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Research Report

Sex Differences in Cardiovascular Disease and Cognitive Dysfunction in Rural West Elderly Texans[1]

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Abstract.
Background: The prevalence of cognitive dysfunction increases in elderly due to cardiovascular disease related risk factors in rural communities like West Texas.
Objective: The purpose of this study was to find risk factors of cardiovascular disease (CVD) related to cognitive dysfunction and their impact on elderly adults in rural West Texans.
Methods: Statistical methods such as Pearson's chi-squared and a multinomial logistic regression were utilized to analyze data. We used SPSS software to detect and understand the nature of the risk factors.
Results: A summary of statistics was obtained by using Pearson's chi-squared test for categorical variables. CVD, diabetes mellitus, and depression were significantly associated with cognitive dysfunction for both males and females ($p = 0.0001$), whereas anxiety was found to be significantly associated with cognitive dysfunction for females ($p = 0.0001$). Age group and race/ethnicity were significantly associated with cognitive dysfunction for both males and females ($p = 0.0001$). By performing a multinomial logistic regression method and controlling for confounders, the significant risk factors ($p < 0.05$)—age (65–84 years), diabetes, and memory loss for age-associated cognitive impairment; diabetes for cognitive impairment no dementia; age (65–84, $\geq$85 years), CVD, diabetes, depression, memory loss, non-Hispanic Whites, and Black/African-Americans for mild cognitive impairment; and age, memory loss, non-Hispanic Whites, Black/African-Americans, and male gender were found for dementia.
Conclusion: CVD related risk factors in developing cognitive dysfunction exist and integrating such risk variables may guide relevant policy interventions to reduce Alzheimer's incidence or dementia in rural communities in West Texans.

Keywords: Alzheimer's disease, cardiovascular disease, cognitive dysfunction FRONTIER database

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INTRODUCTION

Cognitive dysfunction is the loss of intellectual abilities such as a person's thoughts, memories, and reasoning capabilities. Late-onset cognitive dysfunction may lead to cardiovascular disease (CVD) in the United States (U.S.). Cognitive dysfunction and CVD are chronic diseases that are disproportionately distributed among the elderly across the population worldwide. The prevalence of these conditions increase each year, especially in underserved communities such as rural West Texas. Increasing evidence suggests a likely association between CVD, and its risk factors, with incidence of cognitive decline and Alzheimer's disease (AD) [1–4]. Individuals with subclinical CVD are at higher risk for AD and dementia. It is well established that several cardiovascular factors, including hypertension, high LDL cholesterol, low HDL cholesterol, and diabetes are risk factors for dementia and AD in elderly individuals. Dementia and AD patients with hypertension, high LDL cholesterol, low HDL cholesterol, and diabetes who are treated experience less cognitive impairment than similar untreated patients. Therefore, it important to study risk factors for CVD and dementia and AD in a rural population such as West Texas. AD has become one of the most common chronic diseases in developed countries. Estimates indicate that over 13 million people in the U.S. alone will have AD by 2050 [5]. AD is the most common disease associated with dementia. AD typically progresses slowly in three general stages-mild (early stage), moderate (middle stage), and severe (late stage). AD is often diagnosed in the mild dementia stage, when it becomes clear to family members that a person is having significant trouble with recalling and thinking that impacts daily functioning.

AD is synonymous with neurodegenerative and progressive disorder caused by the destruction and damage of neurons. This destruction of neurons begins to affect other parts of the brain that play an important role in one's memory and visuospatial abilities with the earliest symptom being memory loss. Individuals who suffer from AD typically present a vast array of symptoms ranging from non-cognitive symptoms like depression and psychotic symptoms such as hallucinations and behavioral symptoms such as increased aggression and motor hyperactivity. The final stages of AD cause individuals to remain bedridden and ultimately the disease is fatal [6]. It is important to note that the current symptoms used to identify and diagnose AD occur long after changes to the brain of an individual have already occurred, meaning that often times an individual is not diagnosed until the disease has already progressed and cognitive impairment has worsened [7].

It is difficult to determine how many deaths are caused by AD each year because of the procedure in which death causations are recorded. According to data from the Centers for Disease Control and Prevention (CDC), 121,404 people died from the complications of AD in 2017 in the U.S. [8], where Texas State alone had 9,545 deaths [9]. Between 2000 and 2017, the number of deaths from AD as recorded on death certificates has more than doubled, increasing to 145% [9]. AD is also caused by CVD related risk factors.

An estimated 5.7 million Americans have AD. By mid-century, the number of people living with AD in the U.S. was projected to grow to 13.8 million, fueled in large part by the aging baby boomer generation [10]. In 2015, official death certificates recorded 110,561 deaths from AD, making AD the sixth leading cause of death in the U.S. Early diagnosis of AD could have important personal and financial benefits. A mathematical model estimated that early and accurate diagnosis of AD could save up to $7.9 trillion in medical and health care costs [10]. Total annual payments for health care, long-term care, and hospice care for people with AD or other dementias were projected to increase from $277 billion in 2018 to more than $1.1 trillion in 2050. This dramatic four-fold rise includes government spending under Medicare and Medicaid and out-of-pocket spending [10].

Heart disease is a leading cause of death in the U.S. [11], while stroke is the fifth leading cause of death. Together, heart disease and stroke, along with other CVD, are among the most widespread and costly health problems facing the nation today, accounting approximately for $320 billion in health care expenditures and related expenses annually [12]. Currently more than 1 in 3 adults (85.6 million) live with one or more types of CVD [12]. In addition, being the first and fifth leading causes of death, heart disease and stroke result in serious illnesses and disabilities contributing to decreased quality of life and several hundred billion dollars of economic burden every year [13]. CVD is also the leading cause of deaths in Texas [14]. In 2010, an estimated 8.3% of adult Texans reported that they had been diagnosed with CVD [14], implying that there were approximately 1.5 million adults in Texas living with CVD in 2010 [14]. In 2010 in Texas, there were 38,096 CVD related deaths compared to AD at 5,200 deaths [15].

Texas has a racially and ethnically diverse population, wherein the Hispanic population increased

from 9.7 million in 2010 to 11.1 million in 2018 [16]. Meanwhile, the White population has only increased by 458,000. With these differences in growth rates, the Hispanic population in Texas continuing to easily outpace growth among White Texans, and it is likely the state will reach that demographic milestone as soon as 2022. Texas has gained almost four times as many Hispanic residents as non-Hispanic White residents since 2010 [16]. In 2010, less than one-half (46.0%) of the population were non-Hispanic White. Hispanics accounted for nearly two-fifths (37.6%) of the Texas population compared to 16.3% of the U.S. population [17].

Tao et al. [18] conducted a study to investigate the association between major depressive disorder and the subsequent development of AD in elderly patients, over 65 years old from 2002 to 2006 with different health statuses using Taiwan's National Health Insurance Research Database. This study found that patients with depression, very severe health status, or clogged arteries resulting in decreased blood flow were at a higher risk of developing AD. Madaleno et al. [19] conducted a study to evaluate mood, quality of lifestyle, and the presence of CVD risk factors in older women caregivers of patients with AD dementia compared to non-caregivers living in the neighborhood. They found that the CVD risk markers and lifestyle to be similar in caregivers and non-caregivers, but there was a higher prevalence of depression and anxiety among caregivers.

Scheepers et al. [20] examined whether low serum urate (determined in 1968–1969 and 1992–1994) was associated with risk of late-life dementia. Their findings supported the hypothesis that serum urate (sU) has a protective role in the development of dementia, regardless of dementia subtype. This may have important implications in the treatment of dementia and treatment goals for hyperuricemia in patients with gout. Guest [21] described that early diagnosis of AD can help to improve outcomes for the patients by facilitating earlier treatment. Previous literature indicates that neurological disorders accounted for the most Disability Adjusted Life Years (DALYs) of the Global Burden of Disease (10%). More than half of neurological DALYs resulted from the combination of stroke (42%) and dementia (10%) [22]. These two disease conditions pose risk for each other and share the same predisposing factors. However, occurrence of stroke doubles the risk for developing dementia. Shalimova et al. [23] assessed the epidemiology, mechanisms, and consequences of cognitive dysfunction in Type 1 diabetes. They have concluded that both the direct effects of altered glucose metabolism on the brain and diabetes related CVD could explain higher rates of cognitive dysfunction and faster progression in Type 1 diabetes.

Stampfer [24] suggested that growing evidence supports a strong and likely causal association between CVD, and its risk factors, with incidence of cognitive decline and AD. He also concluded that although substantial evidence indicates that diet is a major risk factor for CVD, relatively little research has been conducted on diet and cognitive function or dementia. According to Stampfer it was hypothesized that the participants in Project FRONTIER with CVD were at higher risk for AD. Several CVD risk factors are also similar to those of AD, such as hypertension, high LDL cholesterol, low HDL cholesterol, anxiety, depression, Type 2 diabetes, heavy alcohol consumption, sedentary lifestyle, and poor diet.

There are many government agencies and hospitals that are collecting lifestyle-related chronic disease data and storing them for future records. Statistical analyses are immensely important to analyze these existing data to make scientific decisions on chronic illnesses using statistical methods and predicting future chronic disease progression. Importantly, findings from analysis of huge amounts of lifestyle-related chronic disease data would enhance the knowledge of healthcare researchers and policy makers for innovative intervention in the rural counties including underserved areas: a "Framingham-like" study designed to examine health conditions of adults and elders living in rural communities, and with the goal of applying this knowledge to improve their healthcare. Project FRONTIER is currently being enacted in four West Texas counties, Cochran, Parmer, Bailey, and Hockley, with the ultimate goal of expanding to many rural counties throughout West Texas, aiming to explore questions like what does it mean to live and age in a rural community? These are the type of questions that inspired the initial creation of the Cochran County Aging Study and its expansion into Project FRONTIER. Are rural residents more at risk for AD, dementia, obesity, CVD, diabetes mellitus, and a number of other diseases? If so, what drives these disparities, and what can be done to stem their rising incidence in rural communities? The Cochran County Aging Study began in 2006 with primary focus on the interaction between cardiovascular risk factors and the development of cognitive dysfunction, particularly AD.

This paper aims to 1) explore the risk factors of CVD related to cognitive dysfunction; 2) determine subgroups variations of such diseases; and 3) identify disparities between race and ethnicity groups

among adult patients (≥40 years) through four rural West Texas counties collected by Project FRONTIER (2006–2018). This study will help to understand gender differences in the cognitive dysfunction, AD, and CVD related other chronic diseases and their impact on rural West Texans. It was hypothesized that significant differences of chronic diseases exist among males, females, age, race/ethnicity, geographic area, and socioeconomic status for cognitive dysfunction, and so that proper intervention can be made to prevent diseases and promote health.

MATERIALS AND METHODS

Project FRONTIER

Project FRONTIER (Facing Rural Obstacles to Healthcare Now Through Intervention, Education & Research) is an epidemiological cohort study exploring the natural course of chronic disease development, and its impact on longitudinal cognitive, physical, social, and interpersonal functioning in a multi-ethnic adult sample from rural communities of West Texas. It was initiated in 2006 as the Cochran County Aging Study, by including persons who were 40 or above and lived in one of the counties was eligible to participate. Project FRONTIER captured the participants in four counties, namely Cochran, Parmer, Bailey, and Hockley.

IRB approval

This study protocol was approved by TTUHSC IRB (Texas Tech University Health Sciences Center, Institutional Review Board) NUMBER: L15–158; IRB APPROVAL DATE: 07/06/2015. TTUHSC strictly follows high ethical standards in the Department of Public Health and its other schools.

Sample size and power calculation

The sample size was calculated by using G*Power software (version 3.1.9.4) [25]. A total of 88 subjects were sufficient to detect a statistically significant relationship between categorical variables with 5% level of significance, median effect size = 0.30, and power = 80% when running a chi-squared test. In most of the cases the study samples were large enough; however, a few cases had small sample size.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) software (version 25.0) [26] was used for statistical analysis. The statistical method of Pearson's chi-squared test for categorical variables was used considering statistical level of significance alpha (α) = 0.05. A multinomial logistic regression was performed for categorical dependent variable (Normal Cognition, Age-Associated Cognitive Impairment (AACI), Cognitive Impairment No Dementia (CIND), Mild Cognitive Impairment (MCI), and Dementia) with some categorical independent variables (age, gender, CVD, diabetes, depression, and race/ethnicity) to calculate odds ratios (OR) and 95% confidence intervals (CI), and to determine an association between risk factors and the occurrence of a cognitive dysfunction.

RESULTS

To investigate whether there were any significant relationships between different age groups and anxiety, a study was conducted on Project FRONTIER data using statistical methods. The age groups for the participants were 40–64, 65–84, and ≥85 years and included 462 male and 1,046 female participants. The highest rate of not having anxiety among males was in the age group 40–64 years with a total of 231 individuals and the lowest was in the age group ≥85 years with a total of 14 individuals. The highest rate of anxiety among males was in the age group 40–64 years with 49 individuals and only one male individual ≥85 years of age was found to have anxiety. In the female category, the highest amount of anxiety was observed in the age group 40–64 in which there were 155 individuals. Among females, those ≥85 reported the lowest levels of anxiety with a total of 18 individuals. Anxiety was significantly associated with being females ($p = 0.0130$) but not males ($p = 0.4130$).

Table 1 demonstrates the relationship of CVD among males and females, and among three age groups, 40–64, 65–84, and ≥85. There was a total of 461 males and 1,047 females in this study. In the male age group of ≥85 years, CVD was observed in 3 individuals out of 15 individuals. The highest rate of CVD was seen in males with the age group of 65–84 years, with 36 individuals diagnosed out of 168 individuals. Similar results were noticed among females of the same age group, and only 4 females out of 18 were diagnosed with CVD in the age group of ≥85 years. CVD was significantly associated with the age groups for both males and females ($p = 0.0001$).

To find whether there was a relationship between depression and age groups among males and females, a total of 462 male and 1046 female individuals par-

Table 1
Age and cardiovascular disease for males and females

	Cardiovascular Disease							
	Male				Female			
Age Groups	No	Yes	Total	*p*	No	Yes	Total	*p*
40 to 64	257	21	**278**	0.0001	682	31	**713**	0.0001
65 to 84	132	36	**168**	0.0001	273	43	**316**	0.0001
≥85	12	3	**15**	0.0200	14	4	**18**	0.0180
Total	**401**	**60**	**461**	0.0001	**969**	**78**	**1,047**	0.0001

Table 2
Cognitive dysfunction and diabetes mellitus for males and females

	Diabetes Mellitus							
	Male				Female			
Cognitive Dysfunction	No	Yes	Total	*p*	No	Yes	Total	*p*
Normal Cognition	229	74	**303**	0.0001	628	168	**796**	0.0001
AACI	16	15	**31**	0.8570	32	16	**48**	0.0210
CIND	13	4	**17**	0.0290	13	17	**30**	0.4560
MCI	47	39	**86**	0.3880	92	62	**154**	0.0160
Dementia	8	7	**15**	0.7960	7	3	**10**	0.2060
Total	**313**	**139**	**452**	0.0001	**772**	**0 266**	**1038**	0.0001

AACI, age-associated cognitive impairment; CIND, cognitive impairment no dementia; MCI, mild cognitive impairment.

ticipated in the study. There were 56 males diagnosed with depression in the age group 40–64. In the male age group ≥85 years, there was only one individual with depression. This shows that as age increases among males and females, there was a decreasing trend of depression. In females, depression was highest in age range 40–64 with 194 females suffering from depression, and the lowest was observed in the age ≥85 with one individual. Depression was significantly associated with female age groups ($p = 0.0010$), but it was not significantly associated with male age groups ($p = 0.4100$).

When assessing the relationship between AD and age, the data were available for 244 males and 563 females. The highest number of males suffering from AD was seen in age group 40–64 with 21 males out of 158, the lowest was seen in ≥85 age group with 3 individuals out of 8 males, and 17 individuals out of 78 males in age group 65–84. Among females, 94 out of 402 females in age group 40–64, 31 out of 156 females in age group 65–84, and none in age group ≥85 suffered from AD. AD was not found to be significantly associated with both for male ($p = 0.0730$) and female ($p = 0.3260$) age groups.

Data for 462 males and 1046 females were available to assess the relationship between alcohol consumption and the ages were grouped into 40–64, 65–84, and ≥85 years. The highest amount of alcohol consumption among males was seen within the age group 40–64 years and four individuals had alcohol consumption in 65–84 age group. There was no male in the age group ≥85 who were associated with alcohol consumption. Alcohol was found to be significantly associated with male age groups ($p = 0.0001$). In the female age groups 65–84 and ≥85 years, no individuals consumed alcohol. In the age group 40–64 among females there were 11 females (highest) associated with alcohol consumption. Alcohol was not found to be significantly associated ($p = 0.0750$) for female age groups.

Table 2 shows the relationship between diabetes mellitus and cognitive dysfunction. Of the 452 males, there was a large number of individuals who did not have normal cognition (NC) in comparison to those who did. There was a higher number of females with less than normal cognition levels and a higher rate of having AACI in comparison to males. There was a higher chance of having CIND among females compared to among males. It was observed that a high percentage of males did not have MCI and a high percentage of females had MCI. Rate of dementia was seen less among females than among males. Cognitive dysfunction was found to be significantly associated with diabetes mellitus ($p = 0.0001$) for both males and females.

As it relates to cognitive dysfunction and anxiety, there were 5 classifications within cognitive disorder studies: Normal cognition, AACI, CIND, MCI, and Dementia. Of the 454 male participants, there were 261 individuals who did not have anxiety and did not experience normal cognition. A total of 44 male participants had normal cognition level and anxiety.

Table 3
Cognitive dysfunction and depression for males and females

	Depression							
	Male				Female			
Cognitive dysfunction	No	Yes	Total	*p*	No	Yes	Total	*p*
Normal Cognition	266	39	**305**	0.0001	635	161	**796**	0.0001
AACI	18	13	**31**	0.3690	29	19	**48**	0.1489
CIND	15	2	**17**	0.0016	19	11	**30**	0.1441
MCI	61	25	**86**	0.0001	98	56	**154**	0.0001
Dementia	10	5	**15**	0.1967	7	3	**10**	0.2050
Total	**370**	**84**	**454**	0.0001	**788**	**250**	**1038**	0.0001

AACI, age-associated cognitive impairment; CIND, cognitive impairment no dementia; MCI, mild cognitive impairment.

There were 22 male individuals who did not experience AACI and anxiety. Nine male participants had both anxiety and AACI. Two male participants were diagnosed with CIND and anxiety, whereas 15 did not have anxiety and CIND. MCI and anxiety were seen among 16 male individuals and 70 individuals did not have anxiety and MCI. Dementia and anxiety were seen in one male participant and 14 did not have anxiety or dementia. Overall, anxiety was not found to be significantly associated with cognitive dysfunction ($p = 0.1900$) for male participants. Of the 1,038 female participants, 662 did not have normal cognition levels or anxiety. A total of 134 females had both anxiety and normal cognition. There were 15 females had both AACI and anxiety and 33 did not have either condition. There were 9 female participants who had CIND and anxiety, while 21 did not have CIND or anxiety. In addition, 110 females did not have MCI or anxiety and 44 had both MCI and anxiety. There were 10 females who did not have anxiety or dementia. To compare male and female responses, it was observed that there was a higher rate of female individuals ($n = 134$) who experienced normal cognition and anxiety. AACI was lower among males and females who had anxiety. CIND was at a lower rate among males and females. There were fewer males ($n = 16$) who had MCI in comparison to females ($n = 44$). Females did not have larger percentage of MCI than males. One male was diagnosed with dementia in this investigation. Overall, anxiety was found to be significantly associated with cognitive dysfunction ($p = 0.0001$) for female participants.

Table 3 displays the relationship between cognitive dysfunction and depression for males and females. There were total of 454 male participants and 1,038 female participants. Of the 305 males with normal cognitive functioning, 266 did not have depression and 39 had symptoms of depression. Among the males with AACI ($n = 31$), 18 did not have depression and 13 had depression. Of the males with CIND ($n = 17$), 15 did not have symptom of depression and 2 had depression. For the males with MCI ($n = 86$), 61 did not have depression and 25 had symptoms of depression. For the males with dementia ($n = 15$), 10 did not have depression and 5 had symptoms of dementia. There was a significant association between cognitive dysfunction and depression for males ($p = 0.0001$).

Out of 1,038 female participants, 796 had normal cognition, 48 had AACI, 30 had CIND, 154 had MCI, and 10 had Dementia. Among the females with normal cognition levels, 635 did not have depression and 161 had symptoms of depression. Out of 48 females with AACI, 29 did not have depression and 19 had symptoms of depression. Out of 30 females with CIND, 19 females did not have depression and 11 females had symptoms of depression. Of the 154 females with MCI, 98 females did not have depression and 56 females had depression. Out of 10 females with dementia, 7 did not have depression and 3 had depression. There was a significant association between CD and depression for females ($p = 0.0001$).

The relationship between AD and another form of memory loss with cognitive dysfunction was also investigated for both males and females. There was a total of 237 male participants and 549 female participants associated with some form of cognitive dysfunction. Among 237 male participants, there were 28 males with normal cognition who had highest number symptoms of depression. The second highest number ($n = 7$) of males were with MCI who had symptoms of depression, and none with dementia. There was no significant association found between cognitive dysfunction and AD for males ($p = 0.3300$). There was a total of 549 female participants who had some form of cognitive dysfunction. Of the 438 females with normal cognition, 104 had depression which was the highest number of females with depression in all types of cognitive disorders and only one female with depression in dementia

Table 4
Complaint memory loss and cardiovascular disease for males and females

	Cardiovascular Disease							
	Male				Female			
Age Groups	No	Yes	Total	*p*	No	Yes	Total	*p*
No Memory Loss	320	38	**358**	0.0001	778	54	**832**	0.0001
Memory Loss	80	22	**102**	0.0001	190	24	**214**	0.0001
Total	**400**	**60**	**460**	0.0001	**968**	**78**	**1046**	0.0001

category. The second highest number of 5 females had depression symptoms with AACI. There was no significant association found between cognitive dysfunction and AD for females ($p = 0.0900$).

The relationship between cognitive dysfunction and CVD for males and females was also assessed. Out of 452 male participants with cognitive dysfunction, 30 males had an early stage of normal cognition, the highest number with symptoms of CVD, 20 males with MCI who had symptoms of CVD, and no males were found who had CVD with CIND. There was significant association between cognitive dysfunction and CVD for males ($p = 0.0001$). There was a total of 1,038 female participants with some form of cognitive dysfunction. Of the 796 females with normal cognition, 40 females had CVD which was the highest number of females with CVD in all types of cognitive dysfunction and there was only one female with CVD in the dementia category. There were 28 females who had CVD symptoms with MCI. There was a significant association between cognitive dysfunction and CVD for females ($p = 0.0001$).

The relationship between AD and CVD for males and females was investigated. There was a total of 239 males and 555 female participants. Out of 239 male participants, 6 males had both symptoms of AD and CVD. Of the 200 males without AD, 187 had none of the disease and there were 13 males who had CVD. There was no significant association between AD and CVD for males ($p = 0.0610$, OR = 2.615, 95% CI: 0.928–7.368). There was a total of 555 female participants, 431 had no AD. Of them 22 had CVD and 409 did not have CVD. Out of 124 female participants with AD, 10 had CVD and 114 did not had CVD. There was no significant association between AD and CVD for females ($p = 0.2130$, OR = 1.631, 95% CI: 0.751–3.543).

Table 4 shows the relationship between memory loss and CVD for males and females. There was a total of 460 male and 1,046 female participants. Of the 358 male participants with no memory loss, 30 males had CVD and the rest of them had neither disease. Out of the 102 male participants, 22 males had memory loss and CVD, the remaining 80 males had neither disease. There was a significant association between memory loss and CVD for males ($p = 0.0040$; OR = 2.316, 95% CI: 1.297–4.134). Of the 1,046 female participants, 832 females had no memory loss and 214 females had memory loss. Among the females with no memory loss, 54 had CVD and 778 females had neither disease. Among 214 females with memory loss, 24 females had CVD and the rest of them had neither disease. There was no significant association between memory loss and CVD for males ($p = 0.0190$; OR = 1.820, 95% CI: (1.097–3.019)).

In investigating the relationship between functional impairment with memory loss or other cognitive dysfunction, a total of 102 male and 220 female participants were included. Of the 102 male participants, there were 74 males with no functional impairment from memory or other cognitive loss. Among them ($n = 74$), 17 males had CVD and 57 males had neither disease. Among 30 male participants who had functional impairment from memory or other cognitive loss, 6 males had both diseases, and 22 males had no CVD but had functional impairment from memory or other cognitive loss. There was no significant association between memory loss and CVD for males ($p = 0.8680$, OR = 0.914, 95% CI: (0.319–2.62)). Of the 220 female participants, there were 165 females with no functional impairment from memory or other cognitive loss. Among them ($n = 165$), 22 females had CVD and 143 had neither disease. Among 55 female participants with functional impairment from memory or other cognitive loss, 3 females had both diseases and 52 females who had no CVD but had functional impairment from memory or other cognitive loss. There was no significant association between memory loss and CVD for females ($p = 0.1110$; OR = 0.375, 95% CI: (0.108–1.305)).

Table 5 exhibits participants with cognitive dysfunction categorized by ethnicities (Hispanics and non-Hispanics) both for males and females. There was a total of 453 male participants in which 249 were Hispanics and 204 were non-Hispanics. There

Table 5
Cognitive dysfunction and ethnicity for males and females

	Ethnicity							
	Male				Female			
Cognitive Dysfunction	Hispanics	Non-Hispanics	Total	*p*	Hispanics	Non-Hispanics	Total	*p*
Normal Cognition	153	151	**304**	0.9086	448	346	**794**	0.0001
AACI	19	12	**31**	0.2086	21	27	**48**	0.3864
CIND	11	6	**17**	0.2253	24	6	**30**	0.0010
MCI	59	27	**86**	0.0001	91	63	**154**	0.0240
Dementia	7	8	**15**	0.7962	5	5	**10**	0.9999
Total	**249**	**204**	**453**	0.0345	**589**	**447**	**1036**	0.0001

AACI, age-associated cognitive impairment; CIND, cognitive impairment no dementia; MCI, mild cognitive impairment.

was a total of 1,036 female participants in which 589 Hispanics and 447 non-Hispanics. There was a significant association between cognitive dysfunction and depression for males ($p = 0.0300$) and females ($p = 0.0330$) of Hispanic and non-Hispanic.

A study was completed among males in the age groups with race and ethnicity (Hispanics, non-Hispanic Whites, Black/African-Americans, and Other ethnicities). Of the 466 males, 258 Hispanics, 188 non-Hispanic Whites, 15 Black/African-Americans, and 5 from Other ethnicities participated in the study. The highest number, 185 Hispanic individuals, were observed in age group 40–64. In the age group 65–84, the highest number of individuals were non-Hispanic Whites ($n = 88$). In age group ≥ 85, the largest number of participants were non-Hispanic Whites ($n = 13$). There was a total of 1,055 participants in which 604 were Hispanics, 406 were non-Hispanic Whites, 41 were Black/African-Americans, and 4 females were from Other ethnicities. In the age group 40–64, the highest participants were Hispanic females. In age group 65–84, the highest number of participants were non-Hispanic Whites. Only 18 non-Hispanic White participants were ≥ 85 years. A significant relationship ($p = 0.0001$) was found for both males and females in age groups and race and ethnicities.

A study was conducted across races and ethnicities (Hispanics, non-Hispanic Whites, Black/African-Americans, and Other) taking into consideration whether they utilized any mental health services in the past 12 months. Of the 244 male participants, there were 155 Hispanics, 78 non-Hispanic Whites, 8 Black/African-Americans, and 3 Other ethnicities; and no males responded that they had utilized mental health services. A total of 562 female participants in the study, in which out of 374 Hispanics, 17 individuals reported that they used mental health services. The second highest in the race and ethnicity groups who received mental health services was 5 Black/African-Americans out of 21 female participants. There were 5 individuals who used mental health services out of 165 non-Hispanic White female participants. A significant relationship was found ($p = 0.0001$) between race and ethnicities, and the utilization of mental health services among female participants.

Mental health services were not utilized by any of the male participants among the age groups. Within the age group 40–64, 26 out of the total 402 female participants affirmed that they used mental health services. Of the 157 females, one participant in the age 65–84 used mental health services and none used this service in the ≥ 85 age group. There was a significant association ($p = 0.0130$) found between female age groups and the usage of mental health services.

Assessing the relationship between age groups and whether the individuals could afford a doctor care, the results showed that the highest number of individuals ($n = 67$ out of 260) who could afford to visit a doctor was observed in the age group of 40–64 years. In the age group 65–84 years, 12 males could bear the cost of receiving a doctor care out of the total 141 individuals in the same age group. In the age group of ≥ 85 years, only 2 individuals out of 11 could afford a doctor care. There was a significant association ($p = 0.0001$) found between age groups and possible affordability of a doctor care. A total of 928 female participants were asked in a study of whether they could afford a doctor care within their age groups. Of the 649 participants in the age group of 40–64 years, 211 could afford the cost of a doctor care. In the age group 65–84 years, 31 females could afford a doctor care out of 270 participants, but none in the total of 9 females ≥ 85 years age group could afford a doctor care. There was a significant association ($p = 0.0001$) found between age groups and possible affordability of a doctor care for females.

The relationships between male age groups and professional assistance for mental or emotional problems also assessed. The highest number of males

($n = 13$) out of 158 participants who received such assistance was in the age group 40–64 years. There were 4 out of 79 participants received help for mental or emotional problems in the age group 65–84 years. None of the 8 males received assistance in the ≥85 years age group. There was no significant association found between professional help and age groups for males ($p = 0.4880$). Similar study was conducted in a total of 564 female participants with all age groups. The largest number of females who received such assistance was in the age group 40–64 years with 60 out of 402 participants. There were 10 out of 157 participants received assistance in the age group 65–84 years. None of the 5 participants in the ≥85 age group received assistance. There was a significant association ($p = 0.0160$) found among females within age groups seeking professional or emotional help.

An investigation was conducted among 55 male participants to observe if there was a relationship between race and ethnicity: Hispanics, non-Hispanic Whites, and Black/African American ethnicities, and an affordability of a doctor care. A total of 11 out of 29 male individuals could afford a doctor care among Hispanics, where 22 out of 22 individuals could not afford a doctor care among non-Hispanic White participants. There was a significant association ($p = 0.0080$) found in males of different race and ethnicities and affordability for a doctor. Similarly, we assessed the relationship between race and ethnicities and affordability of a doctor care in females. The highest ability to afford medical care was observed Hispanic females that are 25 out of the 129 participants. However, 55 out of 98 participants among non-Hispanic Whites were unable to bear the expenses. Our analysis found a significant association ($p = 0.0001$) between in females of different race and ethnicities and their affordability for a doctor care.

A total of 244 males among Hispanics, non-Hispanic Whites, Black/African-Americans, and Other ethnicities participated in a study of whether they sought help from a professional for a mental or emotional condition. Of the 155 Hispanics, there were 8 individuals sought assistance which was the highest among the different ethnicities. The next highest was observed among 5 out of 78 non-Hispanic White males. There was a significant relationship ($p = 0.0380$) among race and ethnicities and seeking mental or emotional assistance from a professional. Similar study was conducted in a total of female 562 female participants among Hispanics, non-Hispanic Whites, Black/African-Americans, and Other ethnicities. The number of females sought mental assistance among 46 individuals out of 374 Hispanics, 20 non-Hispanics Whites out of 165, and 3 individuals among 21 Black/African-Americans. The highest number of females not using mental assistance was 328 out of 493 Hispanic females. There was no significant association ($p = 0.9400$) found in females in race and ethnicities, and if they sought help from a professional for their mental or emotional condition.

We performed a multinomial logistic regression, where the dependent variable cognitive dysfunction was categorized into Normal Cognition, AACI, CIND, MCI, and Dementia. The independent variables were considered as age, gender, depression, CVD, diabetes, memory loss, and race/ethnicity. In this multivariable regression analysis, each variable was controlled by other variables. Considering the Normal Cognition as a referent group, the age group 65–84 years (OR = 1.754, 95% CI: 1.039–2.960), diabetes (OR = 1.836, 95% CI: 1.132–2.977), and memory loss (OR = 45.997, 95% CI: 26.674–79.230) were found to be significant risk factors for the AACI. Diabetes (OR = 2.701, 95% CI: 1.475–4.948) was found a significant risk factor for the CIND. Age group 65–84 years (OR = 4.858, 95% CI: 3.414–6.913), ages ≥85 years (OR = 345.319, 95% CI: 68.588–1738.561), CVD (OR = 1.970, 95% CI: 1.229–3.156), diabetes (OR = 1.860, 95% CI: 1.326–2.610), depression (OR = 1.471, 95% CI: 1.004–2.156), memory loss (OR = 4.549, 95% CI: 3.094–6.688), non-Hispanic Whites (OR = 2.774, 95% CI: 1.886–4.082), and Black/African-Americans (OR = 6.399, 95% CI: 3.019–13.561) were found to be potential significant risk factors for MCI. For Dementia, age group 65–84 years (OR = 12.528, 95% CI: 4.957–31.657), memory loss (OR = 4.163, 95% CI: 1.694–10.235), non-Hispanic Whites (OR = 2.887, 95% CI: 1.127–7.392), Black/African-Americans (OR = 22.550, 95% CI: 6.387–79.619), and male gender (OR = 2.449, 95% CI: 1.123–5.342) were found to be significant risk factors.

Table 6 summarizes some p-values for the relationship among the risk factors related to CVD and CD that are already reported in the Results.

DISCUSSION

In this study, we have discussed CVD-related risk factors that influence the development of cognitive dysfunction, AD, and dementia. Some of the results obtained using the Project FRONTIER database were revealed significant associations among the outcome and risk variables. The following are some related

Table 6
p-values for some chronic risk factors in males and females

Risk variables→ ↓	Anxiety	CVD	Depression	Alzheimer's disease	Alcohol	Diabetes	Mental health service/doctor/ professional care	Race and/or Ethnicity
Age groups	$p = 0.413$ (M)[a] $p = 0.013^{*}$ (F)[b]	$p = 0.0001^{***}$ (M) $p = 0.0001^{***}$ (F)	$p = 0.410$ (M) $p = 0.001^{**}$ (F)	$p = 0.073$ (M) $p = 0.326$ (F)	$p = 0.0001^{***}$ (M) $p = 0.075$ (F)	$p = 0.007^{**}$ (M) $p = 0.342$ (F)	$p = 0.0001^{***}$(M)[c] $p = 0.013^{**}$(F) $p = 0.0001^{***}$ (M)[d] $p = 0.0001^{***}$(F) $p = 0.488$ (M)[e] $p = 0.016^{*}$(F)	$p = 0.0001^{***}$(M)[f] $p = 0.0001^{***}$(F)
Cognitivedysfunction	$p = 0.19$ (M) $p = 0.0001^{***}$ (F)	$p = 0.0001^{***}$ (M) $p = 0.0001^{***}$ (F)	$p = 0.0001^{***}$ (M) $p = 0.0001^{***}$ (F)	$p = 0.330$ (M) $p = 0.090$ (F)	$p = 0.525$ (M) $p = 0.678$ (F)	$p = 0.0001^{***}$ (M) $p = 0.0001^{***}$ (F)	– –	$p = 0.030^{*}$(M)[g] $p = 0.033^{*}$(F)
Alzheimer's disease	$p = 0.680$ (M) $p = 0.319$ (F)	$p = 0.061$ (M) $p = 0.213$ (F)	$p = 0.421$ (M) $p = 0.536$ (F)	–	$p = 0.921$ (M) $p = 0.352$ (F)	$p = 0.640$ (M) $p = 0.656$ (F)	–	$p = 0.0001^{***}$(M)[h] $p = 0.062$ (F)
Memory loss	–	$p = 0.004^{**}$ (M) $p = 0.019^{*}$ (F)	–	–	–	–	–	–

[a]male; [b]female; [c]age group versus mental health service; [d]age group versus afford a doctor care; [e]age group versus professional care; [f]age group versus race and ethnicity (Hispanics, non-Hispanic Whites, Black/African-Americans, Other ethnicities); [g]cognitive dysfunction versus ethnicity (Hispanics, non-Hispanics); [h]Alzheimer's disease versus race and ethnicity (Hispanics, non-Hispanic Whites, Black/African-Americans, Other ethnicities) – indicates data not available, still is collecting CVD, cardiovascular disease; *p*, *p*-value, $^{*}p < 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.0001$ (significant at 5%; 1%; 0.01%).

published results which are similar or dissimilar to our findings. Govender et al. [27] conducted a study on a total of 216 participants (167 males and 49 females) with a history of CVD. This study included individuals with developed CVD and risk factors such as age, smoking, hypertension, and diabetes mellitus, and it was found that these individuals were at an increased risk of recurrent cardiovascular events and death. The overall incidence rate of recurrent CVD events was 92.1 per 1000 patient-years. Age, female sex, and diabetes mellitus were significant predictors of recurrent CVD events, where females had a 1.96 times higher risk of recurrent CVD events than males. We found significant association between CVD and age for both males and females. Diabetes mellitus was found to be a significant predictor of CVD for males but not females.

Yu et al. [28] conducted a study that included 29,303 participants from 2005 to 2016. It was found that the trends of severe depression increased among $\geq$20 years ($p = 0.0260$); severe depression increased among $\geq$65 years ($p < 0.001$); and moderate depression increased among 20–39 years ($p = 0.0280$). Compared to male adults, the estimated prevalence of mild depression, moderate depression, and severe depression for female adults were higher. There was an increasing trend of severe depression in the population of $\geq$65 years. We found age group (40–64; 65–84; and $\geq$85) for females to be a significant predictor for depression which was not found to be significant among males. Female participants had higher depression among age groups 40–64 and 65–84 years compared to males.

Gao et al. [29] conducted prevalence studies on dementia and AD which showed a positive association with age. Results from their meta-analysis indicated that an increase in incidence rates of both dementia and AD slowed down with increased age, although the incidence rates did not decline. For every 5-year increase in age, both dementia and AD incidence rates were tripled before age 64, doubled before age 75, and dropped down to an increase of 1.5 times around age 85. In their study, Gao et al. [29] found inconsistent relationship between AD and sex. Our findings show that for the dementia, older age group 65–84 years men has higher cognitive decline than women.

Delker et al. [30] stated that alcohol consumption varies across groups, including those defined by demographic characteristics such as age, race/ethnicity, and gender. With respect to gender, men reported more alcohol consumption and binge drink-

ing than women, especially in older cohorts. Among the participants conducted by the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), 40% of women were abstinent in the past year, compared with 32% of men. In addition, men reported more drinks per drinking occasion than women, as studied by Chan et al. [31]. Likewise, in the 2011 National Survey on Drug Use and Health (NSDUH), 57.4% of men were past-month drinkers compared with only 46.5% of women [32]. We found males in age groups were significantly associated with alcohol consumption than females which was consistent with the findings of Delker et al. [30]. Both males and females were found to have more alcohol consumption in early aged group 40–64 and males consumed higher than females. At age 65 and above there was a sharp decline in alcohol consumption for both males and females.

Ojo and Brooke [33] reviewed the association between diabetes mellitus, cognitive decline and dementia and searched strategies, and electronic databases, EBSCOhost Research and SwetsWise database, and found that the duration of diabetes, glycated hemoglobin levels, and glycemic fluctuations were associated with cognitive decline and dementia. Similarly, hypoglycemia was significantly related to increased risk of developing cognitive decline and dementia. We found there was a significant association between diabetes mellitus and cognitive decline in both males and females, and the rate of the decline was higher in males than females at the beginning age 40–64 of cognition. The likelihood of developing dementia was higher in males than females.

Danna et al. [34] conducted a study on systematic review, which assessed whether adults with comorbid diabetes and depression or depressive symptoms exhibit greater cognitive decline relative to individuals with diabetes alone. Participants were aged 18 years or older with diabetes mellitus, of which some presented with current depression, and measured cognition as an outcome. They concluded that persons with diabetes were at high risk of depression, and that people with comorbid depression and diabetes were more likely to suffer from lower cognitive functioning than their peers. We analyzed diabetes and depression separately and found that they were significantly associated with cognitive dysfunction for both males and females. Males had higher incidence rate of diabetes than females at the beginning of cognition. The incidence of depression was higher in females than males in the age group of 40–65 years and the rate of developing dementia was almost same for both males and females.

Miller et al. [35] stated that CVD and cognitive decline are two related conditions, with distinct sex differences in morbidity and clinical manifestations, response to treatments, and mortality. Although mortality from all-cause CVD has declined in women over the past five years, partly due to increased educational campaigns regarding the recognition of symptoms and application of treatment guidelines, the mortality in women still exceeds that of men. Our findings showed CVD significantly associated with cognitive dysfunction and the likelihood of male cognitive dysfunction related to CVD was higher in case of normal cognition, AACI, MCI, and dementia than females. Dementia was three times higher in males than females.

Jefferson et al. [36] stated that CVD and related risk factors were associated with AD. This association was less well-defined in normal cognition or prodromal AD (MCI). They defined a composite measure of vascular risk using the Framingham Stroke Risk Profile (FSRP) score (i.e., age, systolic blood pressure, anti-hypertensive medication, diabetes, cigarette smoking, CVD history, atrial fibrillation). In NC participants, increasing FSRP was related to worse baseline global cognition, information processing speed, sequencing abilities ($p < 0.0001$), and a worse longitudinal trajectory on all cognitive measures ($p < 0.0001$). In MCI, increasing FSRP correlated with worse longitudinal delayed memory ($p = 0.0040$). In our findings, CVD and related risk factors (age, anxiety (females), alcohol, depression, and diabetes) were associated with AD but that association was not strong enough to be statistically significant for both sexes. However, females have a higher chance to develop AD than males.

Díaz-Venegas et al. [37] examined differences in cognition between Hispanics, non-Hispanic Blacks, and non-Hispanic Whites, and older adults for all age groups (51–59, 60–69, 70–79, 80+) in the U.S. Hispanics had higher cognition than non-Hispanic Blacks for all age groups, but these differences were all within one point. The lower cognition among non-Hispanic Blacks compared to non-Hispanic Whites remained significant after controlling for age, gender, and education, whereas the differences in cognition between Hispanics and non-Hispanic Whites were no longer significant after controlling for these covariates. Their results highlighted the role of education in race and ethnic differences in cognitive function during old age. Education seems beneficial for cognition

in older age for all race/ethnic groups, but Hispanics appear to receive a lower benefit compared to other race and ethnic groups.

We found a significant association between ethnicity (Hispanics and non-Hispanics) and cognitive disorder for both males and females. Hispanics males and females had higher cognition than non-Hispanics. Among male participants, non-Hispanics had higher dementia than Hispanics, whereas in the females these differences were not observed. Race and ethnicities were regrouped into four categories: Hispanics, non-Hispanic Whites, Black/African-Americans, Other ethnicities. We found that males were significantly associated with AD than females. Furthermore, it was observed that there was a significant difference between male age groups, and race and ethnicity, which was found to be the same in case of females.

Castora-Binkley et al. [38] conducted a study to determine if there were differences in cognitive dysfunction among racial and ethnic older adults. The study did not find an association between race and cognitive performance over time, which supports some of the previous literature on differences in cognitive dysfunction by race, Atkinson et al. [39], Karlamangla et al. [40], Masel and Peek [41]. Levine et al. [42] found no evidence that racial difference in cognitive dysfunction could be explained by differences in the frequency or impact of incident stroke between blacks and whites, controlling for baseline cognition, in the nationally representative cohort of older adults.

Garcia et al. [43] documented age and educational differences in cognitive status among White, Blacks, U.S.-born Hispanic, and foreign-born Hispanic adults by sex. The findings highlighted the importance of education in CIND and dementia, particularly among foreign-born Hispanics. Addressing inequalities in education can contribute to reducing racial/ethnic/nativity disparities in CIND and dementia for older adults. Among women, foreign-born Hispanics have higher odds of CIND and dementia than Whites. For men, Blacks have higher odds for CIND and dementia compared to Whites. The higher odds for CIND and dementia across race/ethnic and nativity groups was reduced after controlling for years of education but remained statistically significant for older Black and US-born Hispanic adults.

We did not study the impact of education on cognitive dysfunction. Due to data unavailability on education, we considered data for affordability of mental health service such as a doctor or professional care from Project PRONTIER. We found highest distribution among race/ethnicities.

We found Hispanic males and females received most of the mental health services than non-Hispanic Whites, Black/African-Americans, and Other ethnicities. Though Hispanic ethnicity received most of the mental health services, they still have an increased risk of developing cognitive dysfunction compared to other race/ethnicities in rural West Texas. Further research is needed on the racial and ethnic differences in the pathways of the benefits of educational attainment for late-life cognitive function.

Alonso et al. [44] used a multivariable logistic regression method to estimate odds ratios and 95% CI of MCI/dementia by atrial fibrillation (AF) status and to assess cross sectional correlates of MCI/dementia in 6,432 patients with AF. They found older age, lower body mass index, diabetes mellitus, stroke, and *APOE* genotype were associated with dementia prevalence in participants with AF. We did not include body mass index and *APOE* genotype and found consistent results that older age (65–84 years) and diabetes were significantly associated with AACI and MCI. Diabetes was a significant predictor for CIND and older age (65–84 years) was a significant predictor for Dementia.

Hale et al. [45] found for dementia, woman's annual prevalence of cognitive impairment increase was 1.7% (CI 0.8%—2.6%) and men's 2.0% (CI, 1.0%—2.9%), but in our study we found that men have a higher cognitive decline (higher odds ratio) than women.

Rabin et al. [46] found age (70 years or older) was significantly associated for MCI which was consistent with our results. Ren et al. [47] conducted a cross-sectional study of Chinese elders aged over 80 years and reported that of the 480 participants, 30% were diagnosed with cognitive impairment. Women were significantly associated with an increased risk of cognitive impairment compared to men. We found men were significantly associated with an increased risk of cognitive decline compared to women.

It was the first time we used Project FRONTIER data related to CVD and cognitive dysfunction and covered all the study or sub-study to present the results. Project FRONTIER had a working team who designed the questionnaire and defined the variables. Variable definitions and quantifications were made by the team coordinators of the project. Since Project FRONTIER is still continuing to collect data from rural West Texas participants, in the future, when data becomes available, we will consider more variables

including genetics and environment into our analysis. The findings from this study may be used to modify the existing health policy or develop programs or early interventions for effective disease management, preservation of cognitive functioning throughout the lifespan, and improvement of the overall health of individuals living in rural West Texas.

Strengths and limitations of the study

There were several strengths and limitations in this study.

Strengths: First, this is the only study conducted on the patients living in four underserved counties in Rural West Texas by an IRB approved protocol. Second, data was collected by trained individuals and the study covers CVD-related risk variables associated with the development of cognitive disorders, AD, and dementia diseases from the FRONTIER database. Third, the study found significant risk factors in developing cognitive dysfunction among males and females with elderly age groups. Fourth, the findings of this study will help to make interventions for all age group or specific age groups for the prevention of disease and to improve lifestyle to the aforementioned counties. Fifth, the findings will help to develop a longitudinal study focusing on age groups, which has high incidence of disease to follow up at different times to observe future disease prognosis. Sixth, the findings identified significant risk factors for both males and females in the development of cognitive dysfunction, AD, and dementia among rural West Texans that would help to modify the existing health policy and additional budget for future expenses.

Limitations: First, data were based on prevalent cases identified in a hospital setting at TTUHSC. Second, the data did not include participants' information regarding who died from CVD, AD, or dementia. Third, there was no repeated data collection of the same participants for a long period of time. Fourth, the number of responses from participants for some questions were small for which running a statistical chi-squared test was problematic. Fifth, data were available only for limited variables with moderate sample size on clinical variables rather than genetic or environmental variables of chronic diseases.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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