Research Article

Cardio and cerebrovascular diseases risk among Alzheimer's disease patients and racial/ethnic disparities, based on Hawaii Medicare data

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Abstract

Background: Alzheimer's disease (AD) and cardiovascular and cerebrovascular diseases (CVD) are significant concerns among the elderly, sharing overlapping risk factors. Hawaii's unique demographic profile, characterized by its strong ethnic diversity, shows marked racial health disparities. For instance, the Native Hawaiian/Pacific Islander (NHPI) population is identified as a high-risk group for multiple health conditions, including CVD.

Objective: This study investigates the impact of AD on the risk of developing CVD, with a focus on racial influences, utilizing Hawaii Medicare data.

Methods: Employing nine years of longitudinal Hawaii Medicare data, this study identified elderly patients diagnosed with AD who subsequently developed heart failure (HF), ischemic heart disease (IHD), atrial fibrillation (AF), acute myocardial infarction (AMI), or stroke. To assess the risk of CVD, we utilized multistate models and employed propensity score-matched controls. Additionally, we evaluated racial and ethnic differences in the risk of these diseases, while accounting for other relevant risk factors.

Results: Our findings revealed an elevated risk of AMI, HF, and IHD among individuals diagnosed with AD. Additionally, socioeconomic status (SE) was identified as a crucial factor in the risk of cardio and cerebrovascular diseases. Within the low SE group, NHPIs exhibited increased risks of HF and IHD compared to their white counterparts. Interestingly, NHPIs demonstrated reduced risks of HF in the higher SE group.

Conclusions: The presence of AD increases the likelihood of developing AMI, HF, and IHD. Moreover, the risk of CVD appears to be influenced by race/ethnicity in Hawaii, as well as socioeconomic status.

Keywords

Alzheimer's disease, heart disease, racial groups, stroke

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Introduction

Alzheimer's disease (AD) along with cardiovascular and cerebrovascular diseases (CVD) are major health concerns in the elderly. The prevalence of AD has increased in the United States (US) as the population ages, with approximately 6.9 million individuals aged 65 and older currently living with AD.[1] This makes patients with AD an important focus for healthcare and research.

CVD have been increasingly linked to AD, as supported by a growing body of evidence from epidemiological studies.[2,3] Several well-known risk factors, on cerebrovascular, have been widely identified as risk factors for the development and progression of AD.[4,5] It is important to highlight that, individuals diagnosed with AD often exhibit cerebral infarction in their pathological findings.[6] Cerebral amyloid angiopathy (CAA) which is the accumulation of amyloid within the leptomeninges and cerebral blood vessels, is present in patients with AD.[7,8] Also,

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cerebral microbleeds increasingly recognized neuroimaging findings in AD.[9] Both CCA and cerebral microbleeds are associated with hemorrhagic and ischemic stroke.[9,10] Some view AD either as a systemic disease or as a metastatic disorder leading to heart disorders, and possibly failures in multiple organs.[3] A study that assessed myocardial function from a cohort of AD patients and age-matched controls, detected the presence of amyloid protein aggregates in myocardial tissues, which results in thicker left ventricle in AD patients, making them a high risk group for heart abnormalities.[11] The incidences of ischemic stroke among AD cases and non-AD controls reported to be 37.8 and 23.2 per 1000 person-years.[12] The increase in prevalence of AD would lead to a rise of the already prevalent heart disease and stroke among the elderlies. More research should focus on investigating these risks for AD patients.

Hawaii is home to a significant elderly population, with approximately 19.6% of individuals aged 65 and above, ranking it as the 7th highest in the US.[13] Projections indicate this will rise to 23.8% by 2045, with 60% of this expected to be 75 and above.[14] CVD is a critical health challenge in Hawaii and it alone accounts for 3 out of 10 deaths in Hawaii.[15] Also, AD is the 6th leading cause of death, with approximately 376% increase in AD-related deaths since 2000.[16] Hawaii has the most diverse ethnic populations in the US and significant racial/ethnic health disparities exist in this multiethnic population.[17–21] Native Hawaiians and Pacific Islanders (NHPI) are widely identified as a high-risk group for variety of conditions, including CVD.[17,18] For instance, NHPIs had second-highest CVD death rate in the US.[19] Furthermore, they are at higher risk for ischemic stroke at younger age compared to both whites and Asians.[20] Additionally, NHPIs have been found to be disproportionally affected by several other chronic conditions including diabetes and chronic kidney disease.[21] Considering the increased risk of developing CVD associated with AD, it is plausible that NHPIs with AD are at a significantly higher risk of developing CVD. Hence, it is important to investigate potential racial/ ethnic differences in the CVD risks among AD patients. Such examinations are vital for enhancing the understanding of the epidemiological characteristics of AD and its implications.

In this study, we explored the CVD risk among AD patients using nine years of data from the Hawaii Medicare database. Specifically, we assessed the incidence of heart failure (HF), ischemic heart disease (IHD), atrial fibrillation (AF), acute myocardial infarction (AMI), and stroke. Additionally, we investigated potential racial/ ethnic disparities in these risks. Prior to this, no studies have been conducted on these aspects within the Hawaii population. Our objectives were twofold: (i) to evaluate the risk of developing CVD after an AD diagnosis and (ii) to examine racial/ethnic differences in CVD risk among AD patients.

While the current study focuses on CVD risk among AD patients, it is important to note that previous research has suggested that cardiovascular disease itself may be a risk factor for developing AD, implicating significant anatomical and physiological pathways.[22–24] In prior work, we examined the risk of developing AD among individuals with CVD in Hawaii's elderly population, highlighting the role of racial and ethnic disparities and socioeconomic status in modulating this risk.[24] The present study complements this previous research by shifting the focus from the risk of AD in CVD patients to the risk of CVD in AD patients. Adopting a multistate framework similar to that used in Siriwardhana et al.,[24] we translated key research questions into state-transition problems analyzed using time-to-event data from the Medicare database. Although collecting real-time longitudinal data on disease transitions in a large cohort poses challenges, utilizing health insurance databases like Medicare provides a robust foundation for extracting crucial data on disease progression.

Methods

Data

This is a retrospective cohort analysis study utilizing nine years of Hawaii Medicare data from 2009 to 2017. The Medicare data included information from approximately 3.27 million insurance claims corresponding to 369,131 individuals. The study focused on elderly subjects aged 65 years and older who were diagnosed with AD between January 1, 2009, and December 31, 2017. Among these individuals, we tracked the occurrences of AF, AM, IHD, HF, stroke, and death by following them longitudinally for up to nine years. As covariates, we captured subject demographics and comorbidity information.

The study excluded data from individuals who had AF, AMI, IHD, HF, stroke, and AD conditions prior to January 1, 2009, to avoid systematic bias such data could introduce in the time-to-event analyses. All records of inpatient and outpatient visit data were utilized, and disease conditions were identified using the International Classification of Diseases, 9th and 10th Revisions (ICD-9/ICD-10) diagnosis codes, along with subject disease history accessible from Medicare beneficiary summary files. In Supplemental Table 1, we provide a list of specific ICD codes used to identify conditions: AD, AF, AMI, IHD, HF, and stroke.

Subject race/ethnicity categories were classified as white, Asian, NHPI, and other. The "other" group included underrepresented groups such as American Indian/Alaska Native, African American, Hispanic, and individuals with unknown races. We designated the subject's socioeconomic status using a surrogate indicator given by the dual eligibility (DE) status, which indicates beneficiaries who received both Medicare and Medicaid insurance benefits. Note that

DE status has been widely recognized as an indicator of low-income status.[25–27]

The study protocol was previously approved by the Hawaii Institutional Review Board under the study ID CHS #23362.

Multistate models

The multistate model is a type of statistical model used to analyze data where individuals or entities can transition between multiple states over time. The model involves several distinct states that an individual or entity can occupy, typically defined based on the context of the study, such as health states in medical research (e.g., healthy, diseased, recovered).[24,28,29] It can range from a simple survival model describing the transition between two states to a more complex model with several intermediate and final states. Covariates may influence the transition mechanisms within the system. These models are particularly useful in epidemiological research for tracking the progression of a set of disease conditions in a sequential manner. In these models, state occupation probabilities and hazard rate functions are critical temporal functions. Since data corresponding to these systems are typically subject to right-censoring due to partial movements, the use of conventional statistical methods that require fully observed data may introduce selection bias. Thus, a specific analytical approach capable of handling this data issue is necessary.

As shown in Figures 1 and 2, our work utilized a three-state acyclic illness-death multistate model to address questions focused on the occurrence of CVD conditions/events among AD patients. Our objectives were twofold: (i) to investigate the risk of developing CVD conditions/events among AD patients (Figure 1), and (ii) to examine racial-ethnic disparities in CVD risks among AD patients (Figure 2). Separate models were employed for each CVD condition as appropriate.

Figure 1 illustrates the progression of CVD among individuals with and without AD. Specifically, it presents the twin illness-death model corresponding to cases (AD subjects) and controls (non-AD subjects) for each scenario. Figure 2 illustrates the progression of CVD among AD subjects, followed by the illness-death model.

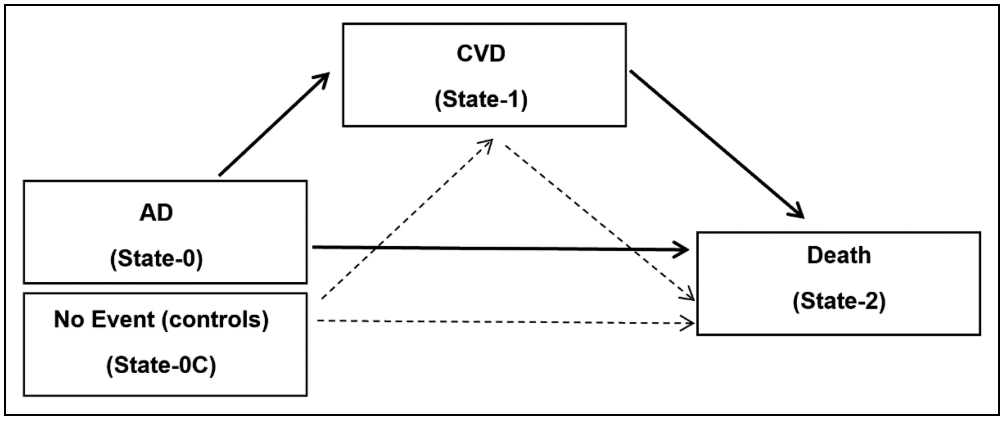

Figure 1. Development of CVD conditions, followed by the illness and death model. In the figure, the State-1 is varying from HF, IHD, AF, AMI, and stroke, generating five different models. The control group corresponds to a set without AD.

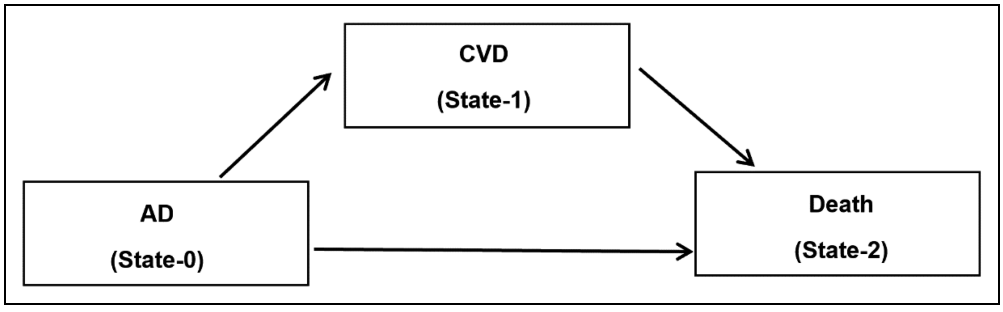

Figure 2. Development of CVD conditions among AD, followed by the illness and death model. A sub-model of the model given in Figure 1 only with subjects had AD.

Selection of controls

Under Aim 1, our plan was to examine the CVD risk following an AD diagnosis, compared to elderly individuals with no AD diagnosis (controls). To establish the control group for each model depicted in Figure 1, we employed the following procedure: individuals who had not been diagnosed with AD but exhibited similar distributions of covariates to the AD patients (cases) were included in the control group using the following mechanism.

First, cases were stratified by the age at the onset of AD. Suppose the subset of cases corresponding to age i is denoted as D_i. Next, we identified a same-age (i.e., age $= i$) subcohort without an AD diagnosis, indicated by C_i. Assume the group sizes of the D_i and C_i subcohorts are n_i^D and n_i^c, respectively. Note that due to the large number of data records in the Medicare database, n_i^c was larger compared to n_i^D ($n_i^D < n_i^c$) for each i. In the next step, we applied a propensity score matching approach to achieve one-to-one covariate-matched controls for cases among D_i within C_i, notate by $\bar{C}_i$ (i.e., $\bar{C}_i \in C_i$ and $n_i^D = n_i^{\bar{C}}$).[30] We carried out the propensity score matching step using a set of variables listed in Supplemental Table 2. Since this approach utilized exact matching for the age variable (i.e., one-to-one matching), in the analysis each case and control were followed from the same time point in their life cycle, which minimizes age-related bias. The propensity score matching allowed us to achieve comparable feature distributions among groups for a reasonable comparison.

Statistical methods

We employed advanced statistical techniques designed to handle multistate data subject to right censoring, enabling the examination of temporal functions and their dependency on covariates. For each multistate model utilized, all transitions among eligible subjects starting from the initial state were recorded based on disease codes and corresponding Medicare claim dates. The Aalen-Johansen nonparametric method was adopted to estimate temporal functions of multistate systems, which remains valid even when the restrictive Markov model assumption is violated, thereby providing flexibility in addressing various real-life scenarios.[31,32] Transition hazard functions were estimated using the Nelson-Aalen rate estimator, and the Aalen-Johansen product-limit integral of hazards was applied to estimate marginal state occupation probabilities.[33] Our analysis assumed random censoring. We empirically calculated 95% pointwise confidence intervals for the selected temporal functions using the bootstrap technique with 1000 resamples. Covariate effects were examined using the Andersen-Klein pseudo-value regression method, a flexible approach that facilitates inference on complex survival models under censored data conditions.[34,35] This pseudo-value regression process begins with a marginal estimator of the targeted quantity, followed by the application of jackknife estimates and generalized estimating equations for inference. The pseudo-value approach in this study was implemented over a time grid spanning 12 to 96 months. To ensure the validity of inferences, all analyses comparing risks between cases and controls accounted for clustering due to the matching procedures employed.[36,37] Transition risks from state 0 to state 1 and from state 0 to state 2 were assessed using the cumulative incidence function, whereas the transition risk from state 1 to state 2 was evaluated using the cumulative hazard function. Further details of the statistical methodologies are provided in the supplementary material. A critical aspect of our study was the examination of racial and ethnic effects on the temporal functions. These analyses were conducted by incorporating the interaction between race/ethnicity and DE status, as the DE variable significantly influenced racial and ethnic effects on several critical transitions of interest in our study. The assessments of racial and ethnic effects accounted for multiple subject-specific factors, including age, gender, and selected disease conditions: chronic kidney disease, diabetes, depression, hyperlipidemia, hypertension, and cancer. All analyses were performed using R version 4.0.1.

Results

Participant features

Supplemental Table 2 provides a summary of the features of AD subjects included in the study. A total of 3122 patients developed AD during the investigation period. The average age of this cohort was 80.83 years, with male subjects comprising 40.02% and DE subjects comprising 22.37%. Regarding race/ethnicity, the cohort was composed of 29.44% Whites, 31.55% Asians, and 22.42% NHPIs. Additionally, 32.81% of the subjects had diabetes, 16.48% had chronic kidney disease, 32.81% had depression, 67.32% had hyperlipidemia, and 40.62% had hypertension.

CVD risks after AD diagnosis

Table 1 presents the findings of our analysis on the CVD risks in individuals with AD compared to control groups. We employed the pseudo-value regression method to estimate the hazard ratio (HR) for transition probabilities between the two groups. In Table 1, HR values above 1 denote a higher risk for the AD group in the respective transition, whereas HR values below 1 suggest a lower risk for the AD group. As detailed in the materials and methods section, the control group consisted of non-AD individuals matched for covariates. The p-values given indicate the statistical significance of the HR, with the null hypothesis positing that the actual HR is 1.

Table 1. Effects of AD on transitions in the multistate model given in figure 1.

	AD to Heart/Stroke (State 0 to 1)		Heart/Stroke (with AD) to Death (State 1 to 2)		AD to Death (State 0 to 2)	
	HR (95% CI)	p-value	HR (95% CI)	p	HR (95% CI)	p
AF	1.005 (0.926, 1.091)	0.9054	1.759 (1.567, 1.976)	<0.0001	2.452 (2.285, 2.632)	<0.0001
AMI	1.947 (1.412, 2.684)	<0.0001	1.536 (1.316, 1.792)	<0.0001	2.346 (2.203, 2.499)	<0.0001
HF	1.413 (1.196, 1.669)	<0.0001	1.245 (1.126, 1.377)	<0.0001	2.379 (2.216, 2.555)	<0.0001
IHD	1.389 (1.178, 1.637)	<0.0001	1.650 (1.458, 1.867)	<0.0001	2.353 (2.188, 2.531)	<0.0001
Stroke	0.926 (0.839, 1.022)	0.1266	1.598 (1.410, 1.812)	<0.0001	2.194 (2.060, 2.338)	<0.0001

Estimated HR values correspond to the effect of the AD group, compared to the control group, by the pseudo value regression approach.

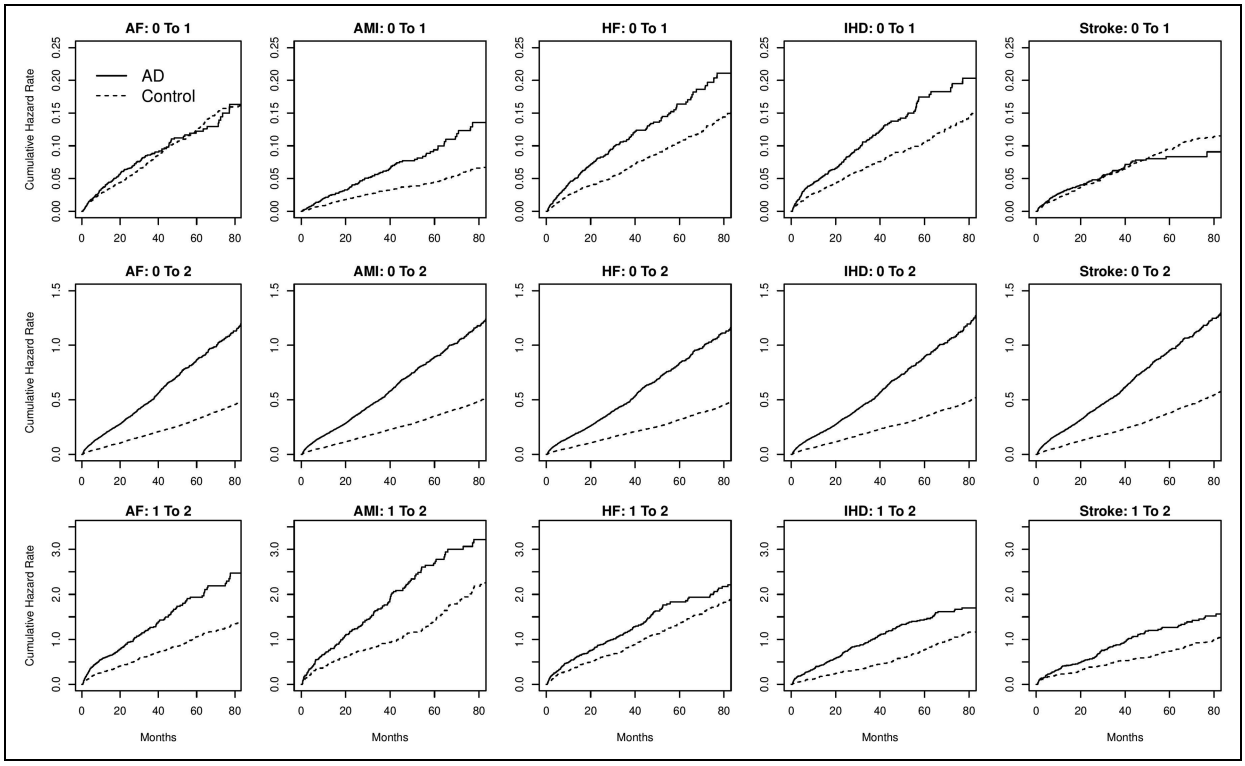

Figure 3. Estimated transition hazard functions with respect to time, corresponding to multistate models given in Figure 1, separately by diseased conditions (AF, AMI, HF, IHD, and stroke) and controls. Plots given in rows 1, 2, and 3 correspond to state-0 to state-1, state-0 to state-2, and state-1 to state-2, transitions in each of the five models.

In the multistate model, the transition from state 0 to state 1 indicates the event of diagnosing a CVD condition (AF, AMI, HF, IHD, or stroke) for AD subjects. One of our primary objectives was to assess the relative risks associated with the diseased group compared to the control group during this transition. Figure 3 illustrates the characteristics of the cumulative hazard functions for both the diseased and control groups in this transition, as shown in the plots in the first row. The analysis results in Table 1 (column 1) showed increased hazards for developing CVD conditions among AD group compared to the control group after following up with subjects for a maximum of 9 years, for AMI (HR = 1.947, $p < 0.0001$), HF (HR = 1.413, $p < 0.0001$), and IHD (HR = 1.389, $p < 0.0001$), at 5% significant level. However, no increased risks found for AF or stroke conditions.

Risk of death after a CVD condition, with history of AD

Table 1 (column 2) shows the risks of death after observing a CVD condition, given that the subjects had diagnosed with AD. The study revealed increased risks for all conditions: AF (HR = 1.759, $p < 0.0001$), AMI (HR = 1.536, $p < 0.0001$), HF (HR = 1.245, $p < 0.0001$), IHD (HR =

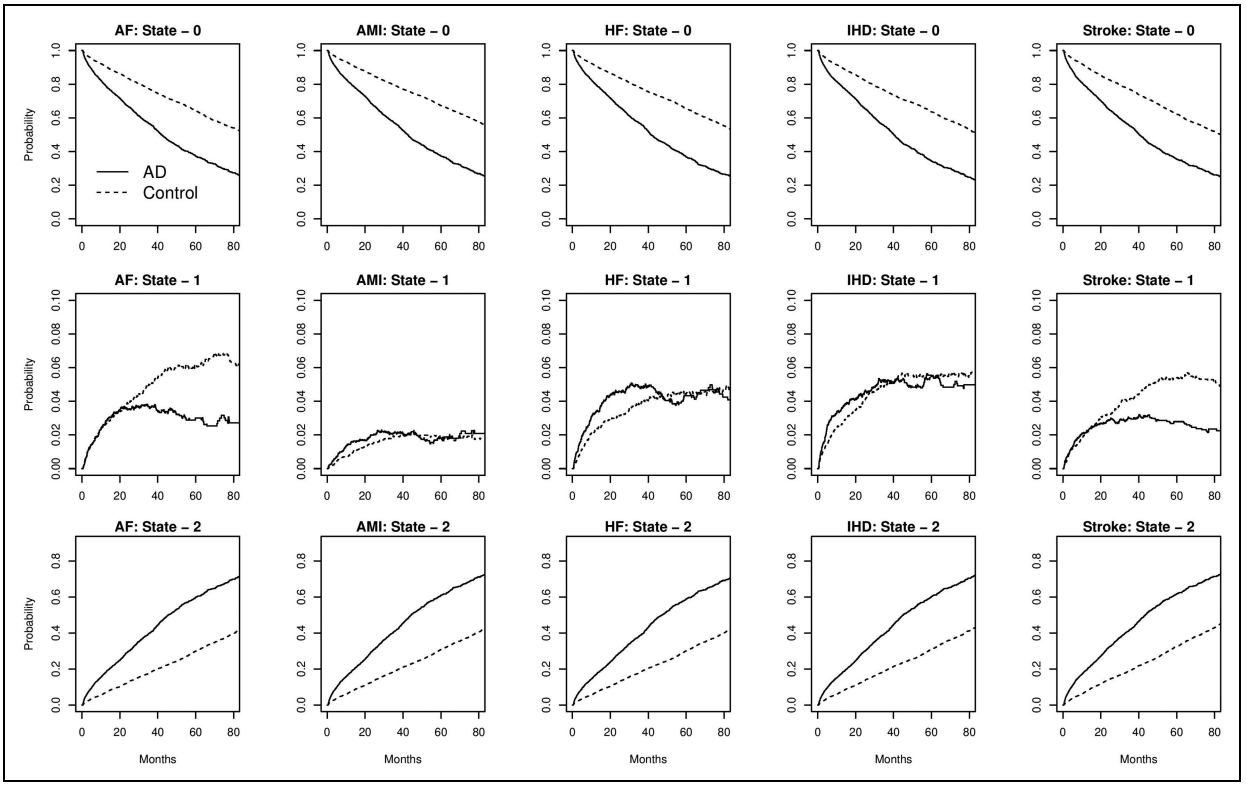

Figure 4. The figure displays the estimated state occupational probabilities over time for individuals with different disease conditions (AF, AMI, HF, IHD, and stroke) and controls, based on the multistate models shown in Figure 1. The plots in the three rows correspond to state-0, state-1, and state-2 estimates, for each of the five disease models.

1.650, $p < 0.0001$), and stroke (HR = 1.598, $p < 0.0001$), compared to the control group. These relationships can also be seen from third row of Figure 3.

Direct risk of death after heart disease or stroke

As one may expect, the study showed an increased risk of mortality among AD patients, which is clearly depicted in the second row of Figure 3.

State occupation probabilities

Figure 4 presents the estimated state occupation probabilities for the multistate models. Examination of these probabilities reveals a continuous decline in the estimated probabilities of state-0 among the AD groups, while the probabilities of state-2 show a steady increase compared to the control group. As detailed in Supplemental Table 3, at 36 months, the estimated state-1 probabilities (%) for the diseased versus control groups were as follows: AF (56.3 versus 76.8), AMI (56.8 versus 79.1), HF (56.6 versus 79.1), IHD (54.9 versus 75.8), and stroke (55.0 versus 76.6). At 72 months, these probabilities (%) were: AF (31.1 versus 57.6), AMI (30.7 versus 61.6), HF (30.2 versus 59.5), IHD (28.8 versus 57.1), and stroke (30.3 versus 55.9). Over time, the estimated state occupation probabilities at state-1 were relatively low, attributable to the transition process from state-1 to state-2.

Racial/ethnic effects on CVD risks after developing AD

Tables 2 and 3 present an analysis of the racial and ethnic effects observed during the transitions from each initial state of the multistate model depicted in Figure 2, specifically from AD to CVD conditions. The analysis results were stratified based on the DE indicator, which corresponds to individuals covered by both Medicare and Medicaid. This stratification was important due to the differing effects observed between these two groups during the transitions, as elaborated upon in subsequent discussions. In our discussion of the analysis results, we will focus separately on the DE group and the Medicare only group.

A primary focus of our study was to investigate the effects on NHPIs relative to Whites and Asians in Hawaii. Consequently, we designated both Asians and Whites as reference groups for this analysis. Table 2 shows that in the DE group, compared to whites, NHPIs had a higher risk of developing HF (HR = 1.468, $p = 0.0017$), IHD (HR = 2.260, $p = 0.0012$), and a borderline

Table 2. Racial/ethnic effects on developing CVD conditions after AD.

		NHPI versus Whites		NHPI versus Asians		Asians versus Whites	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Medicare only	AF	0.581 (0.324, 1.040)	0.0677	0.484 (0.273, 0.857)	0.0128	1.201 (0.960, 1.502)	0.1087
	AMI	1.029 (0.964, 1.098)	0.3866	1.180 (0.870, 1.600)	0.2873	0.872 (0.741, 1.027)	0.1002
	HF	0.449 (0.291, 0.693)	0.0003	0.682 (0.439, 1.065)	0.0921	0.658 (0.468, 0.925)	0.0161
	IHD	0.948 (0.765, 1.175)	0.6261	0.857 (0.668, 1.098)	0.2231	1.106 (0.881, 1.388)	0.3854
	Stroke	0.918 (0.744, 1.133)	0.4250	1.047 (0.831, 1.318)	0.6959	0.877 (0.715, 1.076)	0.2084
Dual Eligible	AF	0.494 (0.360, 0.677)	<0.0001	0.492 (0.300, 0.805)	0.0048	1.004 (0.937, 1.075)	0.9095
	AMI	1.223 (0.998, 1.498)	0.0515	0.965 (0.840, 1.108)	0.6142	1.267 (0.968, 1.659)	0.0851
	HF	1.468 (1.155, 1.866)	0.0017	2.081 (1.464, 2.957)	<0.0001	0.705 (0.481, 1.033)	0.0731
	IHD	2.260 (1.155, 1.866)	0.0012	1.700 (0.987, 2.928)	0.0558	1.329 (0.933, 1.891)	0.1144
	Stroke	0.559 (0.364, 0.857)	0.0077	0.796 (0.611, 1.036)	0.0901	0.702 (0.504, 0.978)	0.0368

Table 2 summarizes the race/ethnicity-based hazard ratio (HR) values observed in the transition probabilities from state 0 to state 1 in the multistate model presented in figure 2. The estimated HR corresponds to a specific racial/ethnic group in comparison to a reference group, using the pseudo-value regression approach. The results were stratified by Dual Eligibility (DE) status.

Table 3. Racial/ethnic effects on the risk of death after AD and a subsequent CVD.

		NHPI versus Whites		NHPI versus Asians		Asians versus Whites	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Medicare only	AF	0.864 (0.791, 0.944)	0.0012	0.754 (0.655, 0.867)	<0.0001	1.146 (0.964, 1.361)	0.1215
	AMI	1.036 (0.968, 1.108)	0.3044	0.963 (0.897, 1.033)	0.2951	1.075 (0.802, 1.440)	0.6282
	HF	0.954 (0.874, 1.041)	0.2885	0.878 (0.801, 0.962)	0.0053	1.087 (0.634, 1.861)	0.7612
	IHD	1.230 (0.975, 1.551)	0.0803	1.062 (0.945, 1.193)	0.3118	1.158 (0.929, 1.442)	0.1899
	Stroke	1.009 (0.964, 1.055)	0.6962	1.036 (0.990, 1.084)	0.1233	0.974 (0.874, 1.084)	0.6316
Dual Eligible	AF	1.709 (1.317, 2.217)	<0.0001	1.450 (1.173, 1.793)	0.0006	1.178 (0.915, 1.516)	0.2032
	AMI	1.583 (1.012, 2.476)	0.0441	1.127 (0.954, 1.330)	0.1579	1.404 (1.002, 1.966)	0.0482
	HF	1.623 (1.034, 2.547)	0.0352	1.139 (0.913, 1.421)	0.2485	1.424 (0.983, 2.062)	0.0612
	IHD	1.574 (1.098, 2.256)	0.0135	1.136 (0.863, 1.495)	0.3627	1.385 (0.961, 1.994)	0.0799
	Stroke	0.986 (0.906, 1.073)	0.7445	1.027 (0.939, 1.123)	0.5578	0.960 (0.760, 1.212)	0.7316

Table 3 summarizes the race/ethnicity-based hazard ratio (HR) values observed in the transition probabilities from state 1 to state 2 in the multistate model presented in figure 2. The estimated HR corresponds to a specific racial/ethnic group in comparison to a reference group, using the pseudo-value regression approach. The results were stratified by Dual Eligibility (DE) status.

increased risk for AMI (HR = 1.223, p = 0.0515). However, NHPIs had reduced chance for AF (HR = 0.494, p < 0.0001) and stroke (HR = 0.494, p = 0.0077). Note that previous analysis of CVD risk on AD subjects, did not revel an increased risk for AF and stroke, thus our interest is to identify risk groups on AMI, IHD, and HF in the current analysis. DE NHPIs also had higher HF risks than Asians (HR = 2.081, p < 0.0001) and a borderline significance for IHD (HR = 1.701, p = 0.0558). NHPIs risk for AF was lower than Asians (HR = 0.492, p = 0.0048). DE Asians had a lower risk of stroke than whites (HR = 0.702, p = 0.0368).

Among the Medicare-only cohort, results were different. In this cohort, we found NHPIs had reduced risks for HF (HR = 0.449, p = 0.0003), and a borderline reduced risk for AF (HR = 0.581, p = 0.0677). NHPIs also had a reduced AF risk compared to Asians (HR = 0.484, p = 0.0128). Additionally, in the Medicare-only group, Asians had reduced risks for compared to whites (HR = 0.658, p = 0.0161).

Racial/ethnic effects on the mortality risk after CVD events, among AD patients

The results of the analysis on racial/ethnic differences in the risk of death after CVD conditions among AD patients are summarized in Table 3.

Within the DE cohort, it was found that NHPIs exhibited an increased risk for several CVD conditions, including AF (HR = 1.709, p < 0.0001), AMI (HR = 1.583, p = 0.0441), HF (HR = 1.623, p = 0.0352), and IHD (HR = 1.574, p = 0.0135). Furthermore, NHPIs within the DE cohort had a higher risk of death after AF compared to Asians (HR = 1.450, p = 0.0006). Additionally, DE Asians were found to have an increased risk of death after AMI compared to whites (HR = 1.404, p = 0.0482).

In the Medicare-only cohort, NHPIs showed a reduced risk of death after AF (HR = 0.864, p = 0.0012). Moreover, in this cohort, NHPIs had a decreased risk of death after both AF (HR = 0.754, p < 0.0001) and HF (HR = 0.878, p = 0.0053) compared to Asians.

Further exploration of racial/ethnic effects with stratification by gender

We conducted an additional exploratory analysis that included stratification by gender to examine the racial/ethnic effects on CVD risk after developing AD and on mortality risk following CVD events. The results of this analysis are provided in Supplemental Tables 4 and 5. This exploratory analysis suggests potential variation in racial/ethnic effects between males and females.

Discussion

In this retrospective, Medicare population-based study, our objective was to investigate the risk of developing CVD conditions/events among AD patients across multiple dimensions. The study outcomes indicated that AD patients are at an increased risk of AMI, HF, and IHD compared to non-AD subjects. However, we did not find statistically significant evidence to support an increased risk for AF and stroke. This assessment employed age-stratified propensity score matching to align the demographics and pre-existing medical conditions of the AD and non-AD groups, thereby minimizing potential biases in the study findings.

While our findings indicate that AD is linked to an elevated risk of various CVD conditions, the mechanisms and causal relationships underlying this association remain unclear. It is plausible that vascular risk factors are more prevalent among AD patients compared to the general population, potentially leading to a higher incidence of vascular events in this group. Prior studies have identified the occurrence of diastolic dysfunction among individuals with AD, along with the existence of intramyocardial deposits of Aβ within their myocardium.[11] It has been postulated that the influence of Aβ-PAOs on cellular functionality in the heart, akin to its impact on the brain, could potentially play a role in the manifestation of myocardial dysfunction.[11,38,39] Previous research has demonstrated that patients with AD exhibit a higher degree of atherosclerosis compared to individuals without dementia. Additionally, the presence of the apolipoprotein-E genotype allele has been associated with increased severity of atherosclerosis.[40]

Hawaii's population is distinct from the general US population, and is considered unique in several respects, particularly due to its significant ethnic diversity, distinct lifestyle, and geographical location. Within this demographic, extensive research has highlighted racial and ethnic health disparities across various contexts. Notably, the NHPI group exhibits increased risks for several health conditions, including diabetes,[41] chronic kidney disease,[21] obesity,[42] and CVD,[15,18] compared to other racial groups residing in Hawaii. The focus on these disparities is particularly pertinent given the rapid growth of the NHPI population, which is recognized as the fastest growing demographic in the US Indeed, between 2000 and 2010, the NHPI population in the US expanded by approximately 40%.[43] In the second phase of this study, we explored racial and ethnic disparities in CVD risk among AD patients. We determined that socioeconomic status, approximated by the DE index, significantly influences the racial impact on CVD risk. While the DE index is recognized as a proxy for low socioeconomic status,[27,44,45] individuals in this category are more susceptible to chronic conditions compared to those with Medicare-only coverage,[46,47] leading to increased Medicare expenditures.[48] Consequently, the DE population has become a critical focus of public health research. Note that, studies indicate that DE patients experience poor short- and long-term outcomes for CVD conditions considered in the study: AMI, AF, HF, IHD, and stroke, compared to their Medicare-only counterparts.[27,49,50]

In our analysis of the DE group, we observed that NHPI AD patients faced a higher risk of developing HF and IHD compared to white individuals. Furthermore, DE NHPIs exhibited a greater HF risk than Asians. However, the results differed when considering the Medicare-only cohort, as NHPIs in this group had reduced risks for HF. These findings suggest that lifestyle behaviors, health education, neighborhood environment, access to high-quality healthcare, and other crucial resources affecting health outcomes could be influenced by socioeconomic status. The intersection of low socioeconomic status and belonging to a disadvantaged minority compounds these detrimental effects, further reinforcing existing health disparities.[51] For instance, a study in a different context shows that Native Hawaiian participants in Hawaii with low socioeconomic status and low education had nearly 2.5 times higher all-cause mortality hazard compared to Japanese Americans in Hawaii with high socioeconomic status and high education.[52]

Based on our findings, we propose that future research should delve deeper into this issue to gain a better understanding. The influence of neighborhood socioeconomic factors on CVD risk has been established in the general population.[53,54] This impact is likely attributed to factors such as physical activity regulation, social interaction, pollution, noise, and heat exposure.[55–57] For example, a study reveals that for each 5 μg/m³ increment in air pollution, the hazard of stroke increases by 24%.[58] Moreover, a person's food environment, including aspects like food access, the ability to acquire food, and food security, significantly influences dietary behaviors and subsequently impacts CVD risk.[59] Rurality and limited access to healthcare are well-known contributors to health disparities.[60,61] In Hawaii, neighboring islands face physician shortages ranging from 32% to 44%, compared to 16% on O'ahu.[62] The statewide physician shortage in cardiology is 33%, but much higher shortages are reported on the Big Island (54%) and Kaua'i (67%).[62] It is important to understand that while social and neighborhood

features may directly affect CVD risks, their interactions with traditional risk factors could also play a role.[63]

The connection between CVD and AD progression has been an important interest of AD research, with numerous studies providing evidence that supports this link. These studies suggest possible mechanistic associations between AD and various CVD conditions, including AF, AMI, HF, IHD, and stroke, all of which were included in the current study.[22–24] It is estimated that one-third of AD-related dementias are associated with modifiable atherosclerotic CVD risk factors, such as hypertension, which contribute to the accumulation of amyloid.[22] In previous work, we investigated the risk of developing AD among individuals with CVD in Hawaii's elderly population, utilizing the same Medicare data and a similar analytical approach. This earlier study demonstrated increased risks of AD following AF, HF, IHD, and stroke. Notably, among individuals with low socioeconomic status (i.e., DE group), NHPIs exhibited higher risks of AD compared to Asians for AF, AMI, HF, IHD, and stroke, and compared to whites for HF, IHD, and stroke. Interestingly, this pattern was reversed in the group with better socioeconomic status, where NHPIs showed reduced risks of AD compared to whites for AF, HF, and IHD, and compared to Asians for HF and IHD. The study by Siriwardhana et al.[24] serves as a natural extension of the current research, exploring CVD risks among individuals with AD. Collectively, these studies highlight the influence of racial-ethnic and socioeconomic factors on the bi-directional relationship between CVD and AD. This body of work suggests a particular vulnerability among NHPIs with low socioeconomic status, both in the progression from CVD to AD and vice versa.

Examining the patterns of care based on DE status allows for the incorporation of a low-income indicator at the individual level in clinical practice. It is important to place greater emphasis on these associations and foster interdisciplinary initiatives that raise awareness among practitioners and AD patients alike. Given the racial diversity and health disparities in a state like Hawaii, comprehending the role of race can potentially yield benefits for elderly patients through the implementation of appropriate evidence-based AD treatments. Engaging in discussions among stakeholders including neurologists, cardiologists, patient representatives/ family members, and other supporting groups could be useful in addressing these aspects. Moving forward, public health policy developments should prioritize high risk groups, focusing on early prevention strategies and effective healthcare resource management. It is worth noting that the healthcare claims captured in the Medicare database within the DE group may more effectively represent disease dynamics compared to the Medicare-only group. This discrepancy can be attributed to the fact that additional health insurance coverage, such as private insurance, tends to be more prevalent among Medicare-only beneficiaries.

There are several limitations of this study that need to be highlighted. It is important to note that disease identification using ICD codes may not be entirely effective in health research studies. However, it is often unavoidable in studies that rely solely on administrative databases, such as Medicare data. Specifically, AD status could be misdiagnosed in patients with other forms of dementia, such as vascular dementia, during patient encounters. Although a careful classification using various other forms of data is preferable, such supporting data was not available for the current study. Additionally, the subjects' disease history prior to the earliest follow-up date of January 1, 2009, was based on records of several major diseases/events. This approach may not comprehensively reflect the disease profile. Consequently, individuals with a prior disease history might be misclassified as healthy or newly diagnosed patients, leading to issues with time-to-event analysis. Hawaii's population is highly diverse, with significant Asian representation from multiple sub-Asian ethnicities. Previous studies have indicated significant health disparities within the Hawaiian Asian population. For example, the Hawaiian Filipino population has been identified as disadvantaged for multiple health conditions, including CVD risk.[64] However, Medicare data does not provide detailed ethnic identities among Asians, even though refined Asian identity data could offer more insights. The study analysis may also lack several other influential factors (e.g., temporal effects along with calendar time or subjects' history of medication). Health insurance databases may not capture an individual's real-time health status, which is crucial for studying progressive diseases. In these databases, data becomes available only when an insurance claim is processed, leading to underreporting of incidents. Factors such as lack of disease awareness, delayed hospital visits, use of multiple insurance plans, or switching among plans can contribute to underreporting of health events. Such issues potentially underestimate transition hazards rather than overestimate them. Since the Medicare population aged 65 and above does not reflect the general elderly population, the generalizability of the study findings can be limited. Despite these limitations, it is important to note that longitudinal health insurance databases, such as Medicare, allow researchers to investigate public health problems related to disease transition and progression, as capturing health status in a continuous timeframe is challenging in real-life situations.

We believe our study aims to offer valuable insights into the CVD risks faced by individuals with AD and shed light on racial and ethnic disparities. The findings hold significant potential for benefiting the community and healthcare stakeholders, particularly in terms of resource allocation to address the identified disparities. These findings can be utilized to develop targeted strategies for managing CVD risks in AD patients and can serve as a guide for future research endeavors in this field.

Conclusion

This study reveals an elevated risk of developing AMI, HF, and IHD among individuals with AD. Additionally, it highlights that these risks vary across different racial groups, with further stratification based on socioeconomic status.

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Statements and declarations

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to third-party agreements, but are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

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