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Neuropsychiatric Symptoms Among Hispanics: Results of the Maracaibo Aging Study

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Abstract

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SUPPLEMENTARY MATERIAL

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Background: Neuropsychiatric symptoms play an important role in diagnosing and clinical follow-up of cognitive impairment and dementia.

Objective: We investigated the relationship between neuropsychiatric symptoms, cognitive impairment, and dementia in Hispanics.

Methods: We included 529 participants (age ≥40 years) from the Maracaibo Aging Study with standardized neuropsychiatric assessments, including the Neuropsychiatric Inventory (NPI). Based on the Clinical Dementia Rating and the Mini-Mental State Examination scores, participants' cognitive status was categorized into normal cognition, mild/moderate, and severe cognitive impairment. Diagnosis of dementia was established in a consensus conference. Statistical analyses included multivariable logistic regression models and area under the curve (AUC).

Results: The mean age of participants was 59.3 years, and 71.8% were women. The proportion of dementia was 6.8%. Disturbed sleep, anxiety, and depression were the most common neuropsychiatric symptoms in the study sample. In crude analyses, the proportions of hallucinations, aberrant motor behavior, agitation/aggression, apathy, delusions, irritability, eating disturbance, depression, and euphoria were differently distributed among cognitive status groups ($p < 0.05$). After accounting for confounders, aberrant motor behavior and agitation/aggression remained significantly associated with cognitive impairment and dementia ($p < 0.05$). The inclusion of the NPI domains significantly improved the AUC to discriminate severe cognitive impairment and dementia above of a basic model that included sex, age, education, alcohol, obesity, serum glucose, total cholesterol, hypertension, and stroke.

Conclusion: Neuropsychiatric symptoms are associated with severe cognitive impairment and dementia. The addition of NPI items to the global cognitive assessment might help early detection of dementia in primary care settings.

Keywords

Aging; Alzheimer's disease; cognitive impairment; dementia; hispanics; neuropsychiatric inventory

INTRODUCTION

Alzheimer's disease (AD) and related dementias represent a major global health challenge problem in older adults, with 40–50 million people currently living with dementia. In addition, given the increased global longevity, communities, governments, and healthcare systems are facing an exacerbated burden of dementias [1]. This situation demands prevention strategies targeted to identify risk factors in the early stages of dementia that delay the onset and reduce the poor outcomes associated with the disease's clinical course. To achieve this, the cognitive changes resembling "normal aging" and denoting dementia onset should be properly differentiated [2]. The first line diagnostic evaluation is usually primary care providers which rely on global cognitive assessment tools and short anamnesis to collect information about the impact of cognitive changes on daily life activities to determine whether further clinical assessment is needed. However, very frequently, this information is not sufficient to properly identify cognitive decline and/or dementia. Because of improved diagnostic accuracy [3, 4] and prediction of outcomes in patients with dementia

[5], recognizing neuropsychiatric symptoms may be a valuable step in the primary care of older adults.

The deficiency of clinical tools and the poorly understood race/ethnicity differences in the epidemiology of dementias aggravates the diagnostic needs in low resource settings. Hispanics are disproportionately affected by AD, with almost a two-fold elevated risk of developing AD [6, 7] and earlier onset of the disease than non-Hispanic whites [8]. Yet Hispanics are underrepresented in clinical research [9], leading to a lack of information regarding the clinical course of dementia in this rapidly growing minority group. Given the current gaps in the literature about dementia in Hispanics living in developing countries, and the need for tackling early detection of dementia, we conducted the present study to investigate the relationship of neuropsychiatric symptoms with cognitive impairment and dementia in a population-based study of older Hispanic adults living in Maracaibo City, Venezuela. Moreover, we tested the hypothesis that the inclusion of neuropsychiatric information improves the sensitivity of a global cognitive assessment such as the Mini-Mental State Examination (MMSE) and the Clinical dementia Rating (CDR) to detect clinically defined dementia.

MATERIALS AND METHODS

Study population

The Maracaibo Aging Study (MAS) is a longitudinal, prospective, community-based, cohort study of individuals, ≥40 years old, residing in the Santa Lucia and Santa Rosa neighborhoods, Maracaibo, Venezuela. The MAS initially included 2,439 subjects ≥55 years old, living in the community of Santa Lucia from 1998 to 2001, which were followed until 2016, undergoing the same standardized assessments. In 2011, the MAS was expanded to include 420 participants, ≥40 years old, living in Santa Rosa de Agua and 109 residing in Santa Lucía; the distance between the two communities is approximately 6 km. These two samples are relatively stable communities with a high density of families of different socioeconomic conditions [10]. The MAS collected information about demographic, clinical, nutritional, cardiovascular, cognitive, and social factors associated with aging. For the present study, we included the 529 subjects recruited in 2011 with available baseline data on the Neuropsychiatric Inventory (NPI) and cognitive evaluations, including dementia assessment and MMSE. Detailed information regarding recruitment strategy, study design, and sample characteristics have been previously reported [10, 11]. Informed consent was obtained for each participant or from a surrogate when appropriate. The Institutional Review Board of the Cardiovascular Center at the University of Zulia in Maracaibo approved the study.

Assessment of behavioral symptoms

The NPI rates each dementia-related behavioral symptom according to frequency (0—4 points), and severity (1–3 points), and the total score is calculated by multiplying the frequency × severity [12]. The scores scale from 0 to 12 points. Eighty-two participants (16.1%) were not able to respond to the NPI inquiries and a family member or a caregiver provided the information about the presence, frequency, and severity of

behavioral symptoms. Trained psychiatrists conducted the NPI interview. The NPI domains included delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances, and eating disturbances [12]. Subjects with an NPI score of zero were classified as “asymptomatic”, whereas those with NPI scores ≥ 1 were classified as “symptomatic”.

Cognitive assessment and dementia diagnoses

Cognitive performance was assessed using the MMSE [13], and cognitive domains were assessed using a full neuropsychological battery of cognitive tests administered by a neuropsychologist [10]. The original MMSE has a maximum score of 30 points [14]. The MMSE scores were divided into normal (24–30 points), low (18–23 points), and very-low MMSE scores (≤17 points). We therefore categorized cognitive status by combining the MMSE and the CDR scores (0.0, 0.5, 1.0, 2.0, and 3.0) [30]. We included both measures as individuals with normal or low MMSE scores can have CDR scores between 0.0 and ≥1.0 (Supplementary Table 1). A total of 360 participants were identified with normal cognitive status, 98 mild-cognitive impairment, and 71 with severe cognitive impairment.

Diagnoses of dementia were made by consensus during a conference of physicians, psychologists, and social workers, who discussed all ancillary information and followed the diagnostic strategy developed for the Washington Heights-Inwood Columbia Aging Project in New York [19]. Besides having a CDR score of 1 or higher to define dementia [30], individuals had cognitive impairment resulting in a functional decline in their social or occupational activities from their previous level of functioning, not explained by other conditions. Dementia diagnoses were classified as AD, Vascular dementia, or other dementia, based on standardized criteria for each illness in the *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition) and specific criteria for each dementia subtype [15]. MMSE scores are significantly associated to the diagnosis of dementia (Supplementary Table 2).

Statistical analyses

Descriptive information is presented as mean ± standard deviation, and frequency as a percentage (%). We calculated the relative frequency of NPI symptoms according to cognitive status and dementia, and a between-group comparison was made with the Chi-square test. The contrast between groups for continuous variables was made with analysis of variance (ANOVA) followed by Tukey *post-hoc* test. To define the independence among NPI items, we used a principal component factor analysis with Oblimin rotation and Kaiser normalization; components were based on a loading of 0.5 or greater. To determine the association of each of the NPI symptoms with cognitive status, two logistic regression models were designed (normal versus mild/moderate cognitive impairment, and normal versus severe cognitive impairment). The models used the cognitive status (Mild/Moderate or Severe Cognitive Impairment) as the exposure/dependent variable and the presence/absence of each NPI symptom as the independent variable adjusted by sex, age, education, alcohol habits, obesity, serum glucose levels, serum total cholesterol levels, previous stroke, and conventional hypertension. The selection of covariables was based on the comparison of

clinical characteristics among categories of cognitive status, and variables with a p-value ≤ 0.15 were selected as potential confounders.

We conducted a receiver-operating characteristic curve analysis to determine the area under the curve (AUC) to discriminate between participants with normal cognitive status versus those with mild/moderate-and severe cognitive impairment, and participants with and without dementia. Two models were designed, the basic model that accounted for sex, age, education, alcohol habits, obesity, serum glucose levels, serum total cholesterol levels, previous stroke, and conventional hypertension, and the second model included in addition to potential confounders, the NPI symptoms. Statistical analyses were performed using SPSS software, and statistical significance was accepted at $p < 0.05$.

RESULTS

Demographic characteristics

Table 1 lists the characteristics of the 529 participants included in the present study. The mean age was 59.3 years old, and 71.8% ($n = 380$) of participants were women. The proportion of dementia was 6.8% ($n = 36$). Across categories of cognitive status (from normal, mild/moderate, and severe cognitive status), individuals with severe cognitive impairment were 13 years older than those with normal cognition ($p = 0.029$), had 7 years less of education ($p < 0.001$), had lower proportions of alcohol habits ($p < 0.001$) and obesity ($p = 0.025$), higher serum levels of glucose and total cholesterol ($p < 0.05$). The proportions of women ($p < 0.001$) and conventional hypertension ($p = 0.021$) were higher. Over 50% of individuals with severe cognitive impairment also had a dementia diagnosis, whereas no individuals had this diagnosis in the other cognitive categories ($p < 0.001$).

NPI domains and cognitive status

In the total sample, more than 50% of the participants had at least one neuropsychiatric symptom (Table 2). The most frequent neuropsychiatric symptoms in the normal cognition group were sleep disturbances (30.3%), anxiety (25.6%), and depression (19.7%). In the mild/moderate cognitive impairment group, the most frequent neuropsychiatric symptoms were the same as in the normal control group, except that the proportion of those experiencing those symptoms was marginally higher: sleep alterations (37.1%), anxiety (34.7%), and depression (25.5%). Finally, the same symptoms were the most frequent in the severe cognitive impairment group, but depression was the most common (33.8%), followed by anxiety (28.2%) and sleep disturbances (25.7%). It is noteworthy that hallucinations were present in the three groups, but the higher occurrence was found in the group of severe cognitive impairment (21.1%).

Because neuropsychiatric symptoms tend to co-occur, we investigated the possibility of reducing the NPI data into clusters of symptoms. We used principal component analysis (Oblimin rotation) after testing for suitability of the data to proceed with factor analysis (Bartlett's test of sphericity, $p = 0.001$, and Kaiser's measure of sampling adequacy = 0.62). Using the criterion of eigenvalues > 1.0, the 12 symptoms were reduced to five factors or components that explained 63.5% of the total variance in the data (Supplementary

Table 3). The first component (22.5% of total variance) denoted a dimension representing 'apathy' and had high loadings on apathy, eating abnormalities, and aberrant motor behavior. The second component represented a 'nighttime disturbances' dimension, including nighttime disturbances and irritability. The third factor represented a 'psychosis' dimension, and had high loadings for delusions, hallucinations, and aberrant motor behavior. The fourth factor represented an 'affective' dimension and had high loadings on anxiety, depression, irritability, disinhibition, and agitation/aggression. The fifth factor represented a 'hyperactivity' dimension, and had high loadings of euphoria, agitation/aggression, and aberrant motor behavior. Because of three of the neuropsychiatric symptoms (aberrant motor behavior, agitation/aggression, and irritability) loaded in more than one component, we analyzed the association between each individual symptom in the different groups defined by cognitive status and adjusting for potential confounders.

After adjustment for sex, age, education, alcohol habits, obesity, serum glucose levels, serum total cholesterol levels, and hypertension, aberrant motor behavior (OR, 8.11; CI, 1.15–17.3; $p = 0.036$) and agitation/aggression (OR, 4.10; CI, 1.44–11.7; $p = 0.008$) were the main NPI domains related to cognitive status defined by MMSE and CDR scores (Table 3).

NPI domains and dementia

The most frequent neuropsychiatric symptoms in individuals clinically diagnosed as having dementia were anxiety (39.1%) and depression (38.9%), followed by sleep disturbances (34%), The dementia group showed a significantly higher frequency of aberrant motor behavior ($p < 0.001$), agitation/aggression ($p < 0.001$), delusions ($p < 0.001$), irritability ($p < 0.014$), depression ($p < 0.016$), eating disorders ($p < 0.012$), and hallucinations ($p = 0.033$) than the dementia-free group (Fig. 1).

After accounting for potential confounders, the presence of aberrant motor behavior, agitation/aggression, delusions, irritability symptoms, an eating disturbance significantly associated with higher probability of having dementia by 4.25 (CI, 1.01–19.6; $p = 0.043$), 6.22- (CI, 2.27–17.1; $p < 0.001$), 4.91-(95% CI 1.43–16.9; $p = 0.012$), 4.65 (CI, 1.81–12.0; $p = 0.002$), and 3.80 (CI, 1.42–10.0; $p = 0.008$) fold-increase; respectively (Fig. 2).

Area under the curve for cognitive status and dementia

Using the receiver-operating characteristics curve analysis, the addition of the neuropsychiatric symptoms collected with the NPI does not improve the sensitivity of the diagnosis of mild/moderate cognitive impairment. However, including the NPI significantly improves the discrimination of severe and cognitive impairment and dementia (Fig. 3). The inclusion of NPI scores in a basic model that accounted for sex, age, education, alcohol habits, obesity, serum glucose levels, serum total cholesterol levels, and conventional hypertension significantly improved the AUC from 0.93% to 0.95% for severe cognitive impairment ($p < 0.003$) and from 0.87% to 0.91% for dementia ($p < 0.05$).

DISCUSSION

Neuropsychiatric symptoms in older adults are frequent reasons for consultation in low resource settings. Because of its population base, sample size, and comprehensive

participant characterization, the MAS can provide insights into the prevalence of neuropsychiatric symptoms and its relationship to cognitive impairment in a Hispanic population, with low levels of education. We explored which of these symptoms were associated with mild/moderate and severe cognitive impairment and also if the recording of them with the NPI improves the sensitivity of a diagnosis based on global assessment tools (MMSE + CDR). Results confirmed higher rates of neuropsychiatric symptoms in the group with severe cognitive impairment and dementia, and intermediate prevalence among those with mild/moderate cognitive impairment in comparison with the normal cognition group.

We found that more than 50% of Hispanic cohort had at least one neuropsychiatric symptom. The prevalence estimates are comparable with prior population-based estimates, after considering some methodological differences [16–19]. Furthermore, the high prevalence of neuropsychiatric symptoms in the overall population was similar to the report by Salazar et al. (2015) [18]. In fact, out of the 12 symptoms, all but four were similar across all the cognitive groups, categorized either clinically or by global assessment measures. Sleep disturbances and anxiety were the most common symptoms in the normal cognition group affecting almost one third of participants, and not significantly different from the groups with cognitive impairment; this is similar to the reports of population-based cohorts in Spain [20] and Brazil [21]. Interestingly, disinhibition in the form of socially inappropriate comments and/or actions was barely reported, even within the group of severe cognitive impairment with an overall prevalence of 0.2%. It is possible that there is a cultural acceptance of age-related changes in the “freedom” of self-expression via speech or action, humor styles, or shame in reporting sexual disinhibition in this population.

After adjustment for potential confounders, none of the neuropsychiatric symptoms was significantly associated to mild/moderate cognitive impairment and only aberrant motor behavior and agitation/aggression were significantly associated with severe cognitive impairment. Aberrant motor behavior, such as s wandering away from home or repetitive, purposeless behaviors were present in about 2% of our cohort, reaching 8% in severe stages of cognitive impairment which is relatively lower than reported in Mexican-Americans [18] and others [22], but is relatively similar to the Brazilian report [21]. Agitation/aggression was found in about 9% of the cohort, but 18% among participants with severe cognitive impairment, this prevalence is almost half of what has been reported in Mexican Americans, but similar to the Brazilian report [21].

Consistently, addition of the neuropsychiatric symptoms added value to the global assessment strategy only for the diagnosis of severe cognitive impairment.

In terms of distinguishing features none of the neuropsychiatric symptoms was found to be more prevalent among those with mild/moderate cognitive impairment in contrast with the normal cognition group. After accounting for potential confounders, aberrant motor behavior, agitation/aggression, delusions, irritability and eating disturbance were significantly associated with dementia.

Improving precision of the clinical diagnosis is key to diminish the burden of dementia. The MMSE scores and cerebrospinal fluid (CSF)-tau levels are useful in the diagnosis of

AD [23]. If these two phenotypes are incorporated within the patient's medical history, risk assessment, neuro-logical examination, and biomarkers such *APOE* genotype, there is approximately a 90% improvement of the dementia diagnosis [24]. However, the incorporation of neuropsychiatric, psychological, and behavioral symptoms might improve diagnostic accuracy, but data is scarce. We found that inclusion of NPI information significantly improved model performance of dementia diagnosis, as well as diagnosis of severe but not mild/moderate cognitive impairment.

Neuropsychiatric information is critical to the clinical management of dementias [25], which justified the inclusion of NPI profile into diagnostic approaches [3, 4]. Indeed, in individuals with MCI, the NPI profile improved the prediction of dementia progression [3,4]. However, these studies lack of Hispanics cohorts (0% from 6%). Based on our findings, the NPI profile might benefit the accuracy of dementia diagnosis in Hispanics. Interestingly, behavioral disturbances are more prominent compared to cognitive symptoms in the early-onset dementias, which may lead to missed cases or misdiagnosis [26]. Moreover, Watermeyer and Calia (2019) correctly note that the conceptual shift from cognitive aspects of AD to biological/biomarker-based approaches is challenging for low- and middle-income countries that may lack the resources and expertise to implement novel and costly diagnostic and intervention strategies [27].

Cognitive impairment was associated with the presence of neuropsychiatric symptoms in two NPI domains. Specifically, severe cognitive impairment was associated with aberrant motor behavior and agitation/aggression, which is usually linked with brain deterioration in more advanced stages of dementia [28]. Cummings et al. [11] reported positive correlations between MMSE scores and NPI delusions, anxiety, disinhibition, and aberrant motor behavior in non-Hispanic AD patients [10]. Interestingly, these authors also found that dementia-free control subjects with abnormal MMSE scores had higher NPI scores in their study, although they did not specify which NPI domains. Moreover, Royall and Palmer [29] recently reported that a latent dementia phenotype (δ) is associated with multiple behavioral and psychological disturbances, and that these associations are linked to general intelligence and not to domain-specific pathologies (e.g., domain-specific memory, executive function). The inclusion of Mexican-Americans in this study is commendable, and suggests that the relationship between cognitive function and psychological/behavioral disturbances in Hispanics/Latinos is an important topic that merits further study.

Our results are consistent with previous studies that examined neuropsychiatric symptoms in relation to cognitive status and dementia in non-Hispanic populations [3, 5]. For example, a study of elderly subjects in Minnesota found that MCI increased the prevalence of most NPI symptoms: 50% of individuals with MCI had at least one neuropsychiatric symptom, compared to 25% of those with normal cognition [16]. Another study of mostly Caucasian subjects in the US reported a relationship between neuropsychiatric symptoms and MCI, and also found that more subjects with dementia exhibited neuropsychiatric symptoms than non-demented individuals [30]. Our findings are particularly consistent with Salazar et al. [31] who reported that among individuals with AD, Mexican Americans had higher NPI behaviors than non-Hispanics; there were no differences between ethnic groups for individuals with clinically diagnosed MCI.

The relationship between anxiety and cognitive impairment in dementias is complex and understudied [32]. For example, Scaricamazza et al. [33] reported higher anxiety scores associated with MCI than AD. Interestingly, in the present study, anxiety scores were highest in the moderate/mild cognitive impairment group (34.7%) compared to normal cognition (25.6%) and severe cognitive impairment (28.2%) groups. Ma [32] notes that anxiety has been studied less compared to depression; that results of various studies regarding anxiety-cognition interactions have been mixed, and that the concept of anxiety requires special consideration. Indeed, there are different types of anxiety [32], and others have proposed that anxiety interacts with other NPI domains. For example, Forrester et al. [4] used latent class analysis and found two behavioral clusters that contain anxiety: a severe cluster (anxiety with agitation) and an affective cluster (anxiety with depression). These results suggest that the relationship between anxiety and cognitive status in AD and related dementias is dependent on other psychological factors, and these interactions might impact mental health outcomes.

The present study must be interpreted within the context of its potential limitations. First, the cross-sectional design does not allow to infer causality, but rather associations between NPI domains, cognitive status, and dementia. Analysis of longitudinal data is needed to replicate our results in terms of risk-development of cognitive decline and dementia. The external validity of our findings will be corroborated with studies of the applicability of NPI instruments in other Hispanic populations. Second, the study included a low number of individuals with dementia at baseline. Given the longitudinal nature of the MAS, we would expect that in participants with normal cognitive status (defined by an MMSE above 23 points), the presence of neuropsychiatry symptoms predicts the incidence of dementia. Third, we did not implement CSF or neuroimaging biomarkers in the diagnosis of dementia; however, the clinical diagnosis case is one of our study's strengths. This study has several strengths to highlight and, given the longitudinal nature of the MAS, this cross-section analysis will help to define variables considered risk and confounders for follow up. Our multidisciplinary team encompassed physicians, including general practitioners, internal medicine, geriatrics, neuropsychiatry, neurologists, nurses, social workers, and psychologists for evaluation and analysis of the findings. Another strength of the MAS is the available data on cardiovascular risk factors. There is considerable evidence that cardiovascular risk factors, including hypertension or diabetes, are associated with psychosocial behavior and cognitive decline in the general population and patients with dementia [34, 35] and the development of dementia. We were then able to adjust our analyses by these two potential confounders. Finally, the MAS included Hispanic participants from a developing country. Although Hispanics share some sociocultural experiences and genetic/biological factors, Hispanics are not a monolithic group [36]. In fact, the prevalence of neuropsychiatric symptoms in Hispanics and Latinos in the US is influenced by familial country of origin [37]. Also, multicultural influences and local admixture might play a role in the observed results, and the possible between-group differences should be considered before aggregating data.

In conclusion, we found that neuropsychiatric symptoms relate to groups with variate cognitive impairment and dementia in Hispanic adults of the MAS, Venezuela. Our study provides new insight regarding the mental health status of a rapidly growing minority in

relation to dementia—one of the major public health diseases in older adults. Therefore, implementation of NPI instruments within the clinical practice might help identify and stratify patients at high risk of developing dementia. The general agreement of our findings with results of previous studies on non-Hispanic populations is encouraging, since Hispanics have been underrepresented in clinical research [38], and the similarity suggests that some findings might generally apply to different populations. Although longitudinal data are needed to replicate our results in terms of risk-development of cognitive decline and dementia, the applicability of NPI instruments in other populations supports the implementation of the assessment of neuropsychiatric symptoms in Hispanic populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

[1]. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, Chisholm D, Collins PY, Cooper JL, Eaton JJ (2018) The Lancet Commission on global mental health and sustainable development. Lancet 392, 1553–1598. [PubMed: 30314863]

[2]. Robinson L, Tang E, Taylor JP (2015) Dementia: Timely diagnosis and early intervention. BMJ 350, h3029. [PubMed: 26079686]

[3]. Burke SL, Cadet T, Alcide A, O'Driscoll J, Maramaldi P (2018) Psychosocial risk factors and Alzheimer's disease: The associative effect of depression, sleep disturbance, and anxiety. Aging Ment Health 22, 1577–1584. [PubMed: 29077487]

[4]. Forrester SN, Gallo JJ, Smith GS, Leoutsakos JM (2016) Patterns of neuropsychiatric symptoms in mild cognitive impairment and risk of dementia. Am J Geriatr Psychiatry 24, 117–125. [PubMed: 26209222]

[5]. Russ TC, Hamer M, Stamatakis E, Starr JM, Batty GD (2011) Psychological distress as a risk factor for dementia death. Arch Intern Med 171, 1858–1859. [PubMed: 22083575]

[6]. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ (2003) Prevalence of dementia in older Latinos: The influence of type 2 diabetes mellitus, stroke and genetic factors. J Am Geriatr Soc 51, 169–177. [PubMed: 12558712]

[7]. Samper-Ternent R, Kuo YF, Ray LA, Ottenbacher KJ, Markides KS, A1 Snih S (2012) Prevalence of health conditions and predictors of mortality in oldest old Mexican Americans and non-Hispanic whites. J Am Med Dir Assoc 13, 254–259. [PubMed: 21450197]

[8]. Clark CM, DeCarli C, Mungas D, Chui HI, Higdon R, Nuñez J, Fernandez H, Negron M, Manly J, Ferris S, Perez A, Torres M, Ewbank D, Glosser G, van Belle G (2005) Earlier onset of Alzheimer disease symptoms in Latino individuals compared with Anglo individuals. Arch Neurol 62, 774–778. [PubMed: 15883265]

[9]. Alvarez P, Rengifo J, Emrani T, Gallagher-Thompson D (2014) Latino older adults and mental health: A review and commentary. Clin Gerontol 37, 33–48.

[10]. Maestre GE, Pino-Ramirez G, Molero AE, Silva ER, Zambrano R, Falque l, Gamero MP, Sulbaran TA (2002) The maracaibo aging study: Population and methodological issues. Neuroepidemiology 21, 194–201. [PubMed: 12065882]

[11]. Maestre GE, Mena LJ, Melgarejo JD, Aguirre-Acevedo DC, Pino-Ramirez G, Urribarri M, Chacon IJ, Chavez CA, Falque-Madrid L, Gaona CA, Terwilliger JD, Lee JH, Scarmeas N (2018) Incidence of dementia in elderly latin americans: Results of the maracaibo aging study. Alzheimers Dementia 14, 140–147.

[12]. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. Neurology 44, 2308–2314. [PubMed: 7991117]

[13]. Tombaugh TN, Mcintyre NJ (1992) The mini-mental state examination: A comprehensive review. J Am Geriatr Soc 40, 922–935. [PubMed: 1512391]

[14]. Folstein MF, Folstein SE, Mchugh PR (1975) “mini-mental state”, a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12, 189–198. [PubMed: 1202204]

[15]. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th ed.), Washington, DC.

[16]. Geda YE, Roberts RO, Knopman DS, Petersen RC, Christianson TJ, Pankratz VS, Smith GE, Boeve BF, Ivnik RJ, Tangalos EG, Rocca WA (2008) Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: Population-based study. Arch Gen Psychiatry 65, 1193–1198. [PubMed: 18838636]

[17]. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC (2000) Mental and behavioral disturbances in dementia: Findings from the cache county study on memory in aging. Am J Psychiatry 157, 708–714. [PubMed: 10784462]

[18]. Salazar R, Royall DR, Palmer RF (2015) Neuropsychiatric symptoms in community-dwelling mexican-americans: Results from the hispanic established population for epidemiological study of the elderly (hepese) study. Int J Geriatr Psychiatry 30, 300–307. [PubMed: 24838594]

[19]. Steinberg M, Tschanz JT, Corcoran C, Steffens DC, Norton MC, Lyketsos CG, Breitner JC (2004) The persistence of neuropsychiatric symptoms in dementia: The cache county study. Int J Geriatr Psychiatry 19, 19–26. [PubMed: 14716695]

[20]. Fernandez-Martinez M, Castro J, Molano A, Zarranz JJ, Rodrigo RM, Ortega R (2008) Prevalence of neuropsychiatric symptoms in alzheimer’s disease and vascular dementia. Curr Alzheimer Res 5, 61–69. [PubMed: 18288933]

[21]. Tatsch MF, Bottino CM, Azevedo D, Hototian SR, Moscoso MA, Folquitto JC, Scalco AZ, Louza MR (2006) Neuropsychiatric symptoms in alzheimer disease and cognitively impaired, nondemented elderly from a community-based sample in brazil: Prevalence and relationship with dementia severity. Am J Geriatr Psychiatry 14, 438–445. [PubMed: 16670248]

[22]. Mega MS, Cummings JL, Fiorello T, Gornbein J (1996) The spectrum of behavioral changes in alzheimer’s disease. Neurology 46, 130–135. [PubMed: 8559361]

[23]. Ganzer S, Arlt S, Schoder V, Buhmann C, Mandelkow EM, Finckh U, Beisiegel U, Naber D, Muller-Thomsen T (2003) CSF-TAU, CSF-ABETA1–42, Apoe-genotype and clinical parameters in the diagnosis of alzheimer’s disease: Combination of csf-tau and mmse yields highest sensitivity and specificity. J Neural Transm (Vienna) 110, 1149–1160. [PubMed: 14523627]

[24]. Sabbagh MN, Lue LF, Fayard D, Shi J (2017) Increasing precision of clinical diagnosis of alzheimer’s disease using a combined algorithm incorporating clinical and novel biomarker data. Neurol Ther 6, 83–95. [PubMed: 28733959]

[25]. Deardorff WJ, Grossberg GT (2019) Behavioral and psychological symptoms in alzheimer’s dementia and vascular dementia. Handb Clin Neurol 165, 5–32. [PubMed: 31727229]

[26]. Ducharme S, Dickerson BC (2015) The neuropsychiatric examination of the young-onset dementias. Psychiatr Clin North Am 38, 249–264. [PubMed: 25998114]

[27]. Watermeyer T, Calia C (2019) Neuropsychological assessment in preclinical and prodromal alzheimer disease: A global perspective. J Glob Health 9, 010317. [PubMed: 31073397]

[28]. Flores YG, Hinton L, Barker JC, Franz CE, Velasquez AJ (2009) Beyond familism: A case study of the ethics of care of a latina caregiver of an elderly parent with dementia. Health Care Women Int 30, 1055–1072. [PubMed: 19894151]

[29]. Royall DR, Palmer RF (2020) δ Scores predict multiple neuropsychiatric symptoms. Int J Geriatr Psychiatry 35, 1341–1348. [PubMed: 32584472]

[30]. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, Dekosky S (2002) Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. Jama 288, 1475–1483. [PubMed: 12243634]

[31]. Salazar R, Dwivedi AK, Royall DR (2017) Cross-ethnic differences in the severity of neuropsychiatric symptoms in persons with mild cognitive impairment and alzheimer's disease. J Neuropsychiatry Clin Neurosci 29, 13–21. [PubMed: 27417070]

[32]. Ma L (2020) Depression, anxiety, and apathy in mild cognitive impairment: Current perspectives. Front Aging Neurosci 12, 9. [PubMed: 32082139]

[33]. Scaricamazza E, Colonna I, Sancesario GM, Assogna F, Orfei MD, Franchini F, Sancesario G, Mercuri NB, Liguori C (2019) Neuropsychiatric symptoms differently affect mild cognitive impairment and alzheimer's disease patients: A retrospective observational study. Neurol Sci 40, 1377–1382. [PubMed: 30903419]

[34]. Rozanski A, Blumenthal JA, Kaplan J (1999) Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 99, 2192–2217. [PubMed: 10217662]

[35]. Shapiro PA (2017) Psychiatric aspects of heart disease (and cardiac aspects of psychiatric disease) in critical care. Crit Care Clin 33, 619–634. [PubMed: 28601137]

[36]. Gonzalez HM, Tarraf W, Fornage M, Gonzalez KA, Chai A, Youngblood M, Abreu MLA, Zeng D, Thomas S, Talavera GA, Gallo LC, Kaplan R, Daviglus ML, Schneiderman N (2019) A Research framework for cognitive aging and alzheimer's disease among diverse us latinos: Design and implementation of the hispanic community health study/study of latinos-investigation of neurocognitive aging (Sol-Inca). Alzheimers Dement 15, 1624–1632. [PubMed: 31759880]

[37]. Alegria M, Mulvaney-day N, Torres M, Polo A, Cao Z, Canino G (2007) Prevalence of psychiatric disorders across latino subgroups in the united states. Am J Public Health 97, 68–75. [PubMed: 17138910]

[38]. George S, Duran N, Norris K (2014) A systematic review of barriers and facilitators to minority research participation among african americans, latinos, asian americans, and pacific islanders. Am J Public Health 104, E16–E31.

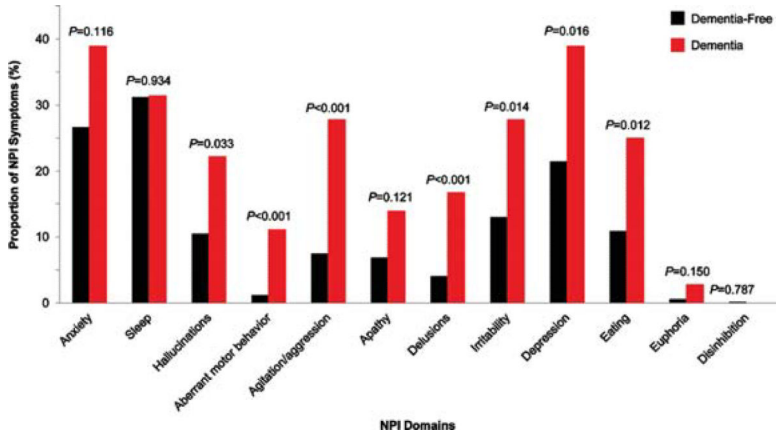

Fig. 1.

The proportion of neuropsychiatric symptoms in subjects with and without dementia at baseline. Neuropsychiatric Inventory (NPI). *p*-values are for the differences between groups.

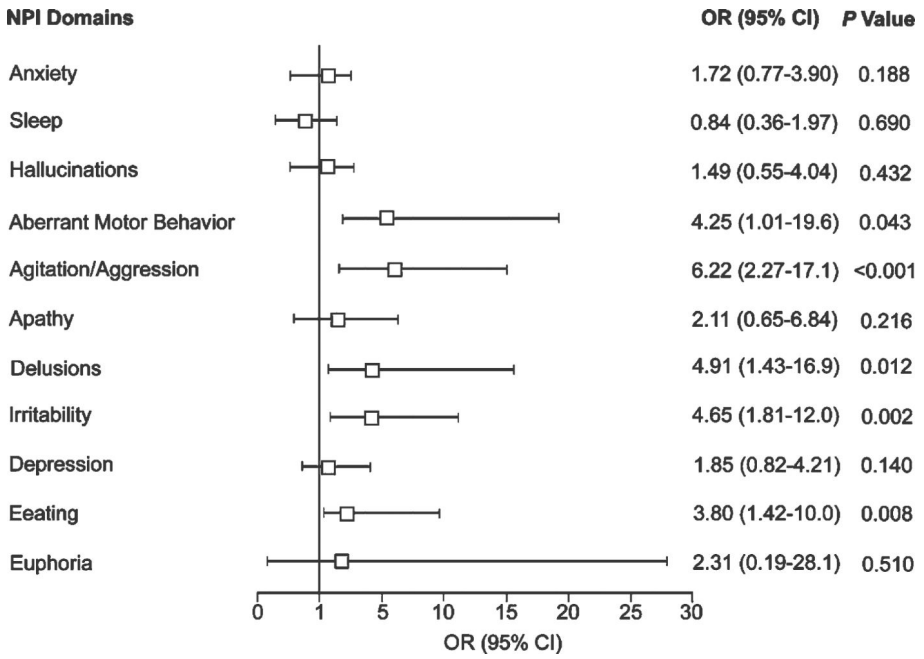

Fig. 2.

Association between NPI domains and dementia. NPI, Neuropsychiatric Inventory; OR, odds ratios; CI, confidence interval. Models accounted for sex, age, education, alcohol habits, obesity, serum glucose levels, serum total cholesterol levels, previous stroke, and conventional hypertension. Statistics were not computed for disinhibition due to absence of symptoms for these categories.

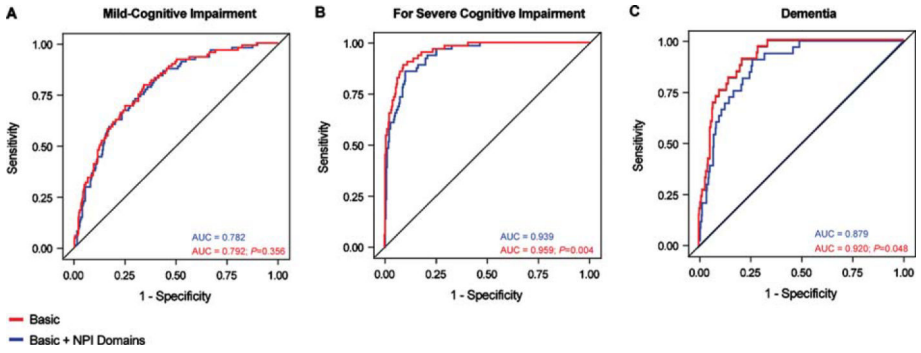

Fig. 3.

Receiver Operating Characteristics Curve for Neuropsychiatric Inventory (NPI) to Discriminate Individuals with and without Mild-Cognitive (A), Severe Cognitive Impairment (B), and Dementia (C). AUC, area under the curve. Basic model accounted for sex, age, education, alcohol habits, obesity, serum glucose levels, serum total cholesterol levels, and conventional hypertension.

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Table 1

Characteristics of participants of the Maracaibo Aging Study

Characteristics	All	Cognitive Status Defined			
		Normal Cognition	Mild/Moderate Cognitive Impairment	Severe Cognitive Impairment	*p* †
	(*n* = 529)	(*n* = 360)	(*n* = 98)	(*N*=71)	
Women, n (%)	380(71.8)	249 (69.0)	79 (80.6)	52 (73.2)	0.079
Age, y	59.3 ± 13.5	56.4 ± 12.4	62.7 ± 12.9	69.6 ± 13.1	**<0.001**
Education, y	7.21 ± 4.7	8.7 ± 4.4	5.3 ± 3.7	2.1 ± 2.5	**<0.001**
History of smoking, n (%)	161 (30.4)	106 (29.4)	27 (27.5)	28 (39.4)	0.195
Alcohol intake, n (%)	236 (44.6)	178 (49.4)	39 (39.8)	19 (26.8)	**0.001**
Obesity, n (%)	191 (36.2)	139 (38.6)	35 (36.5)	17 (23.9)	0.063
Diabetes mellitus, n (%)	75 (14.2)	49 (13.6)	14 (14.3)	12 (16.9)	0.767
Serum glucose level, mg/dL	108.4 ± 36.8	106.4 ± 32.5	108.9 ± 38.9	118.2 ± 50.5‡	**0.046**
Serum total cholesterol, mg/dL	191.8 ± 45.9	189.9 ± 45.9	188.2 ± 45.7	205.7 ± 44.9‡	**0.030**
Serum creatinine, mg/dL	0.87 ± 0.30	0.85 ± 0.24	0.89 ± 0.38	0.92 ± 0.42	0.134
Conventional hypertension, n (%)	315 (59.6)	198 (55.0)	63 (64.3)	54 (76.1)	**0.002**
Use of anti-hypertensive treatment, n (%)	198 (37.4)	131 (39.4)	43 (43.9)	24 (33.8)	0.316
History of CVD, n (%)	54 (10.2)	35 (9.7)	12 (12.2)	7 (9.9)	0.761
Previous stroke, n (%)	15 (2.8)	7(1.9)	6(6.1)	2 (2.8)	0.087
Prevalence of dementia	36 (6.8)	0 (0.0)	0 (0.0)	36 (50.7)	**<0.001**
CDR ≥ 1, n(%)					

CVD, cardiovascular diseases.

*Normal was a MMSE between 24 and 30, mild-cognitive impairment between 18 and 23, and severe cognitive below 17.

†*p*-value of the comparison of characteristics among categories of cognitive status defined by MMSE.

‡In *post hoc* analyses, using the Tukey's test, we found that serum glucose and total cholesterol were different between normal versus severe cognitive impairment ($p = 0.035$, and $p = 0.032$).

Table 2

Prevalence of Neuropsychiatric Symptoms According to Cognitive Status Defined by MMSE and CDR Scores

NPI Symptoms, *n* (%)	Whole Population	Cognitive Status*			
		Normal Cognition	Mild/Moderate-Cognitive Impairment	Severe Cognitive Impairment	*p* †
	(*n* = 529)	(*n* = 360)	(*n* = 98)	(*N*=71)	
Anxiety	146 (27.6)	92 (25.6)	34 (34.7)	20 (28.2)	0.294
Nighttime disturbances	164 (31.2)	110(30.6)	36(37.1)	18 (25.7)	0.804
Hallucinations	60(11.3)	31 (8.6)	14 (14.3)	15(21.1)	**0.001**
Aberrant motor behavior	10(1.9)	2 (0.6)	2 (2.0)	6 (8.4)	**<0.001**
Agitation/aggression	47 (8.9)	27 (7.5)	7(7.1)	13 (18.3)	**0.013**
Apathy	39 (7.4)	23 (6.4)	9 (9.2)	7 (9.9)	0.220
Delusions	26 (4.9)	16 (4.4)	3(3.1)	7 (9.9)	0.146
Irritability	74 (14.0)	48 (13.4)	13 (13.3)	13 (18.3)	0.357
Depression	120 (22.7)	71 (19.7)	25 (25.5)	24 (33.8)	**0.007**
Eating disturbances	63 (11.9)	39(10.8)	13 (13.3)	11 (15.5)	0.231
Euphoria	4 (0.8)	1 (0.3)	0 (0.0)	3 (4.23)	**0.003**
Disinhibition	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0.528

NPI, Neuropsychiatric Inventory. Frequencies (n) and proportion (%) indicates the number of participants with one or more neuropsychiatric symptoms.

*Cognitive status was defined based on the MMSE and CDR scores. Participants with (i) CDR = 0 (normal) and normal or low MMSE scores; or (ii) CDR = 0.5 but normal MMSE score were defined as normal cognition. Mild-cognitive impairment included individuals with (i) CDR = 0 but very-low MMSE scores; or (ii) CDR = 0.5 with low MMSE score; or (iii) CDR= 1 but normal MMSE score. Severe cognitive impairment included individuals with (i) CDR = 1 and low or very-low MMSE score; or (ii) CDR = 0.5 but very-low MMSE score; or (iii) CDR ≥ 2. The MMSE between 24 and 30 was categorized as normal, low between 18 and 23, and very-low cognitive below 17.

†*p*-value of the comparison of characteristics among categories of cognitive status defined by MMSE and CDR scores.

Table 3

Adjusted logistic regression model for the association between neuropsychiatric symptoms and cognitive status defined by MMSE and CDR scores

Neuropsychiatric Symptoms	Cognitive Status*			
	Normal (*n* = 326) versus Mild/Moderate-Cognitive Impairment (*n* = 98)		Normal (*n* = 326) versus Severe Cognitive Impairment (*n* = 71)	
	ORs (95% CI)†	*p*	ORs (95% CI)*	*p*
Anxiety	1.06(0.62–1.81)	0.827	0.74 (0.33–1.64)	0.457
Nighttime disturbances	1.05 (0.62–1.79)	0.855	0.45 (0.20–1.04)	0.062
Hallucinations	1.32(0.63–2.77)	0.465	1.70 (0.63–4.65)	0.298
Aberrant motor behavior	1.35 (0.16–11.54)	0.782	8.11 (1.15–17.34)	**0.036**
Agitation/aggression	0.96 (0.39–2.39)	0.937	4.10(1.44–11.69)	**0.008**
Apathy	0.81 (0.32–2.06)	0.664	1.64 (0.51–5.30)	0.407
Delusions	0.59 (0.16–2.24)	0.438	2.19 (0.55–8.77)	0.267
Irritability	0.91 (0.45–1.86)	0.798	1.98 (0.79–5.00)	0.147
Depression	0.88 (0.48–1.59)	0.661	1.20 (0.54–2.64)	0.659
Eating	1.03 (0.49–2.18)	0.933	2.60 (0.91–7.42)	0.075
Euphoria	NA‡	NA‡	NA‡	NA‡
Disinhibition	NA‡	NA‡	NA‡	NA‡

NPI, Neuropsychiatric Inventory; OR, odds ratios; CI, confidence interval; NA, not available.

*Cognitive status was defined based on the MMSE and CDR scores. Participants with (i) CDR = 0 (normal) and normal or low MMSE scores; or (ii) CDR = 0.5 but normal MMSE score were defined as normal cognition. Mild-cognitive impairment included individuals with (i) CDR = 0 but very-low MMSE scores; or (ii) CDR = 0.5 with low MMSE score; or (iii) CDR= 1 but normal MMSE score. Severity cognitive impairment included individuals with (i) CDR= 1 and low or very-low MMSE score; or (ii) CDR = 0.5 but very-low MMSE score; or (iii) CDR > 2. The MMSE between 24 and 30 was categorized as normal, low between 18 and 23, and very-low cognitive below 17.

†Models accounted for sex, age, education, alcohol habits, obesity, serum glucose levels, serum total cholesterol levels, and hypertension.

‡Models did not compute statistics due to the low/absent number of cases within groups.