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Association of Alzheimer's Disease with Cardiovascular Disease and Depression in Older Adults: Findings from 2018 Nationwide Inpatient Sample

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Abstract

Background: Alzheimer's Disease (AD) and Alzheimer's Disease-Related Dementias (ADRD) significantly impact 6.9 million American older adults, particularly in those with major cardiovascular diseases (CVD) such as Stroke, Congestive Heart Failure (CHF), and Coronary Heart Disease (CHD), along with comorbidities of hypertension (HTN) and depression. Yet their influence is not fully understood, particularly in hospitalized populations. This study investigates how major CVD forms and comorbidities affect the odds of AD/ADRDs and examines their impact on risk of in-hospital mortality among hospitalized older adults.

Methods: We analysed data from the Nationwide Inpatient Sample (NIS), a nationally representative database. Amongst the older adults, 148,772 admissions with a primary AD/ADRD diagnosis were identified. Of them, 15709 died within 30-day hospitalization. Odds ratios (OR) of AD/ADRD associated with CVD and depression were estimated cross-sectionally using multivariate logistic regression with adjusting key covariates. Hazards ratios (HR) of 30-day in-hospital mortality associated with CVD and depression were estimated retrospectively using Cox proportional hazards regression models.

Findings: The prevalence of Alzheimer's was higher among patients with depression (21%), stroke (18%), and hypertension (15%). The adjusted OR (95%CI) of HTN, depression, stroke, and CHF associated with AD/ADRD were 1.23 (1.21- 1.25, $p<0.0001$), 1.96 (1.93-2.00, $p<0.0001$), 1.35 (1.32-1.38, $p<0.0001$) and 0.91 (0.90-0.93, $p<0.0001$), respectively. HR

(95%CI) of 30-day in-hospital mortality in AD/ADRD with stroke was 1.87 (1.77–1.99, p<0.0001), and with CHF was 1.46 (1.41–1.52, p<0.0001).

Conclusions: Comorbidities of HTN and stroke were significantly associated with the odds of AD/ADRD. AD/ADRD patients with stroke and CHF had significantly higher risk of in-hospital mortality than their counterparts. These findings highlight the importance of controlling specific forms of CVD and depression in hospitalization patients.

Keywords: Alzheimer's Disease, Alzheimer's Disease Related Dementia, Stroke, Congestive Heart Failure, Coronary Heart Disease, Peripheral Arterial Disease, Comorbidities, Older Adults, In-Hospital Mortality, Nationwide Inpatient Sample

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Introduction:

Alzheimer's disease (AD) and Alzheimer's disease-related dementias (AD/ADRD) currently affects an estimated 6.9 million Americans aged ≥65, a figure projected to rise to 13.8 million by 2060 without medical breakthroughs (Alzheimer's Association, 2024). AD remains the fifth-leading cause of death among adults aged ≥65 years, with reported deaths increasing by over 140% between 2000 and 2021 increasing the burden economically (Alzheimer's Association, 2024). This burden is expected to rise dramatically, with increase in ages ≥65 years projected to almost double to triple by 2050 (Cheng et al., 2020). In 2024, total costs associated with the healthcare services for older adults with AD are estimated at $360 billion, highlighting its immense public health and economic impact (Alzheimer's Association, 2024). A study done by Cheng et al. (2020) shows that there is a progressive increase in AD and ADRD incidence with advancing age (≥65 years).

Dementia predominantly affects older aged adults who have more co-morbidities. Due to the nature of dementia, individuals often struggle to accurately report their medical condition (Sanderson et al., 2024). Understanding the co-morbid conditions associated with dementia is crucial to manage secondary conditions (Sanderson et al., 2024). Studies have highlighted that, co-morbidities like cardiovascular diseases and its risk factors, such as diabetes, hypertension, obesity, and depression, are strongly linked to dementia progression and the development of Alzheimer's disease (Livingston et al., 2017).

In one of the studies done by Blennow et al. (1991), it was found that White matter lesions (WMLs) in Alzheimer's disease (AD) patients are linked to vascular factors, including

hypertension and ischemic heart disease. While hypertension prevalence was higher among WML patients in that study, it was not statistically significant, but ischemic heart disease was strongly associated with greater WML severity (42% vs. 22%, $p < 0.05$). These findings suggest that ischemic heart disease may contribute to WML progression, exacerbating Alzheimer's disease pathology. (Blennow et al., 1991). In a study conducted by Snowdon et al., 1997, brain infarcts, particularly lacunar infarcts in subcortical regions such as deep white matter, significantly exacerbate dementia symptoms in individuals with Alzheimer's disease (AD, suggesting that vascular factors like atherosclerosis and hypertension play a critical role in modifying the clinical progression of AD. Another study by Finch and Cohen (1997) showed that, elevated blood glucose in late middle age accelerates neuronal damage through oxidative stress and inflammation, which impairs cognitive function, and may act as a metabolic trigger for Alzheimer's disease (Finch and Cohen, 1997). This highlights the importance of addressing and managing cardiovascular risk factors to potentially reduce the burden of dementia.

Evidence shows that, some established cardiovascular diseases like Peripheral Arterial Disease (PAD), Congestive Heart Failure (CHF), Stroke and Coronary Heart Disease (CHD) are found to be closely associated in development of cognitive impairment and Alzheimer's Dementia and Alzheimer's Disease related Dementia. To substantiate this evidence, findings from multiple studies demonstrate the association between specific types of cardiovascular diseases and the development of Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRDs).

For example, in one of the studies, Peripheral arterial disease (PAD) was significantly more common in individuals with Alzheimer's Disease and Vascular Dementia, showing a 2.5-fold increased risk compared to controls (35.2% vs 16.3%, $P < .001$). This highlights a strong association between PAD and dementia progression (Tasci et al., 2017). In another study, in participants with CHF, up to 58% of patients exhibited impairment across various cognitive domains, including memory, reasoning, attention, and psychomotor skills. Impairments were particularly prevalent in tasks requiring conceptual reasoning, psychomotor coordination, and memory recall, highlighting its impact on cognitive function and neuropsychological performance (Bornstein et al., 1995).

In a retrospective cohort study done by Cook et al. (2015), cardiovascular diseases, especially stroke, significantly impacted the progression of AD. The adjusted statistical analyses in the study revealed that AD patients have a 1.3 times increased risk for stroke incidence than non-

AD patients (Cook et al., 2015). Stroke was then further classified into hemorrhagic stroke and ischemic stroke, and analyses was done. Hemorrhagic stroke showed a heightened risk among individuals with AD, with a 200% increased risk of hemorrhagic stroke being substantially elevated in individuals aged 85 and above (Cook et al., 2015). In contrast, ischemic stroke showed no significant relationship with AD in this study. These findings suggest differential impacts of stroke subtypes on AD progression, emphasizing the need for targeted vascular risk management in AD populations (Cook et al., 2015). Meanwhile, results from a large cohort study done by Liang et al. (2023), CHD has been linked to elevate the risk of developing AD and Vascular dementia (VD). The cohort study revealed that individuals with CHD had higher hazard ratios for all-cause dementia (HR: 1.29), AD (HR: 1.24), and VD (HR: 1.78) compared to those without CHD, even after model adjustment (Liang et al., 2023).

Some studies have demonstrated the association of cardiovascular diseases which encompasses various types CVD's collectively, with Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRDs). For example, a study done by Sanderson et al. (2024), exhibited varied associations of various co-morbid conditions with dementia subtypes. Cardiovascular conditions included congestive heart failure (CHF) and atrial fibrillation as separate conditions. It was found that, patients with Alzheimer's disease (AD) and dementia associated with medical conditions showed a decreased risk of CHF (OR: 0.71, 95% CI: 0.67–0.75) and atrial fibrillation (OR: 0.72, 95% CI: 0.68–0.77) compared to controls, indicating a potentially inverse relationship (Sanderson et al., 2024).

In another similar review, done by Du et al., 2022, the cumulative analysis shows that individuals with CVD (collectively encompasses congestive heart failure (CHF), myocardial infarction (MI), and peripheral vascular disease (PVD), exhibit higher risks for developing various types of dementia, including vascular dementia and Alzheimer's dementia. The Data from the study's result showed that presence of CVD was associated with an increased hazard ratio (HR) for AD (HR: 1.21) and vascular dementia (HR: 1.76). The findings further highlight that these cardiovascular conditions collectively contribute to a higher cumulative incidence of ADRD over time (Du et al., 2022).

In a study done by Lee, Cho and Oh. (2020) highlighted that several medical conditions were either self-reported by patients or based on information provided by their relatives and in another study by Tasci et al. (2017), it was unable to capture a comprehensive list of chronic conditions. This underscores the need for research utilizing hospital-diagnosed data, where all

reported healthcare conditions, including chronic illnesses, are systematically recorded within a clinical setting.

Further research is required to comprehensively examine the collective association of various cardiovascular disease (CVD) types with Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRDs) and to identify the specific CVD subtype most strongly associated with AD and ADRDs relative to other subtypes. Utilizing data from the Nationwide Inpatient Sample (NIS) dataset from the year 2018, this study aims to explore the relationship between cardiovascular diseases and the prevalence of AD and ADRDs in older adults.

Study Aims:

1. To explore the relationship between major forms of CVD and the odds of AD and ADRDs in adults aged ≥65 years.
2. To evaluate the impact of co-existing major CVD forms and AD/ADRDs on the risk of in-hospital mortality in the study populations.

Methods:

Study Design and Population:

A cross-sectional (Aim 1) and retrospective cohort (Aim 2) analysis design was employed in the study. Participants who were in the 2018 Nationwide Inpatient Sample (NIS) were analysed. The NIS dataset is a part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest publicly available all-payer inpatient care database in the United States, capturing data from 48 participating states and the District of Columbia. This comprehensive dataset captures a 20% stratified sample of U.S. which includes discharge records from approximately 4,550 hospitals, representing over 97% of the U.S. population. The 2018 NIS dataset provides information on clinical and resource utilization for over 7 million unweighted inpatient stays annually, with a weighted sample size of over 35 million discharges to produce national estimates. The self-weighting design ensures more precise and stable estimates for healthcare trends and outcomes.

For more information visit: https://hcupus.ahrq.gov/db/nation/nis/NIS_Introduction_2018.jsp.

Study variables:

Main Exposure:

The primary exposure in this study is major forms of CVD, which include Congestive Heart Failure (CHF), Coronary Heart Disease (CHD), Peripheral Arterial Disease (PAD), and Stroke. Hospitalizations for these major forms of CVD were identified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. Specifically, CHD was identified using codes (I21, I22, and I25.2); CHF using codes (I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50, and P29.0); hemorrhagic stroke using codes (I60–I62); ischemic stroke using codes (I63.0–I63.9); and PAD using codes (I70, I71, I73, I74, I75, I77.1, and I79) (Tehrani et al., 2013).

Based on these ICD codes, each major form of CVD was analysed to assess its association with prevalent AD and ADRDs. These were then categorized into binary variables (1 = Yes, 0 = No) for CHD, CHF, Stroke, and PAD. Additionally, all these forms were aggregated into a single binary variable representing the presence or absence of CVD.

The secondary exposures included some comorbid conditions like hypertension, diabetes and depression, defined by using ICD-10-CM codes. Hypertension was identified using codes (I10, I11, I12, I13, I15), Type 2 diabetes mellitus using (E11.0-E11.6, E11.8-E11.9), and depression using (F32.0-F32.5, F32.8, F32.9, F32.A, F33.0-F33.4, F33.8, F33.9). These were then categorized into binary variables (1 = Yes, 0 = No) to represent either their presence or their absence.

Outcome:

The primary outcome variables are Alzheimer's Disease (AD) and Alzheimer's Disease-Related Dementias (ADRDs). AD was identified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes G30.0, G30.1, G30.8, and G30.9. ADRDs were classified into six dementia subtypes using ICD-10-CM codes, including vascular dementia (F01.50, F01.51), dementia with Lewy bodies (G31.83), frontotemporal dementia (G31.01), Pick's disease (G31.09), mild cognitive impairment (G31.84), and other dementias (F03.90, F03.91, F10.27, F10.97, F19.97, F02.80, F02.81, F06.0, F06.8, G31.1, G94, G31.89, G31.9, R41.81) (Du et al., 2022).

Based on these ICD-10-CM codes, the prevalence of AD and ADRDs, as the primary diagnoses of interest, was categorized as binary variables (1 = Yes, 0 = No). Additionally, for ADRDs, the subtypes were aggregated into a single binary variable representing the presence or absence of ADRDs, which was then combined and represented into a single binary variable as presence or absence of AD.

The secondary outcome of this study is 30-day in-hospital mortality, determined by examining the patient's discharge status (died = 1, did not die = 0) in combination with the continuous variable which looks at the length of hospital stay (Beydoun et al., 2015). These two variables were analysed together to look at the risk of in-hospital mortality in the study populations, and a new binary variable was created to represent 30-day in-hospital mortality as a categorical outcome (Yes = 1, No = 0).

Covariates:

Potential confounding variables were identified based on prior knowledge of risk factors associated with AD, ADRDs, and major CVD forms. These covariates included demographic factors such as age (65-74 years, ≥75 years; categorical binary variable), sex (male/female), and race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, Native American, Other). Socioeconomic status was represented by income based on zip code as categories ($1 - 45,999, $46,000 - 58,999, $59,000 - 78,999, $79,000+) in 1st, 2nd, 3rd and 4th quartile, while modifiable lifestyle factors included Body Mass Index (BMI), categorized as combination of overweight and obesity, based on the ICD-10-CM code (E66.3) and (E66.0-E66.2, E66.8, E66.9) respectively; and smoking was identified using ICD-10-CM codes (F17.210, F17.211, F17.213, F17.218, and F17.219).

Other comorbidities were defined using ICD-10-CM codes, that included chronic kidney disease (CKD) (N18.1-N18.6, N18.9). To guide the identification of confounders necessary for conditioning in causal effect estimation, a directed acyclic graph (DAG) was constructed using a-priori knowledge and the DAGitty software (https://www.dagitty.net/dags.html) (Tennant et al., 2021).

Statistical Analysis:

Descriptive analyses were conducted to summarize the baseline demographic and clinical characteristics of hospitalized older adults diagnosed with AD, focusing on major CVDs and related comorbidities. Categorical variables were summarized as frequencies and percentages.

Statistical differences between the groups (major CVD forms vs. non-CVD forms, AD vs. non-AD and 30-day in-hospital mortality vs. no mortality) were analysed using chi-square tests for categorical variables (Sherzai et al., 2016). To determine the association of AD with major forms of CVD (specifically stroke, CHF, and CHD) and selected comorbidities (including hypertension and depression), multivariate logistic regression analyses were performed. Adjusted odds ratios (aOR) with 95% confidence intervals (CIs) were calculated, adjusting for demographic factors (age, gender, race, socioeconomic status by zip-code), lifestyle-related factors (BMI, smoking status), and clinical comorbidities (diabetes mellitus, CKD).

Survival analysis was employed to examine the risk of 30-day in-hospital mortality among AD patients, and its combined risk with specific cardiovascular conditions (stroke, CHF, and CHD). Kaplan-Meier survival curves were generated to visualize the difference in survival probabilities and length of hospital stay among AD patients stratified by the presence or absence of stroke. Differences in survival curves between groups were evaluated using log-rank tests. Complementing this, Log-log survival plots were employed to further validate the proportional hazards assumption required for Cox regression analysis. Subsequently, Cox proportional hazards regression was conducted to derive hazard ratios (HR) and 95% CIs for 30-day in-hospital mortality associated with stroke, CHF, and CHD among patients diagnosed with AD. All statistical analyses accounted for demographic variables, comorbid conditions (including hypertension, depression, diabetes, CKD), and lifestyle-related factors (BMI, smoking status). SAS analysis approach for data from complex sampling surveys were utilized because of the survey design of the NIS. Statistical significance was considered at a p-value of <0.05. All statistical analyses were conducted using SAS version 9.4.

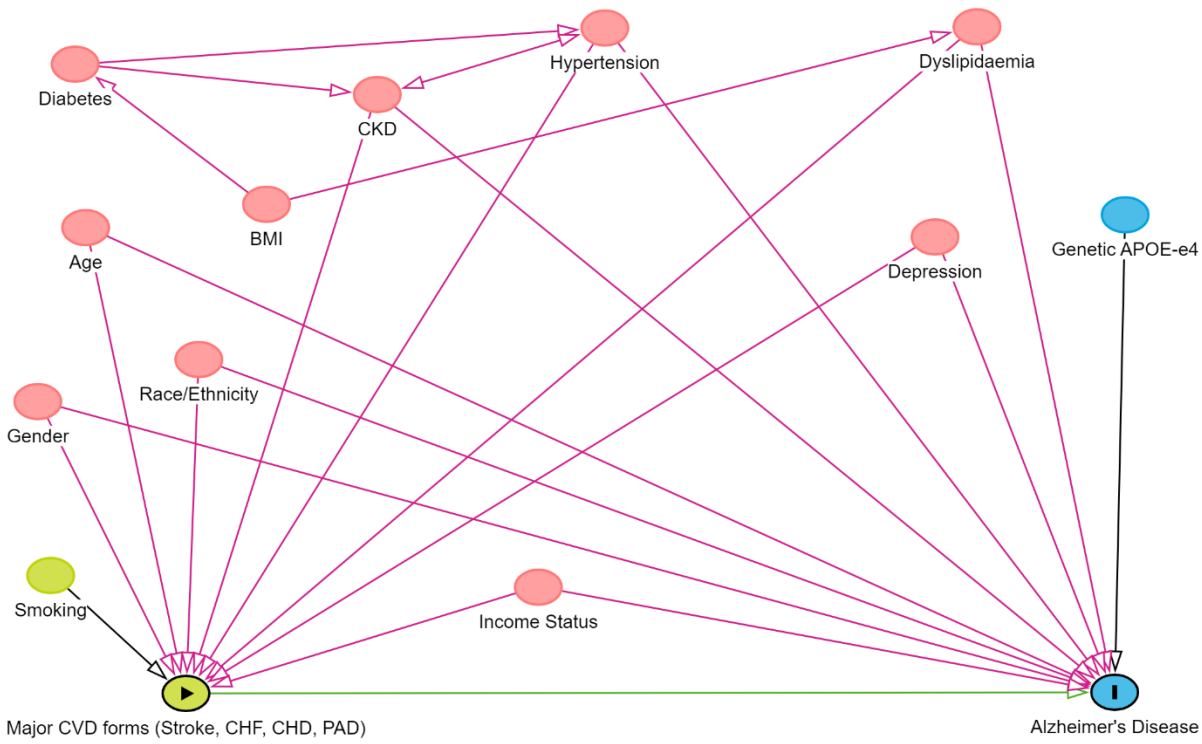

Fig 1: Directed acyclic graph showing association of sociodemographic, behavioural and co-morbidity variables in relation to CVD with AD & ADRDs in older adults.

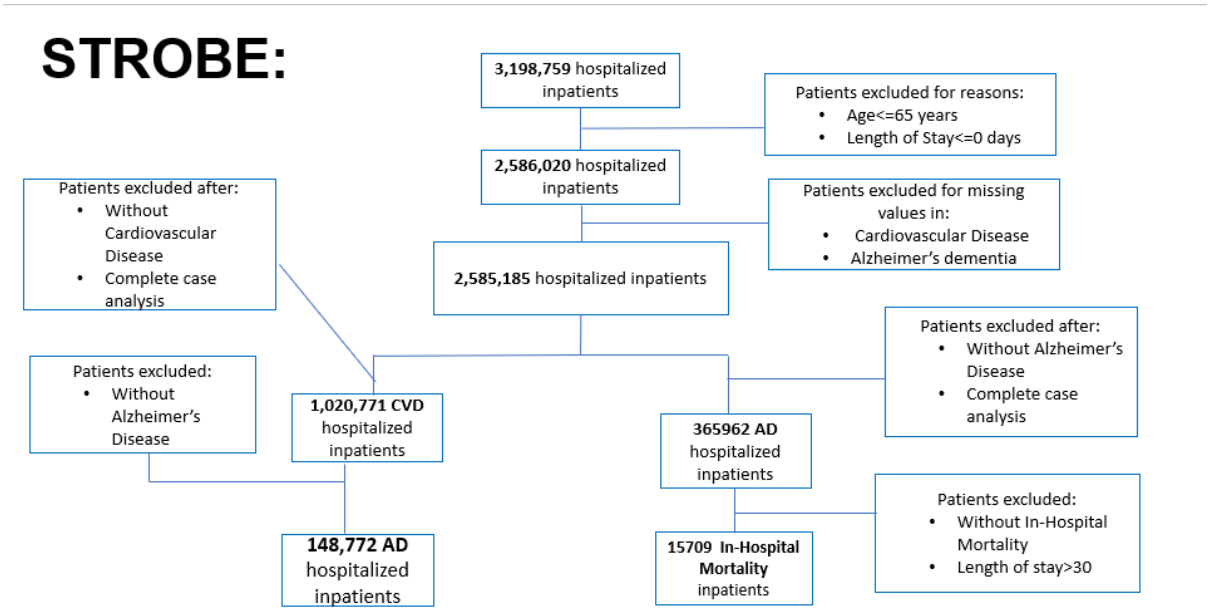

Fig 2: Flow chart displaying eligible sample of hospitalized inpatients with AD and in-hospital mortality.

Results:

From the weighted sample of 3,198,759 hospitalized older adult admissions with cardiovascular conditions in the 2018 NIS database, 148,772 (14.6%) admissions with a primary Dementia diagnosis were identified. Amongst those diagnosed with Dementia, 15709 (4.3%) of which had a secondary diagnosis of 30 day In-Hospital Mortality. Table 1A presents the demographic and clinical characteristics of older adults with major forms of cardiovascular diseases (CVD) and Alzheimer's dementia (AD) in the Nationwide Inpatient Sample (NIS) 2018 dataset. Among hospitalized older adults with CVD, 14.6% were diagnosed with AD. The prevalence of AD significantly differed across major CVD subtypes ($p < 0.0001$). The proportion of individuals with AD was higher among those with stroke (18.3%) compared to those without stroke (14.1%, $p < 0.0001$). When stratified by stroke subtypes, ischemic stroke showed higher prevalence of developing AD (18 per 1000 people), whereas hemorrhagic stroke had a slightly higher prevalence (19 per 1000 people), both significantly greater than individuals without stroke ($p < 0.0001$). Conversely, the prevalence of AD was lower among individuals with coronary heart disease (CHD) (12.8% vs 15.5%, $p < 0.0001$). A similar trend was observed for congestive heart failure (CHF), where AD was present in 14.7% of CHF patients versus 14.1% of those without CHF ($p < 0.0001$). Among the demographic characteristics, age, gender, and race/ethnicity were significantly associated with AD prevalence among hospitalized CVD patients ($p < 0.0001$). Older adults aged 75+ years accounted for 19.8% of AD cases, compared to only 5.7% in the 65–74 age group, indicating a higher likelihood of AD with increasing age ($p < 0.0001$). Females exhibited a significantly higher prevalence of AD (16.6%) compared to males (12.5%) ($p < 0.0001$). Racial differences were also notable; Non-Hispanic Black individuals had the highest AD prevalence (16.6%, $p < 0.0001$).

Amongst the Comorbid-conditions, AD prevalence was notably higher among individuals with hypertension and depression, two key comorbidities in the CVD population. Among older adults hospitalized with CVD, hypertension was significantly associated with a higher prevalence of AD (15.1% vs 12.9%, ($p < 0.0001$). Similarly, depression was linked to a higher prevalence of AD (20.7% vs 13.7%, $p < 0.0001$).

Table 1B presents the clinical and hospital characteristics of older adults with In-Hospital Mortality with major cardiovascular disease (CVD) forms in the dementia patients. Among hospitalized AD patients, those with stroke had a significantly higher in-hospital mortality rate (8.0%) compared to those without stroke (4.0%) ($p < 0.0001$).

This pattern is further illustrated in Figure 3 and Figure 4, which presents the Kaplan-Meier survival curve and log-estimate of survival curves comparing AD patients with and without stroke. The survival probability over time was consistently lower in AD patients with stroke than in those without stroke. Longer hospital stays were associated with an even steeper decline in survival probability, showing stroke's impact on in-hospital mortality risk. The in-hospital mortality rate for AD patients with CHD was (6.9% vs 3.9%, $p < 0.0001$), while AD patients with CHF had an in-hospital mortality rate of (6.0% vs 3.6%, $p < 0.0001$).

Table 2A presents the adjusted and unadjusted odds ratios (ORs) for the association between major cardiovascular diseases (CVD), co-morbidities with Alzheimer's Disease (AD). Stroke demonstrated the strongest association with AD, at adjusted OR of 1.35 (95% CI: 1.32–1.38, $p < 0.0001$) after adjusting for demographics, comorbidities, and behavioral factors. When analyzing stroke subtypes, ischemic stroke had an adjusted OR of 1.28 (95% CI: 1.25–1.31, $p < 0.0001$), whereas hemorrhagic stroke showed a higher adjusted OR of 1.43 (95% CI: 1.38–1.49, $p < 0.0001$), suggesting that hemorrhagic stroke may contribute more strongly to AD risk compared to ischemic stroke.

CHF also exhibited a significant association with AD, with an unadjusted OR of 1.05 (95% CI: 1.03–1.06, $p < 0.0001$). However, after full adjustment, the OR decreased to 0.91 (95% CI: 0.90–0.93, $p < 0.0001$).

Table 2B presents the association between key comorbid conditions and AD, showing that hypertension and depression were highly associated with AD prevalence. Hypertension had an adjusted OR of 1.23 (95% CI: 1.21–1.25, $p < 0.0001$). Depression demonstrated the strongest association with AD, with an adjusted OR of 1.96 (95% CI: 1.93–2.00, $p < 0.0001$).

Table 3 presents the adjusted and unadjusted hazard ratios (HRs) for 30-day in-hospital mortality among AD patients with major cardiovascular disease (CVD) forms.

Among AD patients, stroke was the strongest predictor of in-hospital mortality showing significantly higher mortality risk, with an adjusted HR of 1.87 (95% CI: 1.77–1.99, $p < 0.0001$) after adjusting for demographics, comorbidities, and behavioral factors. CHD also showed a notable association with in-hospital mortality in AD patients, with an adjusted HR of 1.61 (95% CI: 1.54–1.68, $p < 0.0001$) after full adjustment. CHF was another significant predictor, with an adjusted HR of 1.46 (95% CI: 1.41–1.52, $p < 0.0001$) after adjustment.

Table 1A. Demographic and Clinical Characteristics of CVD and Comorbidities with Dementia among hospitalized older aged adults; NIS, 2018

Characteristics`	Overall, Unwt. N = 1020771	Alzheimer's Dementia, Unwt. N (%) = 148772 (14.6)	p-value
Coronary Heart Disease			<0.0001
No	684024 (67.0)	105794 (15.5)	
Yes	336747 (33.0)	42978 (12.8)	
Congestive Heart Failure			<0.0001
No	278881 (27.3)	39448 (14.1)	
Yes	741890 (72.7)	109324 (14.7)	
Stroke			<0.0001
No	915105 (89.6)	129415 (14.1)	
Yes	105666 (10.4)	19357 (18.3)	
Ischemic Stroke			<0.0001
No	935353 (91.6)	133434 (14.3)	
Yes	15338 (1.5)	15338 (18.0)	
Hemorrhagic Stroke			<0.0001
No	995332 (97.5)	143933 (14.5)	
Yes	25439 (2.5)	4839 (19.0)	
Peripheral Arterial Disease			<0.0001
No	955206 (93.6)	140805 (14.7)	
Yes	65565 (6.4)	7967 (12.1)	
Demographics			
Age			<0.0001
65-74 years	377400 (36.9)	21566 (5.7)	
75+ years	643371 (63.1)	127206 (19.8**)**	
Gender			<0.0001
Male	510535 (50.0)	63728 (12.5)	
Female	510236 (50.0)	85044 (16.6)	
Race/Ethnicity N(%)			<0.0001
White	779762 (76.4)	109454 (14.0)	

Black	118404 (11.6)	19680 (16.6)	
Hispanic	72729 (7.1)	11868 (16.3)	
Asian or Pacific Islander	23416 (2.3)	3759 (16.0)	
Native American	4268 (0.4)	532 (12.4)	
Other	22192 (2.1)	3479 (15.6)	
Median household income by ZIP N(%)			<0.0001
$1 - 45,999 (1st Quartile)	286028 (28.0)	41724 (14.6)	
$46,000 - 58,999 (2nd Quartile)	278963 (27.3)	39175 (14.0)	
$59,000 - 78,999 (3rd Quartile)	249987 (24.5)	35710 (14.3)	
$79,000+ (4th Quartile)	205793 (20.1)	32163 (15.6)	
Co-Morbidities			
BMI (Overweight) N(%)			<0.0001
No	848609 (83.1)	135468 (15.9)	
Yes	172162 (16.9)	13304 (17.7)	
Smoking Status (Nicotine Tolerance) N(%)			<0.0001
No	947820 (92.8)	142907 (15.0)	
Yes	72951 (7.1)	5865 (8.0)	
Diabetes Mellitus (Type 2) N(%)			<0.0001
No	587273 (57.5)	91252 (15.5)	
Yes	433498 (42.5)	57520 (13.3)	
Depression			<0.0001
No	892590 (87.4)	122256 (13.7)	
Yes	128181 (12.6)	26516 (20.7)	
Chronic Kidney Disease N(%)			0.8
No	612471 (60.0)	89318 (14.5)	

Yes	408300 (40.0)	59454 (14.5)	
Hypertension			<0.0001
No	255442 (25.0)	33042 (12.9)	
Yes	765329 (75.0)	115730 (15.1)	

Table 1B. Baseline Characteristics of CVD and Comorbidities with In-Hospital Mortality among hospitalized older aged Dementia patients; NIS, 2018

Characteristics	Overall, Unwt. N = 365962	30-day Inhospital Mortality, Unwt. N(%) = 15709 (4.3)	p-value
Stroke			<0.0001
No	347037 (94.8)	14183 (4.0)	
Yes	18925 (5.2)	1526 (8.0)	
Hypertension			<0.0001
No	85618 (23.4)	4298 (5.0)	
Yes	280344 (76.6)	11411 (4.0)	
Depression			<0.0001
No	298510 (81.6)	13655 (4.6)	
Yes	67452 (18.4)	2054 (3.0)	
CHD			<0.0001
No	323707 (88.4)	12792 (3.9)	
Yes	42255 (11.6)	2917 (6.9)	
CHF			<0.0001
No	258291 (70.6)	9229 (3.6)	
Yes	107671 (29.4)	6480 (6.0)	

Table 2A. Multivariate Logistic Regression Analysis of CVD with Dementia among hospitalized older adults

Characteristics	Unadjusted OR (95% CI)	p-value	Model 1 OR (95% CI)	p-value	Model 2 OR (95% CI)	p-value
Major Forms of CVD						
Coronary Heart Disease (CHD)	0.80 (0.78- 0.81)	<0.0001	0.91 (0.90-0.92)	<0.0001	0.89 (0.87-0.90)	<0.0001
Congestive Heart Failure (CHF)	1.05 (1.03- 1.06)	<0.0001	0.87 (0.86-0.88)	<0.0001	0.91 (0.90-0.93)	<0.0001
Peripheral Arterial Disease (PAD)	0.80 (0.77- 0.82)	<0.0001	0.86 (0.84-0.88)	<0.0001	0.85 (0.82-0.87)	<0.0001
Stroke	1.36 (1.33- 1.38)	<0.0001	1.40 (1.38-1.43)	<0.0001	1.35 (1.32-1.38)	<0.0001
Ischemic Stroke	1.31 (1.28-1.34)	<0.0001	1.33 (1.31-1.36)	<0.0001	1.28 (1.25-1.31)	<0.0001
Hemorrhagic Stroke	1.39 (1.34-1.43)	<0.0001	1.49 (1.44-1.55)	<0.0001	1.43 (1.38-1.49)	<0.0001

Model 1: Adjusted for demographics (age, gender, race and income by zip-code).
Model 2: Adjusted for Model 1 plus comorbidities (diabetes, depression, hypertension, CKD and Overweight), behavioural factors (Smoking).

Table 2B. Multivariate Logistic Regression Analysis of Comorbid conditions with Dementia among hospitalized older adults

Characteristics	Unadjusted OR (95% CI)	p-value	Model 1 OR (95% CI)	p-value	Model 2 OR (95% CI)	p-value
Comorbidities						
Diabetes	0.83 (0.82-0.84)	<0.0001	1.05 (1.04-1.07)	<0.0001	1.10 (1.09-1.12)	<0.0001
Hypertension	1.19 (1.18-1.21)	<0.0001	1.26 (1.24-1.28)	<0.0001	1.23 (1.21- 1.25)	<0.0001
Overweight	0.44 (0.43-0.45)	<0.0001	0.65 (0.63-0.67)	<0.0001	0.63 (0.61- 0.64)	<0.0001
Depression	1.64 (1.61-1.67)	<0.0001	1.93 (1.90-1.97)	<0.0001	1.96 (1.93-2.00)	<0.0001
Chronic Kidney Disease	0.99 (0.98-1.01)	0.79	0.92 (0.91-0.93)	<0.0001	0.94 (0.93-0.96)	<0.0001

Model 1: Adjusted for demographics (age, gender, race and income by zip-code).
Model 2: Adjusted for Model 1 plus cardiovascular diseases (CHF, CHD, Stroke & PAD), comorbidities and behavioural factors (Smoking).

Table 3. Cox Proportional Hazards Regression Analysis of In-Hospital Mortality with CVD and other Comorbidities among hospitalized older Dementia patients

Characteristics	Unadjusted HR (95% CI)	p-value	Model 1 HR (95% CI)	p-value	Model 2 HR (95% CI)	p-value
Major Forms of CVD & Comorbidities						
Stroke	1.84 (1.74 - 1.94)	<0.0001	1.83 (1.73 - 1.94)	<0.0001	1.87 (1.77 - 1.99)	<0.0001
CHD	1.77 (1.70 - 1.85)	<0.0001	1.76 (1.68 - 1.84)	<0.0001	1.61 (1.54-1.68)	<0.0001
CHF	1.57 (1.51 - 1.62)	<0.0001	1.52 (1.47 - 1.58)	<0.0001	1.46 (1.41-1.52)	<0.0001
Hypertension	0.79 (0.76- 0.82)	<0.0001	0.78 (0.76- 0.82)	<0.0001	0.77 (0.74-0.80)	<0.0001
Depression	0.66 (0.62-0.69)	<0.0001	0.68 (0.65-0.72)	<0.0001	0.70 (0.67-0.74)	<0.0001

Model 1: Adjusted for demographics (age, gender).
Model 2: Adjusted for Model 1 plus comorbidities (diabetes, CKD and obesity) and behavioural factors (BMI/Obesity & Smoking).

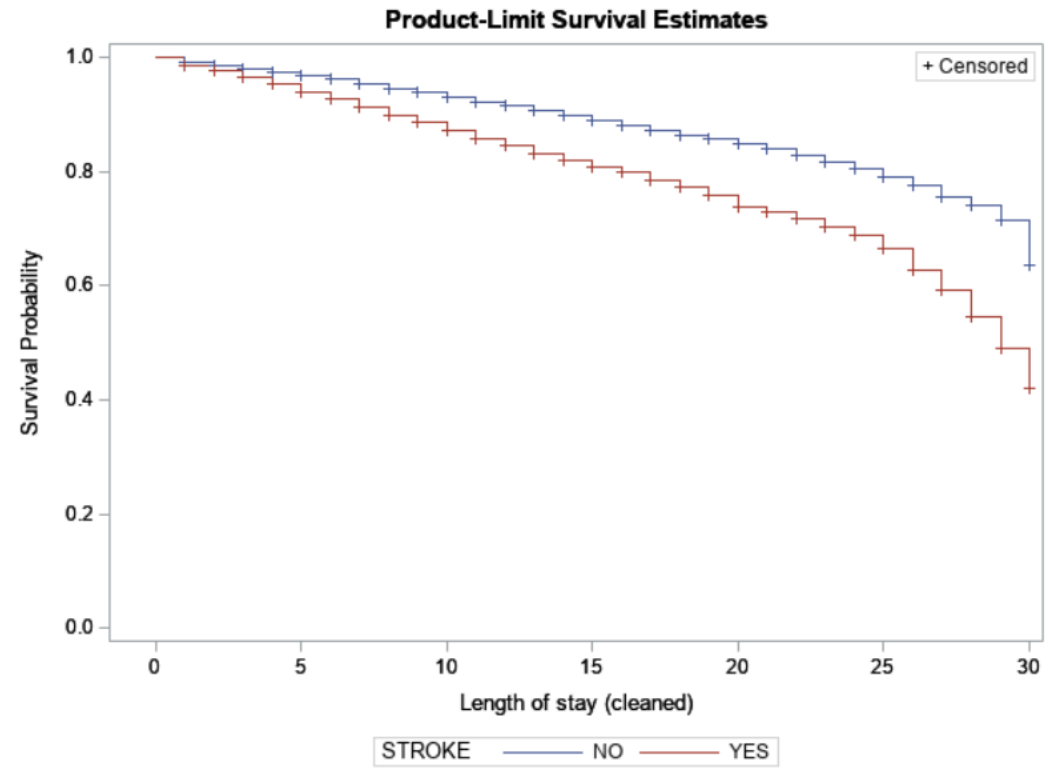

Fig 3: Kaplan-Meier survival curve showing the survival probability over 30 day period comparing AD patients with and without stroke

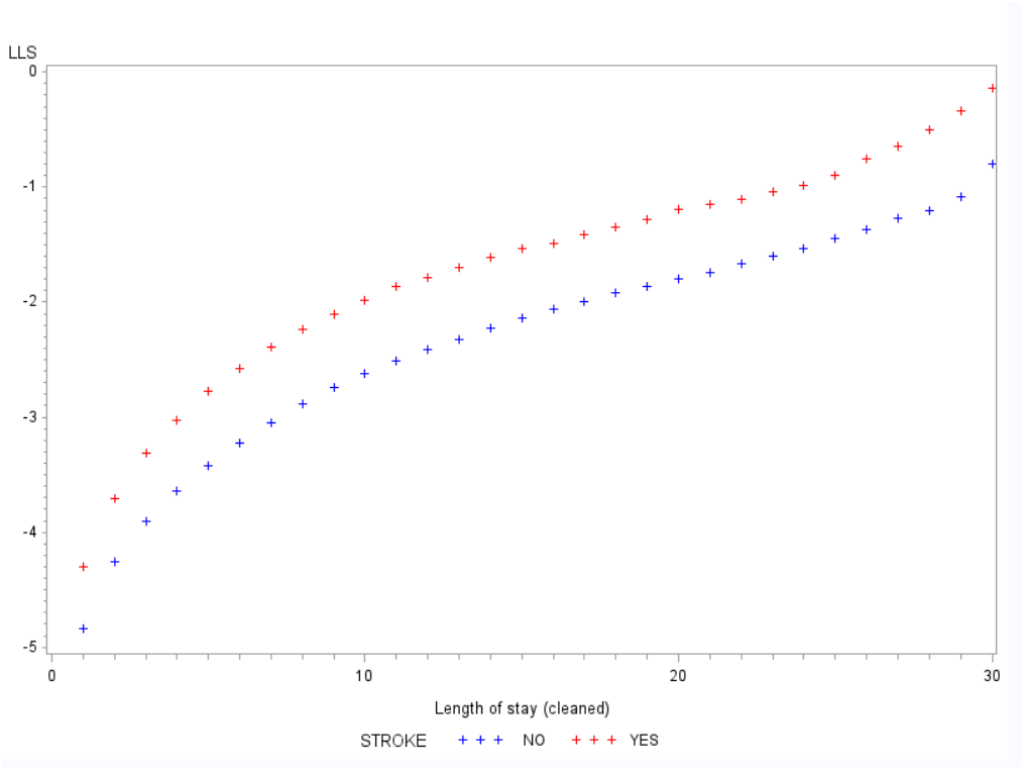

Fig 4: Log-estimate of survival curves showing the survival probability over 30-day period comparing AD patients with and without stroke, validating the proportional hazards assumption.

Discussion:

This study explored the associations of Alzheimer's Disease (AD) with major forms of Cardiovascular Diseases (CVD), and related comorbidities among older adults using a nationally representative inpatient database. Our findings for demographic analyses indicate that AD prevalence was markedly higher among older age groups (>75 years), females, and non-Hispanic Black populations. Older age as a risk factor is well-documented, reflecting cumulative neuropathological changes occurring over a lifetime (Beydoun et al., 2015). Higher AD prevalence in non-Hispanic Black patients corroborates previous studies highlighting racial disparities in dementia risk amongst veterans, which may be driven by structural, socio-economic, and biological factors disproportionately affecting minority populations (Cheng et al., 2020). Out of all the major forms of CVD, our findings revealed a significant positive association between stroke and Alzheimer's Disease. Patients hospitalized with stroke had notably higher prevalence of AD (18.3%) compared to those without stroke. Our results align closely with the findings from a study done by Du et al., 2022, which showed significant association of AD with stroke among breast cancer cohort. This consistency supports the hypothesis that cerebrovascular pathology profoundly influences dementia risk due to ischemic injury, neuronal cell death, lacunes, microinfarcts, disruption of cerebral blood flow, triggering beta amyloid deposition leading to neurodegeneration via hypoperfusion and oxidative stress mechanisms (Tini et al., 2020; Lo Coco et al., 2016). In contrast, in a study by Cook et al., 2015, ischemic stroke showed no significant relationship with AD while Hemorrhagic stroke showed 200% increased AD risk in older adults. The findings from our study showed that both ischemic and hemorrhagic stroke increased the odds of AD development by 28% and 43% respectively. The possible explanation behind this could be, in previous study by Cook et al., 2015, the data was aggregated from Electronic Medical Records and hospital registries often include outpatient, ambulatory, or less severe cases, potentially diluting underestimating the true association since milder ischemic stroke cases might not be documented properly.

Literature has shown that congestive heart failure (CHF) shows higher cognitive impairment prevalence (Bornstein et al., 1995). Conversely, our study observed an inverse association between CHF and AD, which was similar to some of the findings from the literature (Beydoun et al., 2015; Sanderson et al., 2002) which showed a protective effect of CHF on AD. Our finding possibly attributes to survival bias or early mortality in patients with CHF. Our age-stratified analysis (Fig 4 & Fig 5) further clarifies this paradox, showing that CHF prevalence

was higher among younger elderly individuals (65–72 years) but declined steadily with increasing age, whereas AD prevalence increased sharply at older ages (≥80 years). Hence, it is plausible that individuals with CHF experience higher mortality before reaching the typical onset age of AD, creating an artificial protective effect due to competing mortality risks rather than an actual biological protective mechanism.

Coronary heart disease (CHD) showed a similar inverse relationship with AD in our study. Previous studies have indicated inconsistent results regarding CHD's association with dementia. Liang et al. (2023) reported elevated risk of developing dementia in younger age participants with CHD. Our analysis suggests that with time, CHD decreases and is stable in older ages, indirectly lowering AD risk through similar selective mortality patterns observed in populations.

Comorbidities also played a significant role, particularly hypertension and depression, both of which were associated with increased prevalence of AD. Patients with hypertension showed a higher prevalence of AD (15.1%). Similarly, depression was strongly associated with AD, with a substantially greater prevalence among depressed patients (20.7%). Previous studies show that hypertension and depression has substantially elevated dementia risk and also has shown to have a protective association on AD development (Tehrani et al., 2013; Sanderson et al., 2002; Cheng et al., 2020). Our study found elevated dementia risk possibly because of hypertension's role in macrovascular and microvascular damage and dementia's role in accelerated cellular-level aging (Cheng et al., 2020).

Interestingly, our study revealed an inverse association between obesity and AD prevalence, aligning with the paradoxical findings observed by Beydoun et al. (2015), who suggested that obesity in older hospitalized adults have a U-shaped association with AD status which could signify improved metabolic outcomes indirectly protecting against cognitive decline. Additionally, our findings regarding smoking demonstrated a lower likelihood of AD among smokers similar to study done by S.H. Ijaz (2022). This counterintuitive result possibly arises because patients with cardiovascular diseases with known high-risk factors for dementia, may have previously quit smoking due to medical advice or symptom management, thus inflating AD prevalence in non-smokers.

Prior research has demonstrated that AD patients with major forms of CVD face increased risk of adverse hospital outcomes, particularly in-hospital mortality (Tehrani et al., 2013; Yen et al., 2020; Beydoun et al., 2015). Our study revealed an upward trend in log-estimate survival curve

for increased mortality risk among AD patients hospitalized with Stroke compared to non-stroke patients. Similar was noted in CHF and CHD in-hospitalized patients. This increased mortality risk may be attributed to reduced utilization of aggressive interventions (e.g., PCI, CABG), limited diagnostic procedures, increased severity of cardiovascular disease at the time of admission, insurance status among patient admitted with AD and complications arising from Stroke, CHF and CHD sequelae in dementia patients (Beydoun et al., 2015; Tehrani et al., 2013; S.H. Ijaz., 2022).

Previous literature has indicated an inverse relationship between comorbidities like hypertension and depression with in-hospital mortality among AD patients. Beydoun et al. (2015) highlighted that despite significant increases in chronic conditions such as hypertension among hospitalized AD patients, these vascular comorbidities were inversely associated with adverse hospitalization outcomes, suggesting that their detrimental impact may be limited primarily to mid-life rather than older adulthood. Similarly, Yen et al. (2020) observed that hypertension and psychiatric conditions, particularly depression, were inversely associated with mortality among AD inpatients. This paradoxical relationship could be explained by the notion that patients diagnosed with these comorbidities receive more frequent and intensive medical monitoring and care interventions during hospitalization, thereby improving their clinical outcomes and survival probability. Our findings are consistent with these prior observations, demonstrating a similar inverse association between hypertension and depression with in-hospital mortality among AD patients. A plausible explanation aligns with previous studies, wherein closer clinical management, and proactive medical and psychiatric interventions likely lead to better inpatient outcomes.

Our study has several notable strengths that enhance its validity and applicability. Firstly, the utilization of the Nationwide Inpatient Sample (NIS), a large, nationally representative dataset, significantly enhances the external validity and generalizability of our findings to the broader population of hospitalized older adults (Beydoun et al., 2015). The NIS database encompasses diverse demographic groups and healthcare settings across the United States, thereby increasing the reliability of our observed associations between Alzheimer's Disease (AD), cardiovascular diseases (CVD), depression, and mortality outcomes. Moreover, the hospital-based diagnostic information derived from ICD-10-CM codes reduces the potential for recall bias, a common issue in retrospective studies relying on self-reported diagnoses (Sherzai et al., 2016). Additionally, our extensive sample size allows for robust statistical power, enabling

precise estimation of associations and reducing the likelihood of type II errors (Beydoun et al., 2015).

Despite this, our study has several limitations. The cross-sectional nature of the NIS dataset limits our ability to establish temporal sequences or causal relationships of AD with comorbidities of CVD conditions and depression. Additionally, as the NIS focuses solely on hospitalized patients, it excludes nonhospitalized individuals with CVD or dementia, potentially leading to underrepresentation of milder cases of dementia and cardiovascular conditions that do not typically result in hospitalization (Sherzai et al., 2016). Reliance on ICD-10-CM coding introduces potential misclassification biases, but for this purpose AHRQ periodically ensures quality checks with internal and external validation (Beydoun et al., 2015). Lastly, due to the administrative nature of the dataset, essential clinical details such as the severity of cognitive impairment, the exact duration of disease conditions, medication usage, and lifestyle factors are unavailable, impacting our study findings significantly, emphasizing the need for further studies with comprehensive clinical assessments to validate and expand upon our observations.

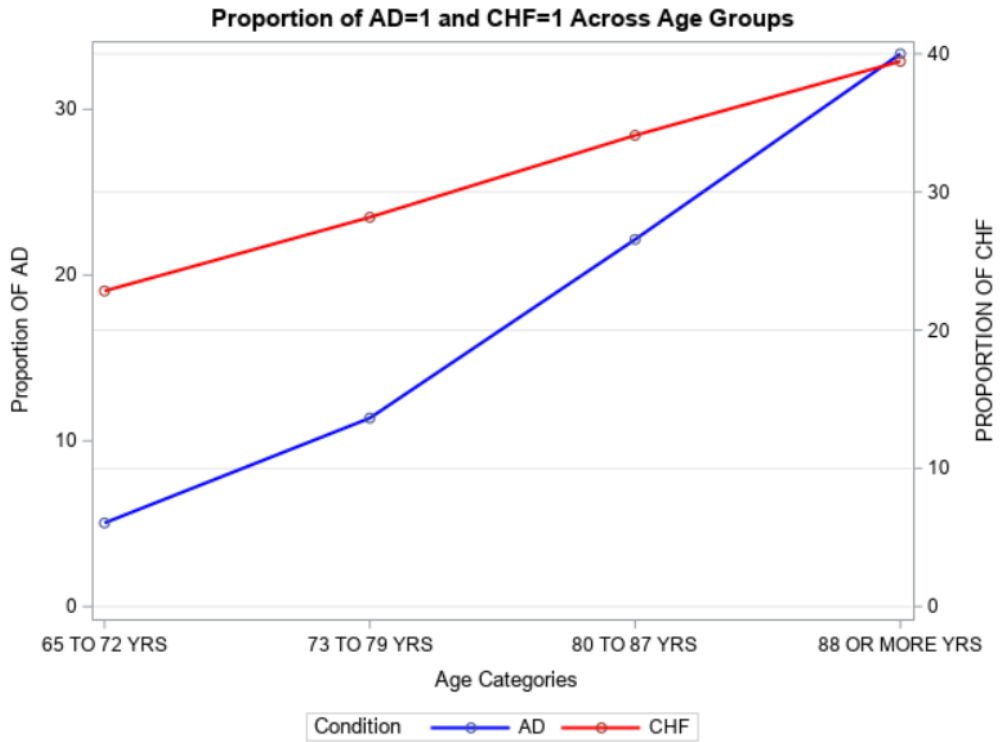

Fig 5: Age-stratified analysis showing proportion of AD and CHF participants across age groups

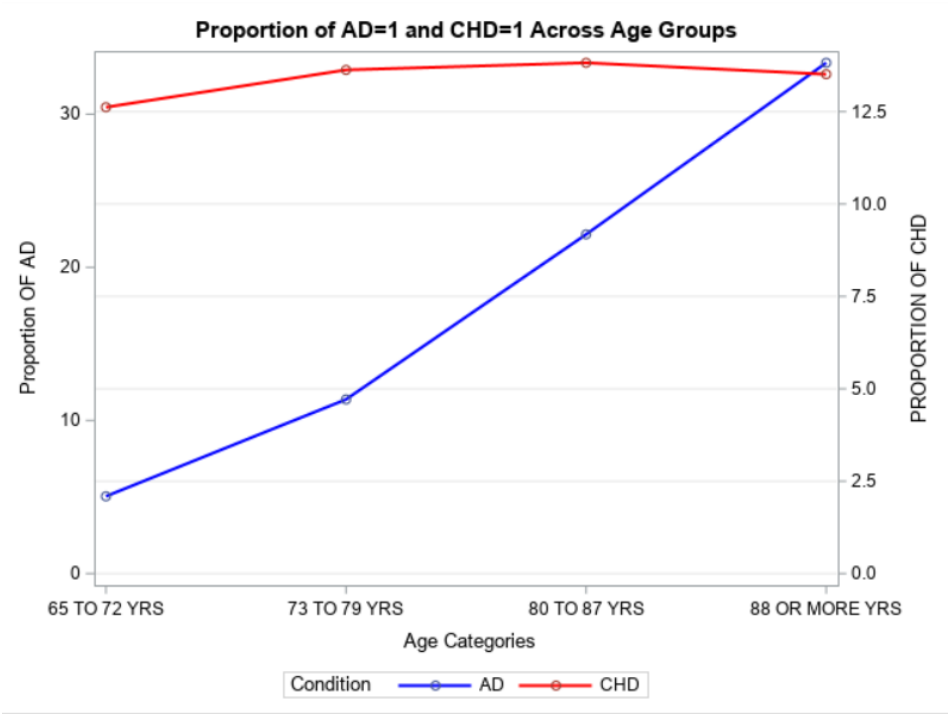

Fig 5: Age-stratified analysis showing proportion of AD and CHD participants across age groups

Conclusion:

In this nationwide inpatient analysis, Alzheimer's Disease (AD) among older adults was significantly associated with cardiovascular diseases (CVD), notably with an elevated prevalence in stroke patients, while congestive heart failure (CHF) and coronary heart disease (CHD) appeared protective. These observed associations may partly reflect age-driven differences, as CHF and CHD prevalences decrease with advancing age, contrasting the sharply rising prevalence of AD in older cohorts. Comorbid conditions, particularly hypertension and depression, showed notable positive associations with AD, underscoring their critical role in dementia risk profiles. Additionally, stroke, CHF, and CHD were each associated with increased in-hospital mortality in AD patients, highlighting the compounded risk posed by co-existing cardiovascular conditions in dementia cases. These findings emphasize the necessity for integrated clinical management strategies targeting vascular and psychiatric comorbidities to potentially mitigate dementia risk and associated mortality. Given the retrospective nature and reliance on hospital administrative databases, future longitudinal studies should investigate temporal relationships and causal mechanisms in detail, informing targeted preventive

interventions and resource management to enhance patient outcomes and reduce healthcare burdens among older adults.

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