Heart rate variability (HRV) has recently emerged as a noninvasive measure to assess cardiovascular autonomic function quantitatively.1,2 HRV is the beat-to-beat alterations in the sinus rhythm, which result from the interactions between sympathetic and parasympathetic activity. Reduced HRV has been shown to be a strong predictor of cardiovascular events and mortality.3–6 and has been proposed as a prognostic factor for cardiovascular disease risk stratification and management.1 Furthermore, HRV has been increasingly suggested to be associated with several vascular risk factors for cognitive impairment such as hypertension,2,7–9 diabetes mellitus,8,11 depression,12 and subclinical inflammation.13 In particular, reduced HRV has been recognized as a hallmark of early cardiac autonomic neuropathy,14 which is, in turn, associated with impaired fasting plasma glucose15 and insulin sensitivity.16

The link among HRV, cardiac autonomic neuropathy, in particular, and cognitive impairment is of particular importance when we consider minority ethnic populations such as Mexican Americans who are at high risk for cardiovascular disease, type 2 diabetes mellitus, obesity, and insulin resistance compared with their non-Hispanic white counterparts.17–21 For example, subjects with type 2 diabetes mellitus have a 2-fold increased risk for cognitive impairment and later dementia compared with those without diabetes mellitus.22 Identifying subclinical mechanisms and predictors of cognitive impairment in a population with poor cardiovascular prognosis will constitute a noninvasive clue for risk of cognitive impairment and may lead to more targeted screening and early preventive strategies to delay the progression of cognitive impairment.

Despite the potential association of HRV with cognitive function and with many of its risk factors, the direct association of HRV with cognitive function has been less explored and less understood, particularly in high-risk minority populations. In this study, we sought to determine the cross-sectional association of HRV with cognitive function in a cohort of elderly Mexican Americans and whether this association persists above and beyond traditional cardiovascular risk factors.

Methods

Study Population
Participants in this study were from the Sacramento Area Latino Study on Aging (SALSA). SALSA is a prospective cohort study of 1789 community-dwelling Mexican Americans residing in California’s Sacramento Valley and aged 60 to 101 years at baseline in 1998 and 1999. The original goal of the SALSA study was to identify vascular, metabolic, and social correlates of dementia, cognitive function, functional limitation, and depressive symptoms among Mexican Americans, an understudied ethnic group. Biological and...
clinical data were collected on participants in home visits every 12 to 15 months for a maximum of 7 visits. SALSA has been approved by the Institutional Review Board at the University of Michigan and the University of California, San Francisco and Davis. Details on the study design have been published elsewhere.23 HRV, our predictor of interest, was measured for a subsample of the SALSA participants (n=869) at study visit 5 or 6.

**Measures**

**Assessment of HRV**

HRV was measured using ANS2000 (Autonomic Nervous System; D. E. Hokanson, Inc, Bellevue, WA), a validated device that has an ECG monitor and respiration pacer measuring variability in the heart rate in response to deep breathing.24 The examination took place in the morning with the participant fasting overnight. Briefly, HRV is the change in the time of consecutive heart beats, with a heart beat measured as the time between the peak of 1 R wave to the peak of the next, also referred as the R-R interval. Changes in the length of the normal R-R interval define HRV. Most commonly, HRV is determined by either time or frequency domain measures. In this analysis, we use the mean circular resultant (MCR), also known as the R bar, which is a time domain measure of HRV.

**Calculation of MCR**

RR variation was measured during a 6-minute test with participants in a supine position and breathing at a standard rate of 5 breaths per minute. The latter was achieved with the aid of a respiration pacer. RR variations were recorded for 6 minutes, but only the middle 5 minutes were used for analysis, allowing room for beginning and ending. Thus, a total of 25 breath cycles were included in the 5-minute analysis.

The calculation of MCR, also known as R bar, is based on vector analysis. The latter uses a technique that plots the time of the R-wave spike on a circular graph that rotates in synchrony with the participant’s breathing cycle. As such, there is a record for the time at which the R wave spikes and the period of the respiratory cycle to which it corresponds. Both components are included in the statistical computation of MCR. For a detailed description of the MCR calculation, see Weinberg and Pfeifer.21 In brief, the timing (T) and periodicity (λ) of an R-wave spike are plotted as a point on the unit circle, and the mean vector of all R waves is then calculated as a function of these 2 parameters (T and λ). The length of the calculated mean vector is the MCR. MCR bar tends to be shorter when the R-wave spikes are uniformly distributed, and MCR bar tends to be longer when the R-wave spikes cluster toward one region of the circle, that is, depicting periodicity in the process. Therefore, lower MCR, which denotes reduced HRV, is treated as a risk factor for cognitive function in this analysis. MCR measurement is proved to be resistant to ectopic beats and less affected by intrinsic heart rate and thus is a preferred method for the assessment of parasympathetic function. The HRV data were reviewed and edited into final form by Y.D. (coauthor). In the remaining text, we will refer to MCR as R bar.

**Assessment of Cognitive Function**

Cognitive function was assessed at the time of HRV measurement using the modified Mini-Mental State Examination (3MSE) and the Spanish and English verbal learning test (SEVLT). The 3MSE is a 100-point test of global cognitive function and was validated and field tested in both English and Spanish. Compared with the Mini-Mental State Examination, the 3MSE shows better reliability, test–re-test properties, better sensitivity and specificity, and fewer ceiling effects.25,27 The SEVLT is a 15-point verbal memory recall test with four 15-word memory trials, an interference list, followed by a fifth trial that is usually used as the test score.26,29 SEVLT was developed for use in SALSA29 and has been validated in both English and Spanish and has been used in other studies. Higher scores on both tests indicate better cognitive performance.

**Covariates**

We used baseline sociodemographics such as age, country of birth (nativity) that we coded as US born or Mexican born, years of education completed, and marital status (married versus other). For the remaining covariates, we used those collected at the same study visit of HRV measurement. We measured systolic and diastolic blood pressures using a digital blood pressure monitor. We measured standing height and weight, and we calculated the body mass index (kg/m²). We defined type 2 diabetes mellitus as a self-report of a physician diagnosis, use of diabetes mellitus medication, or a fasted glucose level ≥126 mg/dL.30 We defined hypertension as a report of a physician diagnosis, use of hypertension medication, a systolic blood pressure >140 mm Hg, or a diastolic blood pressure >90 mm Hg.31 We defined stroke on the basis of a physician diagnosis, including hospitalization. We assessed cardiac failure as a self-report of congestive heart failure. We assessed depressive symptoms using the 20-item Center for Epidemiological Studies-Depression Scale (CESD; range, 0–60),32 and we defined elevated depressive symptoms as CESD ≥16. We assessed dementia using a 3-stage process that included (1) cognitive screening tests, (2) the Spanish and English neuropsychological assessment scales33 and the Informant Questionnaire on Cognitive Decline in the Elderly, and (3) case adjudication by neuropsychologists and neuropsychologists resulting in participants being classified as normal, demented, or cognitively impaired but not demented (CIND). Consistent with previous publications, we combined the demented and CIND cases into 1 group, which we refer to as dementia/CIND. Further details on the dementia screening process are published elsewhere.34

**Statistical Analysis**

For ease of interpretation, we used quartile of R bar (quartile 4=reduced to high R bar). Given that R bar measurement was only performed in a subsample of our SALSA cohort, we first presented a comparison of the baseline characteristics for participants with and without R bar data using ANOVA or χ² tests as appropriate (Table 1). Second, we presented the bivariate associations of quartile of R bar with important covariates using ANOVA or χ² tests as appropriate (Table 2; Figure); this analysis uses covariates that were assessed at the same study visit at which R bar was measured. Finally, to examine the associations of quartile of R bar with performance on cognitive tests (3MSE and SEVLT), we fit unadjusted and multivariable-adjusted linear regression models (Table 3). First, we fit an unadjusted model, then we added adjustment for socioeconomic and demographic risk factors, including age, sex, education, and marital status, in model 2, and after that we added adjustment for education and marital status in model 3.
for comorbidities, including type 2 diabetes mellitus, hypertension, stroke, and depressive symptoms, in model 3. The multivariable analysis also uses covariates assessed at the same study visit at which R bar was measured. The selection of these covariates was based on their associations with both R bar and cognitive outcomes. We provided the $R^2$ statistic to indicate the relative contribution of each set of covariates that we adjusted for in the linear regression models.

**Results**

Our results from Table 1 suggest that participants for whom HRV data were collected (n=869) were significantly younger, had more years of education, and were less likely to have had a comorbidity at baseline, such as cardiac failure, stroke, type 2 diabetes mellitus, hypertension, dementia/CIND, and elevated depressive symptoms, compared with SALSA participants for whom HRV data were not collected.

Of the study sample included in this analysis (Table 2), a total of 58.6% were women, 48.5% were born in Mexico, 60% were married, and the mean years of education was 8 years (SD, 5.4). At the time of HRV measurement, the mean age of our study sample was 75.6 years (SD, 6.1), with a mean body mass index of 29.3 kg/m², a mean systolic blood pressure of 142.6 mm Hg, and a mean diastolic blood pressure of 77.0 mm Hg. Reduced R bar (ie, lower quartile) was associated with older age, being a woman, being unmarried, and with lower mean years of education. Reduced R bar was also associated with higher systolic blood pressure and higher insulin levels.

### Table 2. Bivariate Associations of Heart Rate Variability, as R Bar, With Sample Characteristics at the Time of Heart Rate Variability Assessment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartiles of R Bar (n=869)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>75.6 (6.1)</td>
</tr>
<tr>
<td>Sex, n (%)*</td>
<td>509 (58.6)</td>
</tr>
<tr>
<td>Women</td>
<td>357 (41.1)</td>
</tr>
<tr>
<td>Marital status, n (%)*</td>
<td>521 (60.0)</td>
</tr>
<tr>
<td>Education, y, mean (SD)*</td>
<td>8.2 (5.4)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>29.3 (5.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>142.6 (21.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.0 (11.4)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>110.3 (40.3)</td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>26.2 (32.2)</td>
</tr>
<tr>
<td>C-reactive protein, mean (SD)</td>
<td>3.8 (7.3)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and HRV, heart rate variability.
*Measured at baseline.
In the Figure, we present the bivariate association of quartile of R bar with vascular-related comorbidities at the time of HRV measurement. In our sample, a total of 14.3% reported having had a stroke, 9.7% had cardiac failure, 41.8% had type 2 diabetes mellitus, 93.7% had hypertension, 12.2% had a diagnosis of dementia/CIND, and 21.3% had elevated depressive symptoms (Center for Epidemiological Studies-Depression Scale [CESD] ≥16). Reduced R bar (lower quartile) was significantly associated with higher prevalence of stroke, type 2 diabetes mellitus, hypertension, dementia/CIND diagnosis, and elevated depressive symptoms (P<0.01). R bar was not associated with the presence of cardiac failure (P>0.05).

Our multivariable analysis of the associations between R bar and cognitive scores on the 3MSE is presented in Table 3. In unadjusted models, having reduced R bar was associated with lower SEVLT scores although the effect estimates were modest. Adjusting for sociodemographics in model 2 and for comorbidities in model 3 attenuated the associations and became nonsignificant.

### Table 3. Multivariable Associations of Heart Rate Variability, as R Bar, With Cognitive Function From Linear Regression Models

<table>
<thead>
<tr>
<th>Heart Rate Variability</th>
<th>Unadjusted</th>
<th>Demographic Adjusted</th>
<th>Fully Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>-11.4 (1.4)</td>
<td>-6.5 (1.2)</td>
<td>-4.0 (1.0)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>-6.9 (1.3)</td>
<td>-3.0 (1.2)</td>
<td>-2.0 (1.0)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>-3.0 (1.3)</td>
<td>-1.4 (1.2)</td>
<td>-0.9 (0.9)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>R² statistic</td>
<td>8.7%</td>
<td>30.4%</td>
<td>34.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart Rate Variability</th>
<th>Unadjusted</th>
<th>Demographic Adjusted</th>
<th>Fully Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>-1.02 (0.33)</td>
<td>-0.07 (0.30)</td>
<td>0.30 (0.30)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>-0.94 (0.31)</td>
<td>-0.04 (0.29)</td>
<td>0.19 (0.28)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>-0.09 (0.31)</td>
<td>0.26 (0.28)</td>
<td>0.35 (0.27)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>R² statistic</td>
<td>2.1%</td>
<td>23.0%</td>
<td>24.7%</td>
</tr>
</tbody>
</table>

3MSE indicates modified Mini–Mental State Examination; and SEVLT, Spanish and English Verbal Learning Test.

In other words, cardiac autonomic function and the sympa-thetic and parasympathetic activity interact to maintain blood pressure within a normal range. HRV and blood pressure variability have been shown to be inversely associated.3,16 Furthermore, fluctuations in blood pressure (ie, blood pressure variability) are associated with cognitive impairment17,18 and with structural brain changes related to hypertension, such as cerebral white matter lesions,19 and stroke, such as lacunar infarctions.40 Furthermore, HRV may influence cognitive function by cardiac autonomic neuropathy and its associations with type 2 diabetes mellitus,10,11 impaired plasma glucose,15 and insulin sensitivity.16 Sensitivity analysis of our
main regression models suggests that in our cohort of elderly Latinos, years of education explain most, among other sociodemographics, of the observed associations between HRV and cognitive function. Comorbidities, including diabetes mellitus, stroke, and elevated depressive symptoms, further explain some of the HRV-cognitive function association. Given that education triggers a cascade of behavioral and risk factor change, which in turn may influence comorbidities, targeting education may provide a potential opportunity for prevention and management. However, given the cross-sectional nature of our study, the interpretation of our findings should be performed with caution until future prospective studies confirm the predictive role of HRV and the role of potential underlying mechanisms.

Our findings were consistent with some studies that examined the associations of HRV and cognitive function. For example, cross-sectional results from a subsample (n=311) of elderly disabled women in the Women’s Health and Aging Study have shown that the lowest quartile of an HRV index of decreased parasympathetic activity was independently associated with 3× to 6× greater odds of cognitive impairment based on the Mini-Mental State Examination. Recent results from the Vietnam Era Twin Registry (n=416) have shown that reduced HRV was associated with worse verbal recall scores but not with visual, learning, or memory tests. Further reports among patients with mild cognitive impairment (n=42) have shown that reduced HRV (time and frequency measures) was independently associated with increased white matter lesions. Finally, results from a case–control study of a small sample of patients admitted for cognitive disturbances have shown that measures of HRV were lower in subjects with Alzheimer disease than in those with mild cognitive impairment or who were cognitively normal. In the latter study, HRV was significantly associated with the degree of cognitive impairment. However, our findings were not consistent with those from the Whitehall II cohort study of middle-aged men and women. Results from the Whitehall study showed no cross-sectional or longitudinal associations between HRV and cognitive function or decline; cognition was assessed on the basis of several domains, including memory, vocabulary, phonemic, and semantic fluency.

Our study has some limitations that are worth noting. Given the cross-sectional nature of our study, we could not examine the temporality of the association, that is, whether HRV preceded and consequently resulted in cognitive impairment. As such, it may be possible that reduced HRV is a consequence of cardiac autonomic dysfunction that accompanies cognitive impairment or may be a cross-correlate of other factors influencing cognitive impairment. Thus, despite a statistically significant association between reduced HRV and worse cognitive function from our fully adjusted models, the interpretation of our findings needs to be performed with caution. Evaluation of the temporality of the HRV-cognitive function association and the role of other covariates as potential confounders or mediators cannot be determined from our cross-sectional findings. Disentangling the timing of these associations and the role of HRV as a predictor and a potential prognostic factor of cognitive impairment needs to be elucidated in future prospective studies. Furthermore, although we adjusted for potential confounders, we cannot rule out the possibility of residual confounding in the observed associations. In particular, given the role of education in shaping cognitive function, the lack of data on the quality of education may have resulted in residual confounding, despite our adjustment for years of education completed. We also acknowledge that HRV measurement in the SALSA sample was not random. Those for whom HRV was measured were younger and healthier than those for whom HRV was not measured. As such, we cannot rule out the possibility of selection bias, yet toward the null. Finally, although we had information on many of the comorbidities that play a role in the link between HRV and cognitive function, such as hypertension and diabetes mellitus, we did not have imaging data on our HRV sample. As such, we could not examine whether HRV may also be associated with structural brain changes in our cohort.

However, our study has many strengths. Importantly, our results take advantage of a unique and understudied ethnic group. Mexican Americans are disproportionately burdened with obesity and type 2 diabetes mellitus, which are linked to cardiac autonomic neuropathy and are major risk factors for cognitive impairment as well. Exploring these associations will help us better define predictors of cognitive impairment and will help in elucidating underlying subclinical pathways. Furthermore, unlike the majority of the literature that included small sample sizes and patient or clinical samples, our data come from a large population-based study of community-dwelling older adults, and our analysis includes a relatively large sample size.

**Perspectives**

In conclusion, in our community-dwelling cohort of elderly Mexican Americans, we provided evidence that reduced HRV, indicative of cardiac autonomic dysfunction and reduced parasympathetic control of the heart rate, was cross-sectionally associated with worse performance on the test of global cognitive function. Our findings shed light on the role of autonomic dysfunction as a predictor of cognitive impairment. Future studies are needed to explore these associations prospectively and to explore underlying pathways including brain imaging studies.

**Sources of Funding**

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**Disclosures**

None.

**References**


Novelty and Significance

What Is New?

• This is the first study to examine the association of heart rate variability and cognitive performance among community-dwelling elderly Mexican Americans.
• Our study includes a relatively large sample size that provides accurate estimates of the associations of interest and a well-established measure of heart rate variability.

What Is Relevant?

• Heart rate variability is a hallmark of cardiac autonomic dysfunction and is associated with major cardiovascular risk factors of cognitive impairment.
• Mexican Americans are an understudied ethnic group with a high-risk cardiovascular risk factor profile.

Summary

Reduced heart rate variability was associated with worse cognitive performance among community-dwelling older adults. The association of heart rate variability and cognition persists above and beyond traditional cardiovascular risk factors. Our findings provide insight on the role of heart rate variability as a subclinical predictor of cognitive function.
Reduced Heart Rate Variability Is Associated With Worse Cognitive Performance in Elderly Mexican Americans
Adina Zeki Al Hazzouri, Mary N. Haan, Yingzi Deng, John Neuhaus and Kristine Yaffe

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