were predominantly older adults (mean age = 72 years, SD = 11), male (97%), and White (73%). Dementia prevalence in participants without insomnia or depression was 12%. In those with both insomnia and depression, dementia

Abbreviations: ADRD, Alzheimer's disease or related dementia; CCW, Chronic Conditions Warehouse; CI, Confidence Interval; CMS, Center for Medicare & Medicaid Services; DE, Depressive episodes; EF, Ejection fraction; HF, Heart failure; SD, Standard Deviation; VA, Veterans Administration; VHA, Veterans Health Administration

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<https://doi.org/10.1016/j.jagp.2023.01.026>

prevalence was 34%. For insomnia alone and depression alone, dementia prevalence was 21% and 24%, respectively. Mortality followed a similar pattern with highest 30-day and 365-day mortality higher in those with both insomnia and depression. **Conclusions:** These results suggest that persons with both insomnia and depression are at an increased risk of ADRD and mortality compared to persons with one or neither condition. Screening for both insomnia and depression, especially in patients with other ADRD risk factors, could lead to earlier identification of ADRD. Understanding comorbid conditions which may represent earlier signs of ADRD may be critical in the identification of ADRD risk. (Am J Geriatr Psychiatry 2023; 31:428–437)

HIGHLIGHTS

- **What is the primary question addressed by this study?**

What is the prevalence of Alzheimer disease and related dementias (ADRD) among Veterans hospitalized for heart failure that also have insomnia, depression, or comorbid insomnia and depression?

- **What is the main finding of this study?**

Comorbid insomnia and depression are associated with the highest prevalence of ADRD at 34 per 100 persons. This is significantly higher than persons with either insomnia (21 per 100) or depression (24 per 100).

- **What is the meaning of the finding?**

Persons with comorbid insomnia and depression are at a highest risk of ADRD, and it is clinically important to screen for both insomnia and depression in persons hospitalized for heart failure as this may lead to earlier ADRD detection.

Heart failure (HF) is a highly prevalent medical condition in the United States.¹ Older adults are more likely to experience significant functional challenges and disability following HF.² Unfortunately, Alzheimer's disease or related dementia (ADRD) diagnoses are highly prevalent among patients with HF, complicating medical management,³ increasing healthcare costs,^{4,5} and often indicating a worse prognosis for both diseases.^{6,7} Thus, characterizing factors associated with increased risk of ADRD among HF patients, especially factors that could be addressed in the hospital setting, is an important step towards improving clinical outcomes in this patient subgroup.

Patients with HF who also have a comorbid primary insomnia and/or depression diagnosis may be at increased risk of ADRD. Insomnia (i.e., difficulties falling asleep, staying asleep, waking up too early⁸) and depressive episodes are commonly diagnosed in medical populations, and HF patients in particular.^{9,10} These symptoms have been linked with decrements in the domains of cognitive function that are most commonly impaired in ADRD (i.

e., attention, memory, decision-making^{11–14}), and may be warning signs of ADRD. Insomnia frequently precedes ADRD,¹⁵ and a growing body of literature suggests that later-life onset of depressive episodes in particular is prodromal to ADRD.^{16,17} Critically, while symptoms of depressive episodes and insomnia often overlap in older adults,¹⁸ these disorders have dissociable impacts. Research shows that insomnia and depressive episodes impact functioning via overlapping and disparate mechanisms,^{19,20} and, since insomnia worsens depressive symptom severity and vice versa, these disorders may have synergistic impacts on function.^{19,21} Thus, patients with HF who have both comorbidities versus one may be at the greatest risk for ADRD. However, the separate and overlapping prevalence of insomnia and depressive episodes in HF patients with ADRD is unknown, and characteristics of patients with these comorbidities have not been examined in the literature, an important initial step towards understanding potential contributions of insomnia and depressive episodes to outcomes of patients with comorbid HF and ADRD.

Thus, the present study examined these important knowledge gaps. We conducted an epidemiological analysis using data from all older veterans with HF within the United States Department of Veterans Affairs (VA) system. First, we examined the prevalence of comorbid insomnia and depressive episodes among HF patients with and without ADRD, expecting that patients with both comorbidities would be at the greatest risk for ADRD. Second, we described demographic, psychiatric, medical, and mortality factors associated with these comorbidities. Third, we compared prevalence of ADRD and deaths within 30 and 365 days among those with comorbid insomnia and depressive episodes compared to insomnia or depressive episodes alone, and those with neither comorbidity.

METHODS

Participants and Procedures

Secondary data analyses were conducted on a cohort study of 373,897 veterans that were admitted to a sample of 129 US VA Medical Centers with a primary admission diagnosis of heart failure between October 1, 2011 and September 30, 2020 were identified via the Veterans Health Administration (VHA) electronic medical records and hospitalization claims. In instances where participants had multiple HF-related admissions, one hospitalization was randomly selected for analysis rather than selecting the first or last hospitalization to minimize bias towards healthier or sicker disease progression. VHA electronic records were used to collect information about demographics, medical and psychiatric comorbidity, prior healthcare utilization and mortality. All study procedures were approved by the Institutional Review Board at the *blinded for review*.

Measures

Insomnia, Depressive Episodes, and ADRD

Insomnia diagnoses (i.e., primary insomnia, organic insomnia, insomnia due to a medical or mental health condition), depressive episodes (i.e., major depressive disorder single or recurrent episode, Bipolar I disorder most recent episode depressed,

adjustment disorder), and ADRD diagnoses (i.e., Alzheimer's disease, Pick's disease, presenile or vascular or frontotemporal dementia, cerebral or senile degeneration, dementia) were identified via ICD-9 or ICD-10 diagnoses in the VHA medical record. ADRD codes were determined using the Chronic Conditions Warehouse (CCW) definition of 'Alzheimer's Disease and Related Disorders or Senile Dementia.'²² Instead of the standard 3 year lookback period from CCW, we used a one-year lookback period to keep the recommended lookback period for depression and ADRD consistent.²³

Sample Characteristics

Demographic data (i.e., sex, age, race/ethnicity) were collected through the VHA electronic medical records. Psychiatric and medical diagnoses from the year prior to admission were recorded from VA coding data.

Mortality

All-cause mortality within 30- and 365-day of admission was measured with the previously validated VHA Vital Status File, which integrates mortality data from various federal sources.²⁴

Data Analysis

Data analysis for this study was done using a descriptive epidemiology framework.²⁵ We defined the target population as older adults living with heart failure, the outcome as an ADRD diagnosis, and insomnia, depressive episodes, or insomnia and depressive episodes (i.e., Insomnia-DE) as other health characteristics. We tabulated frequencies to determine the prevalence of ADRD in the four subgroups (insomnia, depression, Insomnia-DE, neither Insomnia-DE), and also calculated prevalence differences across these four groups. Point prevalence for the cohort was calculated and multiplied by 100 to interpret the results in prevalence per 100 persons or percent of persons with ADRD. Prevalence difference for ADRD diagnosis and 30- and 365-day mortality was determined by subtracting the prevalence of one group from a comparison group (Prevalence Difference = Prevalence [Group 1]–Prevalence [Group 2]).

RESULTS

Sample Characteristics

Of the 373,897 patients, 27% had depressive episodes, compared to 4% with only insomnia or 6% Insomnia-DE. Approximately 62% of the sample had neither depressive episodes nor insomnia, and 17% of the overall sample had an ADRD diagnosis. A majority of the sample was male and White, and the average age was 72 ($SD = 11$ years). The sample endorsed a variety of health and psychiatric complications: the most common medical comorbidities were diabetes, obesity, and a solid tumor history. A small proportion of patients were diagnosed with an alcohol or drug use disorder. Approximately 12% of the sample died within 30 days of admission, and 34% died within 365 days. The average number of chronic heart failure inpatient admissions in the past year for the overall sample was 2 ($SD = 2$) and the mean length of stay for chronic heart failure inpatient admissions in the past year was 6 days ($SD = 11$). The descriptive characteristics appeared similar across the analytic subgroups. Detailed results are shown in [Table 1](#).

Prevalence

There were 21.6 cases per 100 persons of ADRD in the insomnia only group (95% confidence interval (CI) = 21.3, 21.9), 23.9 cases per 100 persons (95% CI 23.8, 24.0) in the depressive episode only group, and 33.7 cases per 100 persons (95% CI 33.4, 34.0) in the group with Insomnia-DE (see [Table 2](#)). Comparatively, there were 12.2 per 100 persons (95% CI 12.1, 12.3) in the neither Insomnia-DE group. Prevalence difference estimates are shown in [Table 3](#), suggesting the highest prevalence was seen in the group with Insomnia-DE; the insomnia only and depression only groups had higher prevalence than the neither Insomnia-DE group, and the depression group had a slightly higher prevalence than the insomnia groups.

Regarding 30- and 365-day mortality, the Insomnia-DE group had a mortality rate of 47.9 per 100 persons (95% CI 46.1, 49.6) and 45.4 per 100 (95% CI 44.4, 46.4), for 30-day and 365-day mortality, respectively. The mortality in the insomnia only group was 35.1 per 100 persons (95% CI 33.1, 37.1) and 30.7 per 100 persons (95% CI 29.5, 31.8), and in the depression only group was 39.1 per 100 (95% CI 38.2, 39.9) and

35.5 per 100 (95% CI 35.0, 36.0) for 30- and 365-day, respectively. The group with neither Insomnia-DE showed mortality rates of 22.6 per 100 (95% CI 22.1, 23.1) and 20.0 per 100 (95% CI 19.8, 20.3) for 30- and 365-day. Prevalence difference estimates suggest the Insomnia-DE group had mortality rates between 9% and 14% points higher than the depression or insomnia only groups, and up to 25% points higher than the neither Insomnia-DE group (see [Table 3](#)). Note that the 365-day mortality variable omitted the 30-day mortality cases.

Group Characteristics

In the group with neither Insomnia-DE, older age, being Black or Hispanic (compared to White patients), particular medical factors (i.e., anemia, history of tumor), and a history of psychosis were associated with higher ADRD prevalence, whereas obesity and drug use disorder were associated with lower prevalence of ADRD (see [Table 2](#)). Interestingly, the insomnia and depressive episodes comorbidity groups showed similar patterns to the group with neither Insomnia-DE, but several exceptions were evident for the group with Insomnia-DE. In this group, patients who were white and male instead had a higher prevalence of ADRD, and obesity and substance use disorders increased risk for ADRD.

DISCUSSION

This study was the first to examine prevalence of ADRD among Veterans hospitalized for heart failure with insomnia, depressive episodes, Insomnia-DE, or neither Insomnia-DE. Consistent with our expectations, the prevalence of ADRD was highest in the Insomnia-DE group. Specifically, compared to a group with neither insomnia or depressive episodes, the prevalence of ADRD was nearly doubled among patients with insomnia or depressive episodes and nearly tripled in the group with Insomnia-DE, indicating that these comorbidities signal a marked increase in risk. Critically, the group with Insomnia-DE also had the highest rates of 30-day (48%) and 365-day (45%) mortality following admission. These results suggest that the presence of one or both comorbidities may indicate increased risk of ADRD

TABLE 1. Descriptive Characteristics for the Full Sample and Analytic Subgroups

Characteristic	Overall (N = 373,897)	Insomnia only (N = 15,995)	Depressive episode only (N = 100,482)	Insomnia-DE (N = 24,026)	Neither Insomnia-DE (N = 233,394)	p-value
ADRD Diagnosis, N (%)	64,162 (17%)	3,470 (21%)	24,058 (24%)	8,098 (34%)	28,536 (12%)	< .001
Age at index admission, M (SD)	72 (11)	75 (11)	70 (11)	71 (11)	73 (11)	< .001
Age Group, N (%)						< .001
18-54	16,801 (5%)	508 (3%)	5,542 (6%)	1,251 (5%)	9,500 (4%)	
55-64	72,674 (19%)	2,325 (15%)	24,259 (24%)	5,073 (21%)	41,017 (18%)	
65-74	135,417 (36%)	5,470 (34%)	39,305 (39%)	9,484 (40%)	81,158 (35%)	
75-84	86,251 (23%)	4,195 (26%)	18,710 (19%)	4,756 (20%)	58,590 (25%)	
85 +	62,748 (17%)	3,497 (22%)	12,665 (12%)	3,462 (14%)	43,124 (18%)	
Sex, N (%)						< .001
Female	9,543 (3%)	370 (2%)	3,685 (4%)	920 (4%)	4,568 (2%)	
Male	364,341 (97%)	15,625 (98%)	96,794 (96%)	23,105 (96%)	228,817 (98%)	
Race, N (%)						< .001
White	271,383 (73%)	12,226 (76%)	73,278 (73%)	18,254 (76%)	167,625 (72%)	
Black	74,478 (20%)	2,634 (17%)	19,808 (20%)	4,064 (17%)	47,972 (21%)	
Other	462 (0.1%)	19 (0.1%)	116 (0.1%)	29 (0.1%)	298 (0.1%)	
Hispanic	26,562 (7%)	1,089 (7%)	7,102 (7%)	1,647 (7%)	16,724 (7%)	
Not stated	1012 (0.3%)	27 (0.2%)	178 (0.2%)	32 (0.1%)	775 (0.3%)	
Complicated and Uncomplicated Diabetes, N (%)	193,765 (52%)	8,048 (50%)	57,456 (57%)	13,642 (57%)	114,619 (49%)	< .001
Solid tumor without metastasis, N (%)	60,349 (16%)	2,929 (18%)	16,076 (16%)	4,130 (17%)	37,214 (16%)	< .001
Obesity, N (%)	92,011 (25%)	3,842 (24%)	30,143 (30%)	7,553 (31%)	50,473 (22%)	< .001
Weight loss, N (%)	33,308 (9%)	1,917 (12%)	10,876 (11%)	3,680 (15%)	16,835 (7%)	< .001
Anemia, N (%)	9,162 (3%)	568 (4%)	2,772 (3%)	976 (4%)	4,846 (2%)	< .001
Alcohol abuse, N (%)	35,887 (10%)	1,583 (10%)	14,899 (15%)	4,448 (19%)	14,957 (6%)	< .001
Drug abuse, N (%)	24,184 (7%)	916 (6%)	11,659 (12%)	3,607 (15%)	8,002 (3%)	< .001
Psychosis, N (%)	18,529 (5%)	754 (5%)	8,495 (9%)	2,380 (10%)	6,900 (3%)	< .001
Myocardial infarction, N (%)	57,851 (16%)	2,958 (19%)	18,128 (18%)	5,226 (22%)	31,539 (14%)	< .001
Stroke, N (%)	41,728 (11%)	1,755 (11%)	14,118 (14%)	3,384 (14%)	22,471 (10%)	< .001
Atrial fibrillation, N (%)	131,682 (35%)	6,794 (43%)	34,511 (34%)	9,475 (39%)	80,902 (35%)	< .001
Coronary artery bypass surgery, N (%)	3,479 (1%)	217 (1%)	1141 (1%)	304 (1%)	1,817 (1%)	< .001
ER Visits in past year, M (SD)	3 (4)	3 (4)	3 (5)	5 (6)	2 (3)	< .001
EF Value	44 (15)	44 (15)	45 (15)	45 (15)	44 (15)	< .001
EF Category, N (%)						< .001
≤ 35%	82,356 (22%)	3,820 (24%)	22,351 (22%)	5,402 (23%)	50,783 (22%)	
> 35%	184,292 (49%)	8,576 (54%)	54,144 (54%)	13,744 (57%)	107,828 (46%)	
Missing EF	107,249 (29%)	3,599 (23%)	23,987 (24%)	4,880 (20%)	74,783 (32%)	
Smoking Status, N (%)						< .001
Smoker or former smoker	318,066 (85%)	13,741 (86%)	88,744 (88%)	21,366 (89%)	194,215 (83%)	
Never smoked	40,059 (11%)	1,746 (11%)	9,001 (9%)	1,936 (8%)	27,376 (12%)	
Missing	15,772 (4%)	508 (3%)	2,737 (3%)	724 (3%)	11,803 (5%)	
CHF past year	2 (2)	2 (2)	2 (2)	3 (2)	2 (1)	< .001
CHF length of stay past year	6 (11)	8 (12)	8 (14)	11 (17)	5 (9)	< .001
Past year total cost, M (SD)	30,157 (51823)	35,613 (57,873)	39,076 (61,947)	48,792 (67,672)	24,025 (42,891)	< .001
30 Day Mortality, N (%)	44,348 (12%)	2,243 (14%)	11,787 (12%)	3,014 (13%)	27,304 (12%)	< .001
365 Day Mortality, N (%)	127,526 (34%)	6,315 (40%)	34,829 (35%)	9,216 (38%)	77,166 (33%)	< .001

Note. EF = Ejection Fraction; ER = Emergency Room; CHF = Coronary Heart Failure.

and mortality among patients with HF and have important implications for clinical practice.

It is possible that bidirectional relationships between insomnia symptoms, depressive episodes, and ADRD may provide some explanation for the increased risk for ADRD that we observed. Indeed, both insomnia²⁶ and depression²⁷ are separately known to worsen symptoms observed in ADRD (e.g., increased fatigue; decrements in attention, decision-

making, memory, and mood^{11-14,28}), and insomnia can worsen symptoms of depression, and vice versa.²⁹ Our analyses suggest that the presence of both comorbidities is 10% points higher of ADRD prevalence compared to insomnia or depression alone, suggesting that each of these symptom clusters may confer unique risk to ADRD. Moreover, ADRD has been found to contribute to worsened sleep disturbances³⁰ and depressive mood symptoms.³¹ While

TABLE 2. Crude Prevalence of ADRD Per 100 Patients Among Subgroups

Characteristic	Insomnia Only		Depressive Episodes Only		Insomnia-DE		Neither Insomnia-DE	
	Prev.	95% CI	Prev.	95% CI	Prev.	95% CI	Prev.	95% CI
<i>Overall</i>	21.6	21.3, 21.9	23.9	23.8, 24.0	33.7	33.4, 34.0	12.2	12.1, 12.3
<i>Sex</i>								
Male	21.8	21.1, 22.4	24.2	24.0, 24.5	34.2	33.5, 34.8	12.2	12.1, 12.4
Female	17.8	13.9, 21.7	16.3	15.1, 17.5	22.3	19.6, 25.0	11.4	10.5, 12.3
<i>Age Group</i>								
18–54	2.4	1.1, 3.7	4.3	3.8, 4.9	8.5	6.9, 10.0	1.3	1.1, 1.5
55–64	7.8	6.7, 8.9	8.6	8.3, 9.0	16.1	15.1, 17.1	3.1	2.9, 3.2
65–74	13.2	12.3, 14.1	18.9	18.5, 19.3	29.3	28.4, 30.2	6.8	6.6, 7.0
75–84	25.3	24.0, 26.6	38.9	38.2, 40.0	47.6	46.2, 49.0	15.2	14.9, 15.5
85+	42.6	41.0, 44.3	55.4	54.5, 56.3	61.6	60.0, 63.2	29.5	29.0, 29.9
<i>Race/Ethnicity</i>								
White	21.0	20.3, 21.7	24.2	23.9, 25.0	34.2	33.5, 34.9	11.9	11.7, 12.0
Black	23.9	22.3, 25.5	22.6	22.0, 23.1	32.1	30.7, 33.6	13.4	13.1, 13.7
Other	15.8	0.00 ^a , 32.2	24.1	16.4, 31.9	31.0	14.2, 47.9	10.7	7.2, 14.3
Hispanic	24.7	22.1, 27.3	25.0	24.0, 26.0	32.7	30.4, 34.9	12.7	12.2, 13.2
Not listed	7.4	0.00 ^a , 17.3	14.0	8.9, 19.1	15.6	3.0, 28.2	4.0	2.6, 5.4
<i>Diabetes (Complicated and Un-complicated)</i>								
Yes	21.0	20.2, 21.9	23.7	23.4, 24.1	34.2	33.4, 35.0	12.0	11.8, 12.2
No	22.3	21.4, 23.3	24.3	23.8, 24.7	33.0	32.1, 33.9	12.4	12.2, 12.6
<i>Tumor</i>								
Yes	21.0	19.5, 22.5	25.1	24.5, 25.8	35.0	33.5, 36.4	13.3	12.9, 13.6
No	21.9	21.1, 22.6	23.7	23.4, 24.0	33.4	32.8, 34.1	12.0	11.9, 12.2
<i>Obesity</i>								
Yes	16.0	14.9, 17.2	16.7	16.3, 17.1	26.5	25.5, 27.5	8.1	7.8, 8.3
No	23.5	22.7, 24.2	27.0	26.7, 27.4	37.0	36.3, 37.7	13.4	13.2, 13.5
<i>Weight loss</i>								
Yes	34.6	32.5, 36.8	37.2	36.3, 38.1	46.8	45.2, 48.4	25.2	24.5, 25.8
No	19.9	19.3, 20.6	22.3	22.1, 22.6	31.3	30.7, 32.0	11.2	11.1, 11.4
<i>Anemia</i>								
Yes	30.1	26.3, 33.9	32.5	30.7, 34.2	39.8	36.7, 42.8	18.8	17.7, 19.9
No	21.4	20.7, 22.0	23.7	23.4, 24.0	33.4	32.8, 34.1	12.1	12.0, 12.2
<i>Alcohol abuse</i>								
Yes	20.1	18.1, 22.1	18.3	17.7, 18.9	25.8	24.5, 27.1	12.0	11.5, 12.5
No	21.9	21.2, 22.5	24.9	24.6, 25.2	35.5	34.8, 26.2	12.2	12.1, 12.4
<i>Drug abuse</i>								
Yes	16.4	14.0, 18.8	14.6	14.0, 15.3	25.3	23.9, 26.7	9.5	8.8, 10.1
No	22.0	21.4, 22.7	25.2	24.9, 25.5	35.2	34.5, 35.8	12.3	12.2, 12.5
<i>Psychosis</i>								
Yes	37.7	34.2, 41.1	34.7	33.7, 35.7	45.1	43.1, 47.1	29.8	28.7, 30.9
No	20.9	20.3, 21.5	23.0	22.7, 23.2	32.5	31.8, 33.1	11.7	11.6, 11.8
<i>Myocardial Infarction</i>								
Yes	23.7	22.2, 25.2	25.8	25.1, 26.4	35.1	33.8, 36.3	15.2	14.8, 15.6
No	21.2	20.5, 21.9	23.5	23.2, 23.8	33.3	32.7, 34.0	11.8	11.6, 11.9
<i>Stroke</i>								
Yes	31.5	29.3, 33.6	36.2	35.4, 37.0	46.2	44.6, 47.9	20.7	20.2, 21.2
No	20.5	19.8, 21.2	21.9	21.7, 22.2	31.6	31.0, 32.3	11.3	11.2, 11.5
<i>Atrial Fibrillation</i>								
Yes	24.8	23.8, 25.9	29.2	28.8, 29.7	36.7	37.7, 39.7	15.0	14.8, 15.3
No	19.4	18.6, 20.2	21.2	20.9, 21.5	30.5	29.7, 21.2	10.8	10.6, 10.9
<i>Coronary Artery Bypass Surgery</i>								
Yes	20.3	14.9, 25.6	17.1	14.9, 19.3	27.0	21.9, 32.0	9.3	8.0, 10.6
No	21.7	21.1, 22.4	24.0	23.8, 24.3	33.8	33.2, 34.4	12.2	12.1, 12.4
<i>EF Value</i>								
< 35%	19.2	18.0, 20.5	22.4	21.8, 22.9	32.1	30.9, 33.3	11.7	11.4, 12.0
≥ 35%	22.5	21.7, 23.4	24.2	23.9, 24.6	33.5	32.7, 34.3	13.0	12.8, 13.2
Missing	22.3	20.9, 23.6	24.7	24.2, 25.3	36.0	34.7, 37.4	11.4	11.2, 11.6
<i>Smoking Status</i>								
Current or Former	21.2	20.6, 21.9	23.2	23.0, 23.5	33.0	32.3, 33.6	12.1	12.0, 12.3

(continued)

TABLE 2. (continued)

Characteristic	Insomnia Only		Depressive Episodes Only		Insomnia-DE		Neither Insomnia-DE	
	Prev.	95% CI	Prev.	95% CI	Prev.	95% CI	Prev.	95% CI
Never Smoked	24.1	22.1, 26.1	27.7	26.7, 28.6	37.1	35.0, 39.3	12.7	12.3, 13.1
Missing	25.8	22.0, 29.6	34.4	32.6, 36.2	46.7	43.1, 50.3	12.8	12.2, 13.4
<i>Died within 30 days</i>								
Yes	35.1	33.1, 37.1	39.1	38.2, 39.9	47.8	46.1, 49.6	22.6	22.1, 23.1
No	19.5	18.8, 20.2	21.9	21.7, 22.2	31.7	31.0, 32.3	10.8	10.7, 11.0
<i>Died within 365 days</i>								
Yes	30.7	29.5, 31.8	35.5	35.0, 36.0	45.4	44.4, 46.4	20.0	19.8, 20.3
No	15.8	15.1, 16.6	17.8	17.5, 18.1	26.4	25.7, 27.1	8.4	8.2, 8.5

^a Note: Confidence interval was negative and fixed to 0.

the nature of our sample precludes parsing out the directionality of these effects in our study, the extant literature does suggest a potentially synergistic relationship between these clusters of symptoms that could worsen the symptom profile of patients with ADRD and contribute to more deleterious treatment outcomes.

Indeed, our findings preliminarily suggest that the presence of both comorbidities increases mortality risk. We found that rates of 30-day and 365-day mortality were 9% and 13%–15% points higher in the comorbid group compared to the depression and insomnia groups, respectively. Patients with HF and ADRD may be particularly susceptible to impacts of

TABLE 3. Prevalence, Death within 30 Days, and Death within 365 Days Differences Across Groups

Prevalence	Insomnia Only	Depression Only	Insomnia-DE	Neither Insomnia-DE
<i>ADRD prevalence</i>				
Insomnia only (Prevalence = 21.6)	–	2.3 ^a (1.6, 3.0)	12.1 ^a (11.2, 13.0)	9.4 ^a (8.8, 10.1)
Depression only (Prevalence = 23.9)		–	9.8 ^a (9.1, 10.5)	11.7 ^a (11.4, 12.0)
Insomnia-DE (Prevalence = 33.7)			–	21.5 ^a (20.9, 22.1)
Neither Insomnia-DE (Prevalence = 12.2)				–
<i>Died within 30 days</i>				
Insomnia only (Prevalence = 35.1)	–	4.0 ^a (1.8, 6.2)	12.7 ^a (10.0, 15.4)	12.5 ^a (10.5, 14.5)
Depression only (Prevalence = 39.1)		–	8.7 ^a (6.7, 10.7)	16.5 ^a (15.5, 17.5)
Insomnia-DE (Prevalence = 47.8)			–	25.2 ^a (23.3, 27.1)
Neither Insomnia-DE (Prevalence = 22.6)				–
<i>Died within 365 days</i>				
Insomnia only (Prevalence = 30.7)	–	4.8 ^a (3.6, 6.0)	14.7 ^a (13.2, 16.2)	10.7 ^a (9.5, 11.9)
Depression only (Prevalence = 35.5)		–	9.9 ^a (9.5, 11.9)	15.5 ^a (14.9, 16.1)
Insomnia-DE (Prevalence = 45.4)			–	25.4 ^a (24.3, 26.5)
Neither Insomnia-DE (Prevalence = 20.0)				–

Note: Prevalence or mortality rate difference and 95% confidence interval presented in table. Statistics in left-hand column refers to the prevalence or mortality rate presented in Table 2. Wald test examines if the prevalence difference is different from zero with 1 degree of freedom. Results should be interpreted as percentage point differences (i.e., differences between prevalence of the different groups) and not percentage differences (i.e., a difference divided by a reference value).

^a p < .001.

both comorbidities. There is literature showing that insomnia may increase vulnerability to HF sequelae or the neural impacts of ADRD by interfering with the body's natural immunological,^{32,33} physiologic,^{34,35} and neural repair processes.³⁶ Moreover, depression is associated with worse cardiovascular health,¹⁰ reduced ability to function,³⁷ and reduced motivation for recovery³⁸ which are factors that can buffer against the stress of significant medical concerns.³⁹ Thus, it is plausible that due to the overlap of insomnia and depression, participants may decline more rapidly due a feedback loop of a diminished ability for the body to repair itself due to insomnia followed by reduced functioning and low motivation to recovery due to depression, although additional longitudinal research is needed to investigate this question further.

It is also possible that there are characteristics associated with the subgroups examined in this study that may contribute to these prevalence differences. First, a higher prevalence of ADRD in groups with more comorbidities makes sense given that ADRD is a multifactorial disease. Indeed, the presence of an association between increased comorbidities (anemia, tumor history, mental health, etc.) observed in this study is consistent with the higher risk of ADRD among medical populations in general. Second, some medical comorbidities may contribute to differential risk for ADRD in particular subgroups; for example, vascular disease has been identified as a risk factor for vascular depressive episodes and ADRD.^{40,41} Third, subsamples of patients may face greater risk of ADRD due to factors that are not wholly explained by medical comorbidities. We found that patients with Insomnia-DE who were white were at significantly higher risk for ADRD, whereas patients in the other three groups who were Black or Hispanic showed a higher prevalence of ADRD. It is possible that factors such as social determinants of health impact risk for ADRD as well, and these results highlight the importance of examining comorbidity effects within patient subgroups in subsequent research.

Limitations of this study include the reliance on billing codes for depressive episodes and insomnia, which prohibited the ability to look at how the severity of either disorder influenced ADRD. Moreover, due to the cross-sectional nature of our diagnostic sampling, we cannot examine any order of effects

between insomnia, depressive episodes, and or ADRD or infer any causal mechanisms based on the results of this study. The results in Table 3 are not adjusted for multiple comparisons, and any interpretation of a single within-category result should be done using a Bonferroni correction (0.05 divided by the number of categories) to interpret statistical significance. Additionally, because this sample was 97% male, additional research is needed to examine if these findings generalize to women. Finally, results from this study can only be interpreted amongst patients with heart failure, and it is unclear if the patterns observed in this study replicate among patients with differing levels of cardiovascular health.

Despite the limitations, this study was the first to examine associations between insomnia, depressive episodes, and ADRD in a nationally-representative epidemiological sample of Veterans with heart failure, a group at particularly high risk for ADRD. Our findings show that the presence of insomnia or depressive episodes increase risk for ADRD and subsequent 30- and 365-day mortality, with patients with Insomnia-DE having a 22% higher risk of ADRD versus patients with neither insomnia nor depressive episodes. Additional research is needed to explore the mechanisms that could explain increased ADRD risk when both insomnia and depressive episodes are present. The results of such research could lead to improvements in providing care to Veterans and other older adults living with heart failure.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

AUTHOR CONTRIBUTIONS

ZJK and MLB initially came up with the idea for this manuscript and drafted it with assistance from RF. LJ and ZJK conducted the analyses with assistance from RF. JM, MSD, TB, MS, JMP, CMK, W-CW, and JLR provided manuscript edits and feedback. All authors reviewed and approved the final version prior to submission.

DISCLOSURES

The authors have no disclosures to report.

APPENDIX 1: ICD-9 AND ICD-10 CODES

Insomnia codes: 307.42, 327.00, 327.09, 327.01, G47.01, 327.02, F51.05, 780.51, 780.52, G47.00, F51.01, F51.03, F51.04, F51.09, and G47.09.

Depression codes: 296.2, 296.3, F33, 296.5, F31.3, F31.4, F31.4, 300.4, F34.1, 309, 311, F20.4, F32, F41.2, and F43.2.

Alzheimer disease and related dementia codes: 331.0, G30.0, G30.1, G30.8, or G30.9, 331.11, G31.01, 331.19, G31.09, 331, 290.0, 331.2, G31.1, 290.10, 290.11, 290.12, or 290.13, 290.20, 290.13, 290.21, 290.3, 290.40, 290.41, 290.42, F01.51, 290.43, F01.50, 294.0, F04, 294.10, F02.80, 294.11, F03.90, 294.20, F03.90, F03.91, 294.8, F06.8, 797, G13.8, F05, F06.1, G31.2, G94, R41.81, and R54.

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