Subjective cognitive complaints and cardiovascular risk factors in older Mexican Americans: A cross-sectional study.

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ABSTRACT

Background: Subjective cognitive complaints (SCC) are associated with higher risk of mild cognitive impairment (MCI) and dementia. Cardiovascular risk factors (CVRF) have been also associated with cognitive decline, MCI, and dementia. Few studies have examined the associated of CVRF and SCC.
Methods: Participants were cognitively normal Mexican Americans from the HABLE study. Participants were categorized as with and without SCC, and SCC was also measured as a continuous variable. CVRF diagnosis were ascertained during consensus review. Cognitive measures used were MMSE, Trails B, SEVLT, and digit span. Logistic regression and linear regression were used to asses the association of SCC with CVRF and cognitive scores.
Results: A total of 673 participants [mean age 63.3 (SD=7.71), 69.2% female] were included. SCC was present in 323 participants (47.99%). Dyslipidemia and depression were associated with SCC. Individuals with dyslipidemia had 1.72 times the odds (95% CI = 1.20 to 2.47) of SCC, and those with depression had 3.15 times the odds (95% CI = 2.16 to 4.59) of self-reporting SCC. Higher SCC scores, were significantly associated with MMSE (B = 0.07; SE = 0.03; p = 0.02), and SEVLT immediate and delayed (B= -0.03; SE = 0.00; p = 0.000 and B = -0.03; SE = 0.00; p = 0.000, respectively).
Conclusions: In a cognitively normal Mexican Americans sample of older adults, depression and dyslipidemia were correlated with self-reported SCC. A greater self-perception of cognitive decline correlated with lower scores on the MMSE and SEVLT.

1. BACKGROUND

Subjective cognitive complaints (SCC), defined as a self-reported decline in memory and cognitive functioning, have been described as an intermediate stage between normal cognition and mild cognitive impairment (MCI) or Alzheimer's disease (AD) [1]. According to the CDC, the prevalence of SCC in adults 45 years of age and older is 11.1% and 11.7% in subjects aged 65 years and older [2]. SCC have been found to be higher in males than females [3]. In individuals with normal cognition who report impairment in activities of daily living, SCC

significantly correlate with future diagnoses of MCI and dementia [3,4]. Additionally, cognitively normal individuals with SCC have been found to score lower on various measures of cognitive functioning [5,6]. Park et al showed interaction between SCC and lower performance in verbal and visuospatial memory [7], and Hall et al demonstrated in an older Mexican American cohort, that individuals with SCC had poorer performance on measures of global cognition, attention, and executive function [8].

Cardiovascular risk factors (CVRF), such as hypertension, diabetes, dyslipidemia, and obesity, have also been associated with cognitive

decline and an increased risk of MCI and developing dementia [9]. As the presence of SCC also increases the risk for cognitive decline, it may be useful to assess the relationship between CVRF and SCC. The few studies that have examined this association have shown mixed results. Jorm et al, in a community-based study of older adults, and Sterling et al, studying older African Americans, did not find significant associations between individual CVRF and SCC [10,11]. In a study about SCC prevalence among Whites, Blacks, and Hispanics, Gupta found a higher prevalence of selected chronic conditions in those with SCC, for all racial groups [12]. Chen et al also found and association of CVRF and SCC in a community US survey of 19,000 individuals aged 18 to 99 [13].

The presence of SCC has consistently been associated with depression. In a systematic review done by Hill et al, researchers concluded that cross-sectional studies consistently reported the association among SCC and depression, while findings in longitudinal studies were mixed [14]. Chung-Shian et al reported that 55.8% of depressed subjects in their cohort presented SCC [5]. SCC and depression have been shown to be independent risks for developing MCI and dementia, with the risk increasing when they co-exist [15]. Individuals diagnosed with major depression disease have shown impairment in attention, memory, executive function, and psychomotor processing domains [16]. The strong association between CVRF and depression suggests that any study of the relationship of CVRF and SCC will need to assess depression as a possible confounding variable [17,18].

Despite SCC representing a risk factor for cognitive decline, there is a dearth of research on ethnic or racial minority groups. Hispanics are the second fastest growing ethnic group in the USA, and 65% of Hispanics are of Mexican origin [19]. With the expected increase in the Hispanic population, it is predicted that over 3.5 million Hispanics will suffer Alzheimer's Disease and related dementias by 2060 [20]. Mexican Americans have a higher prevalence of CVRF and depression when compared to non-Hispanic Whites [21,22]. Understanding the impact of these factors on cognition may enhance our ability to predict cognitive decline and allow for early intervention to reduce the risk of dementia in this high-risk group. The current study will investigate the relationship between SCC, CVRF and depression in a sample of older, cognitive normal community-dwelling Mexican Americans. We also investigated the association of SCC with objective measures of global cognition, memory, attention, and executive function. It is hypothesized that CVRF will be associated with SCC, and that this association will be independent of depression. Additionally, we expect that individuals with SCC will perform worse in objective tests of global cognition, memory, attention, and executive function.

2. METHODS

2.1. Study design and setting

The Health and Aging Brain Study – Health Disparities (HABS-HD) is an ongoing longitudinal study at the Institute for Translational Research in the University of North Texas Health Science Center. The HABS-HD study is conducted under IRB approved protocols and each participant (or his/her legal representative) signs written informed consent. All HABS-HD data is available to the scientific community through the UNTHSC Institute for Translational Research (ITR) website [23]. The HABLE study methodology, including recruitment, inclusion and exclusion criteria, interview and functional exam, cognitive assessment, informant interview, imaging, and blood collection have been described in detail elsewhere [24].

2.2. Participants

One thousand seven hundred and five subjects were enrolled in the study baseline visit between October 2017 and June 2020. From those, 890 were Mexican American. A diagnosis of normal cognition was given to 673 subjects using a consensus-based algorithm (clinical dementia

rating score sum of boxes score = 0, and cognitive scores > 1.5 SD z-score adjusted norms). Three hundred and twenty-three participants (49.9%) with normal cognition reported SCC. The final sample was composed of 673 cognitively normal subjects, with and without SCC, who self-report their ethnicity as Mexican American, with complete data in cardiovascular risk factors, neuropsychological tests and covariates of interest.

2.3. Subjective cognitive complaints (SCC) measurement

For analysis, we used SCC as a categorical variable (0 = without SCC, 1 = with SCC). Participants who respond yes to the question: "Are you experiencing any problems with your memory or recent changes in your thinking ability?" were included in the SCC category. SCC were also measured as a continuous variable with the 14 item Subjective Memory Complaints Questionnaire (SCMQ), a brief questionnaire with proven reliability and validity [25]. Items 1 to 4 measure global memory function, and the last 10 items measure everyday memory function [7]. Higher scores indicate a greater self-perception of memory and cognitive decline.

2.4. Predicting Variables

A diagnosis of hypertension, diabetes, dyslipidemia, obesity, and depression were ascertained during consensus review using the following criteria:

- Hypertension: self-reported medical diagnosis, use of blood pressure – lowering drugs, and/or average of two blood pressure measurements > 140/90.
- Diabetes: self-reported medical diagnosis, current use of insulin or oral hypoglycemic agents, and/or HbA1c > 6.5%.
- Dyslipidemia: self-reported medical diagnosis of high cholesterol and or triglycerides, use of cholesterol- lowering drugs, total cholesterol > 200 mg/dL, and/or triglycerides > 150 mg/dL.
- Obesity: BMI index of 30.0 or higher.
- Depression: self-reported medical diagnosis, use of antidepressants, and/or geriatric depression scale score > 12.

2.5. Cognitive measures

Global cognition was assessed with the Mini-Mental State Examination (MMSE) [26]. Trails B was used as a measure of executive function [27]. The Spanish English Verbal Learning Test (SEVLT) evaluated immediate and delayed memory [28], and the WMS-III Digit Span (DS) was used as a measured of attention [29].

2.6. Covariates

Age, sex, and total years of education were entered as covariates.

2.7. Statistical analysis

Baseline demographic data were analyzed using chi-squared tests for categorical variables, and t tests for continuous variables. Multivariate logistic regression was utilized to assess the relationship of CVRF and depression to SCC. Hypertension, diabetes, dyslipidemia, obesity, and depression, the predictors in the models, were entered i as categorical variables (0 = absent, 1 = present). The presence of SCC, the dependent variable, was entered as a categorical variable (0 = without SCC, 1 = with SCC). Linear regression was used to test is SMCQ scores, as a continuous variable, can predict cognitive performance. MMSE raw scores were used for analyses; for Trails B, SEVLT, and DS raw scores were transformed to z-scores to facilitate effect size comparisons. Trails B higher scores indicate worse performance, so we inverted the z-score before analyses. After this transformation, for all neurophysiological

tests, a higher z-score indicated better performance.

First, all variables were entered into logistic regression analysis, using the "enter" method. We generated four models. Model 1 included only demographic variables as predictors of having SCC. Model 2 used demographic variables plus cardiovascular risk factors. Model 3 included demographic variables plus depression diagnosis. Finally, the last model included all the variables, demographic, cardiovascular risk factors, and depression. Then, we conducted a linear regression to analyze the association of SMCQ scores, the independent variable, with test performance, using each test score a separate outcome. Age, sex, years of education, and cardiovascular risk factors were entered as covariates in the models. Statistical significance was set to $p \leq 0.05$. All data were analyzed using SPSS version 28 for Windows (SPSS INC., Chicago, IL).

3. RESULTS

3.1. Baseline characteristics

The total sample included 673 cognitively normal participants with a mean age of 63.3 (7.71); 69.2% of the total sample were female. Three hundred and twenty-three subjects reported SCC (47.99%). Subjects with and without SCC did not differ on age, education or gender. We found a significant difference in SMCQ total score ($p = < 0.0001$), dyslipidemia ($p = 0.0008$), and depression ($p = < 0.0001$) between the two groups Table 1. presents the prevalence rates for categorical variables, and mean and standard deviation for continuous variables of interest.

Table 1
Sample characteristics

	Total Sample (673)	Without SCC (350)	With SCC (323)	t (95% CI)	p
Age (mean, SD)	63.3 (7.71)	62.9 (7.71)	63.74 (7.71)	1.41 (-0.33 to 2.01)	0.16
Education (mean, SD)	9.68 (4.53)	9.95 (4.70)	9.38 (4.33)	-1.63 (-1.26 to 0.12)	0.10
SMCQ total	4.08 (3.38)	2.57 (2.55)	5.71 (3.42)	13.56 (2.68 to 3.59)	< 0.0001
MMSE	26.86 (2.73)	26.99 (2.77)	26.73 (2.69)	-1.23 (-0.67 to 0.15)	0.21
SEVLT immediate	0.20 (0.83)	0.24 (0.86)	0.16 (0.80)	-1.24 (-0.20 to 0.04)	0.21
SEVLT delayed	0.26 (0.79)	0.29 (0.84)	0.22 (0.73)	-1.15 (-0.18 to 0.04)	0.25
Trails B	0.11 (0.87)	0.07 (0.95)	0.14 (0.77)	1.04 (-0.06 to 0.20)	0.29
DS	0.03 (0.91)	-0.02 (0.94)	0.09 (0.86)	1.58 (-0.02 to 0.24)	0.11
				X^2 (95% CI)	p
Gender female (n, %)	466 (69.2)	232 (66.3)	234 (72.4)	2.93 (-0.88 to 12.96)	0.09
HTN (n, %)	442 (65.7)	226 (64.6)	216 (66.9)	0.39 (-4.87 to 9.41)	0.09
DM (n, %)	237 (35.2)	116 (33.1)	121 (37.5)	1.42 (-2.81 to 11.57)	0.23
Dyslipidemia (n, %)	447 (66.4)	212 (60.6)	235 (72.8)	12.2 (5.07 to 19.12)	0.0008
Obesity (n, %)	343 (54.8)	179 (54.4)	164 (55.2)	0.04 (-6.69 to 8.27)	0.84
Depression (n, %)	210 (31.2)	66 (18.9)	144 (44.6)	51.58 (18.77 to 32.32)	< 0.0001

3.1. Association of CVRF and depression with self-reported SCC

Table 2 shows Models 1, 2, 3 and 4 of the multivariate logistic regression analyses. Model 1 shows that there was no association of age, gender and education with self-reported SCC. In Model 2, controlling for demographic variables, the only cardiovascular risk factor significantly associated with SCC was dyslipidemia. A depression diagnosis was strongly associated with self-reported SCC independently of demographic variables (Model 3). Finally, Model 4 demonstrates that dyslipidemia and depression diagnoses were associated with SCC. Individuals with dyslipidemia had 1.72 times the odds (95% CI = 1.20 to 2.47) of SCC, and those with depression had 3.15 times the odds (95% CI = 2.16 to 4.59) of self-reporting SCC.

3.2. Association of SMCQ scores with objective cognitive measures

The estimated beta coefficients, and their standard errors, for the linear regression testing the association of SMCQ scores and cognitive measures are presented in Table 3. Higher SMCQ scores, suggesting greater self-perception of cognitive decline, were significantly associated with lower scores in the MMSE, a measure of global cognition (B = 0.07; SE = 0.03; p = 0.02), and measures of immediate and delayed memory (B= -0.03; SE = 0.00; p = 0.000 and B = -0.03; SE = 0.00; p = 0.000, respectively). Trails B and digit span were not associated with SMCQ scores.

4. DISCUSSION

In our community-based sample of cognitively normal Mexican American older adults, we found an association among self-reported SCC and a diagnosis of depression and dyslipidemia, even after controlling for demographics like age, sex, and education. Forty eight percent of our cohort self-reported SCC, and those with a greater self-perception of cognitive decline, determined by higher SMCQ scores, performed worse in objective measures of global cognition and memory.

Consistent with available literature [30,31], we found a strong association between a depression diagnosis and self-reported SCC. Prior research suggests that despite the strong correlation between depression and SCC, they independently can lead to cognitive disorders through

Table 2
Multivariate Models of associations of SCC, N = 323

	Model 1 Odds ratio (95% CI)	Model 2 (Odds ratio (95% CI)	Model 3 Odds ratio (95% CI)	Model 4 Odds ratio (95% CI)
Demographics				
Age	1.01 (0.99 to 1.03)	1.00 (0.98 to 1.02)	1.01 (0.99 to 1.03)	1.00 (0.98 to 1.03)
Education	0.97 (0.94 to 1.01)	0.97 (0.94 to 1.01)	0.99 (0.95 to 1.03)	0.98 (0.95 to 1.02)
Gender	1.37 (0.98 to 1.91)	1.41 (0.99 to 2.01)	1.11 (0.78 to 1.57)	1.16 (0.80 to 1.67)
Cardiovascular risk factors				
Hypertension		0.96 (0.67 to 1.38)		0.92 (0.63 to 1.33)
Diabetes		1.02 (0.72 to 1.45)		0.90 (0.63 to 1.30)
Dyslipidemia		1.87 (1.32 to 2.66) *		1.72 (1.20 to 2.47) *
Obesity		0.97 (0.69 to 1.35)		0.90 (0.64 to 1.27)
Depression			3.35 (2.35 to 4.78) *	3.15 (2.16 to 4.59) *

Notes: *$p \leq 0.05$; Model 1 – demographic variables; Model 2 – demographic variables and cardiovascular risk factors; Model 3 – demographic variables and depression diagnosis; Model 4 – demographic variables, cardiovascular risk factors and depression diagnosis.

Table 3
Linear Regression: SMCQ scores and neuropsychological tests

	B	SE	p
MMSE	0.07	0.03	0.02*
SEVLT Immediate	-0.03	0.00	0.000*
SEVLT Delayed	-0.03	0.00	0.000*
Trails B	-0.01	0.01	0.21
Digit Span	-0.008	0.01	0.44

* After adjusting for age, sex, years of education, and cardiovascular risk factors.

different neurobiological pathways [32]. The mechanism behind these changes may arise from abnormal glucocorticoid levels, persistent activation of hypothalamic-pituitary-adrenal axis (HPA axis), and possibly subsequent deposition of amyloid-beta [33,34]. Additionally, brain structural changes, particularly in the hippocampus, may play a role. Depression was associated was associated with atrophy of the right hippocampus, and decrease in right hippocampal volumes were associated with lower scores in the MMSE [35].

However, a few interesting caveats may exist. One study found that in elderly people with major depressive disorder, subjective memory complaints were associated with worse performance on cognitive measures, especially on cognitive testing. (12) However, another study espoused that while perceived subjective cognitive decline (SCD) was associated with depressive symptoms, SCD was not associated with decreased performance on objective tests of cognition [36]. In addition to differing sample sizes and varied cognitive tests, one interesting explanation for the differing conclusions may be demographic discrepancies. In populations of Caucasians and African Americans, ethnicity may be a confounding variable which plays a role in determining whether or not SCC correlates to objective memory measurements. While literature seems discordant, these varied findings highlight the necessity of using both SCC and objective cognitive measures to develop a better picture of patient's cognitive state.

In our cohort, depression was strongly associated with the presence of subjective cognitive complaints. Research about the effects of antidepressant treatment on SCC are not conclusive. An acute treatment study with and antidepressant regimen for two months, showed no beneficial effects of the treatment on SCC [37]. Another study demonstrated improvement of SCC after antidepressant treatment for 6 months [38]. As far as we know, at this time, there are no studies analyzing the effects of antidepressant treatments on SCC in the MA population.

Literature about the relationship of diabetes, hypertension, and other chronic conditions with SCC have reported inconsistent and mixed results [14]. We did not find any significant association between hypertension, diabetes, and obesity and self-reported SCC, which is consistent with other studies [10,39]. In our cohort, having a diagnosis of dyslipidemia was associated with the presence of self-reported SCC. Contrary to our findings, in a systematic review, Hill et al reported two studies that examined SCC and dyslipidemia, and both found no relationship [14] The differences may be explained by different methodology, specifically, cohort characteristics, scales used to quantify SCC, cognitive measures utilized, and different diagnostic criteria of CVRF.

We investigated the relationship of higher SMCQ scores, representing greater self-perception of cognitive decline, to objective measures of global cognition, memory, executive function and attention. We found that higher SMCQ scores were significantly associated with lower scores on global cognition and memory measures, but not with executive function or attention tests. These findings are consistent with other studies of Hispanics such as the SOL-INCA study [40], and previous findings in the HABS-HD cohort [8]. Stenfors et al did not find an association between SCC and executive function after adjusting for depression [41], which is similar to our findings. Other researchers report that SCC were associated with depressive symptoms but not with objective measures of cognition [42].

Limitations of the study, and of the cohort, must be considered. As a cross sectional study, we are unable to evaluate the relationship between SCC, CVRF and cognition over time. The HABS-HD study is longitudinal which will allow clarification on the causal effect of CVRF and SCC, and the value of SCC to predict future cognitive decline. Another limitation is that we did not take in account other factors that may moderate the relationship of cardiovascular risk factors, subjective cognitive complaints, and objective measures, such as multimorbidity, the role of medication, neuroimaging findings, or APO*e*4 status. Also, we only used one question to assign groups with and without SCC. The SMCQ is a validated instrument but is not designed to be used specifically in Hispanics. It is important for future studies to use SCC instruments validated for use in Hispanics. Additionally, the HABLE cohort may have unique characteristics that may limit generalizability.

5. CONCLUSION

For older cognitively normal Mexican Americans, depression and dyslipidemia were significantly correlated with self-reported SCC. A greater self-perception of cognitive decline, quantified by the SMCQ 14 items questionnaire, correlated with lower scores on the MMSE and SEVLT but not with Trails B nor digit span scores. While these findings are somewhat different from the results of other studies, a local population-focused approach may allow for improved cognitive screening tailored to the needs of the community. In the future, better understanding the contributions of demographic-specific risk factors and covariates to SCC may be useful in identifying those who may need intervention or assistance. More research is necessary to analyze the value of SCC as predictors of future diagnosis of MCI or dementia in older Hispanics.

Declaration of Competing Interest

Sid O'Bryant has multiple patents in neurodegenerative diseases and is the founding scientist for Cx Precision Medicine, Inc. Leigh Johnson owns an interest in Cx Precision Medicine, Inc. Raul Vintimilla, Ezek Matthew, and James Hall report no conflict of interest.

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