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RESEARCH ARTICLE

Prevalence and impact of neuropsychiatric symptoms in normal aging and neurodegenerative syndromes: A population-based study from Latin America

Ana M. Rodriguez Salgado[1] | Isaac Acosta[2,3] | Dani J. Kim[4] | Jenny Zitser[5] | Ana Luisa Sosa[2,3] | Daisy Acosta[6] | Ivonne Z. Jimenez-Velasquez[7] | Mariella Guerra[8] | Aquiles Salas[9] | Adolfo Valvuerdi[10] | Juan C. Llibre-Guerra[11] | Christine Jeyachandran[12] | Ricardo López Contreras[13] | Heike Hesse[14] | Caroline Tanner[15] | Juan J. Llibre Rodriguez[16] | Matthew Prina[4,17] | Jorge J. Llibre-Guerra[18]

[1]Global Brain Health Institute, University of San Francisco California, San Francisco, California, USA

[2]Laboratory of the Dementias, National Institute of Neurology and Neurosurgery, Mexico City, Mexico

[3]National Autonomous University of Mexico, Mexico City, Mexico

[4]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[5]Department of Neurology, Movement Disorders Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[6]Universidad Nacional Pedro Henriquez Ureña (UNPHU), Internal Medicine Department, Geriatric Section, Santo Domingo, Dominican Republic

[7]Internal Medicine Department, Geriatrics Program, School of Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

[8]Instituto de la Memoria Depresion y Enfermedades de Riesgo IMEDER, Lima, Perú

[9]Medicine Department, Caracas University Hospital, Faculty of Medicine, Universidad Central de Venezuela, Caracas, Venezuela

[10]Medical University of Matanzas, Matanzas, Cuba

[11]Department of Neurology, Hospital de Salamanca, Salamanca, Spain

[12]Faculty of Medicine and Health, University of New South Wales, Sydney, Australia

[13]Memory Clinic, Neurology Service, Salvadoran Social Security Institute, San Salvador, El Salvador

[14]Universidad Tecnológica Centroamericana, Tegucigalpa, Honduras

[15]Department of Neurology, Weill Institute for Neurosciences, University of California-San Francisco, San Francisco, California, USA

[16]Facultad de Medicina Finlay-Albarran, Medical University of Havana, Havana, Cuba

[17]Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle, UK

[18]Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

Correspondence
Jorge J. Llibre Guerra, Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, MO, USA.
Email: jllibre-guerra@wustl.edu

Abstract

BACKGROUND: Neuropsychiatric symptoms (NPSs) are common in neurodegenerative diseases; however, little is known about the prevalence of NPSs in Hispanic populations.

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METHODS: Using data from community-dwelling participants age 65 years and older enrolled in the 10/66 study ($N = 11,768$), we aimed to estimate the prevalence of NPSs in Hispanic populations with dementia, parkinsonism, and parkinsonism-dementia (PDD) relative to healthy aging. The Neuropsychiatric Inventory Questionnaire (NPI-Q) was used to assess NPSs.

RESULTS: NPSs were highly prevalent in Hispanic populations with neurodegenerative disease; approximately 34.3%, 56.1%, and 61.2% of the participants with parkinsonism, dementia, and PDD exhibited three or more NPSs, respectively. NPSs were the major contributor to caregiver burden.

DISCUSSION: Clinicians involved in the care of elderly populations should proactively screen for NPSs, especially in patients with parkinsonism, dementia, and PPD, and develop intervention plans to support families and caregivers.

KEYWORDS
dementia, Hispanic, neuropsychiatric symptoms, parkinsonism, parkinsonism-dementia

HIGHLIGHTS

- Neuropsychiatric symptoms (NPSs) are highly prevalent in Hispanic populations with neurodegenerative diseases.
- In healthy Hispanic populations, NPSs are predominantly mild and not clinically significant.
- The most common NPSs include depression, sleep disorders, irritability, and agitation.
- NPSs explain a substantial proportion of the variance in global caregiver burden.

1 | BACKGROUND

The upcoming demographic shifts toward older populations have prompted efforts to estimate health care burden over the coming decades, particularly for age-associated neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD).[1,2] Neuropsychiatric symptoms (NPSs) are a common occurrence in such syndromes and are associated with major adverse effects on daily function, quality of life, increased caregiver burden, and an increased risk of institutionalization.[3–9] Several studies have estimated the prevalence of NPSs. Depending on the methodology and disease stage, it has been estimated that NPSs affect 32% to 75% of people with PD and 50% to 80% of patients with AD.[10–12]

Studies in parkinsonism and PD have traditionally focused on motor features. However, recent evidence suggests that neuropsychiatric features may be present early in the course of the disease, leading to the need to better understand non-motor features such as NPSs in PD.[13,14] Similarly, although dementia, including dementia due to AD, is usually considered a cognitive disorder with a predominant amnestic presentation, almost all people diagnosed with AD develop NPSs at some stage during their disease.[15] Although several studies have started to explore and estimate the prevalence of NPSs in dementia and parkinsonism, most studies are conducted in clinical settings and are subject to referral bias that might overestimate the prevalence of NPSs at a community level. Furthermore, the overwhelming majority of the epidemiological studies in neurodegenerative diseases and NPSs have been carried out in high-income countries (HICs) in rather homogeneous populations (predominantly non-Hispanic Whites) with little to no representation of diverse populations,[16] raising concerns about their generalizability. As a result, information on the prevalence and correlates of NPSs in Hispanic populations is limited.

In Latin America (LatAm), neurological disorders are now the leading cause of disability.[17] AD and PD are the most common neurodegenerative diseases in LatAm, and the region will face a significant increase in the burden of these diseases in the next decade.[18–21] However, NPSs in dementia and parkinsonism have rarely been studied in LatAm populations.[22–25] No study has assessed the prevalence of NPSs in dementia and parkinsonism in a large population-based study from multiple countries in LatAm and using the same methodology. Furthermore, although there are known racial disparities in dementia and parkinsonism, little is known regarding NPSs across all races/ethnicities.

The present study used data collected through the 10/66 population-based study to estimate the prevalence and correlates

of NPSs, in a population-based study of persons with parkinsonism, dementia and PDD. In addition, we sought to examine the impact of NPSs on caregiver burden. The present research features a regional, multicenter study using the same protocols and diagnostic assessments from six LatAm countries (Cuba, Dominican Republic [DR], Puerto Rico [PR], Mexico, Venezuela, and Peru).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (eg, PubMed) sources to explore prevalence of neuropsychiatric symptoms (NPSs) in Hispanic populations with dementia, parkinsonism, and parkinsonism-dementia (PDD). The overwhelming majority of the epidemiological studies in neurodegenerative diseases and NPSs have been carried out in high-income countries (HICs) in rather homogeneous populations (predominantly non-Hispanic White) with little to no representation of Hispanic populations.
2. **Interpretation**: We describe the frequency of NPSs in the largest sample of Hispanic participants reported to date, including elders without neurodegenerative syndromes, dementia, parkinsonism, and PPD. NPSs are highly prevalent in Hispanic populations. A higher frequency of NPSs was associated with higher levels of caregiver burden (CB).
3. **Future directions**: Our findings provide insights about the frequency and impact of NPSs in Hispanic populations, highlighting the need for the screening of NPSs and the need to introduce early interventions to support families and caregivers. Future studies should include cross-population comparisons using harmonized assessments.

2 | METHODS

2.1 | Setting and study participants

Primary analyses in this study utilized data from community-dwelling participants enrolled in the 10/66 study ($N = 12{,}865$).[26,27] The 10/66 study is a population-based cohort study, comprising, in principle, all older residents 65 years of age and older, living in eight geographically defined urban and rural catchment area sites in six LatAm countries.[26,27] Urban sites were selected to comprise mixed socioeconomic status households. Urban sites were located in Cuba (one catchment area comprising sites in Havana and Matanzas, $n = 2944$), DR (Santo Domingo, $n = 2011$), PR (Bayamon, $n = 2{,}009$), Venezuela (Caracas, $n = 1965$), Peru (Lima, $n = 1381$), and Mexico (Mexico City, $n = 1003$). Rural sites, remote from major population centers with low-density population agriculture and related trades as the primary local employment, were located in Peru (Canete Province, $n = 552$) and Mexico (Morelos State, $n = 1000$). The response rates in the 10/66 study range from 80% to 95%, with an average across sites of 88.5%. Site characteristics are summarized elsewhere.[26] Written informed consent was obtained from all participants and their study partners. This project was approved by local institutional review boards and the King's College London Research Ethics Committee. The full protocol for the 10/66 population-based surveys is available in an open-access publication.[26,28]

2.2 | Measures

The 10/66 protocols included, but are not limited to, a cognitive assessment, a structured interview of geriatric mental status, sociodemographic data and risk factors for dementia, a full neurological disease assessment, and a physical and neurological exam. All interviewers and field examiners received uniform and standardized training in Spanish language, and by qualified clinicians. Full details are available elsewhere.[27] The measures directly related to the present analyses are described below.

2.2.1 | Dementia

Dementia was diagnosed using the cross-culturally validated 10/66 dementia diagnosis algorithm, for which strong concurrent and predictive validity has been demonstrated.[29,30] Dementia diagnosis was established following: (1) a structured clinical interview; (2) a cognitive test battery including (a) the Community Screening Instrument for Dementia (CSI-D),[31] (b) a verbal fluency task, and (c) the modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word list learning task with delayed recall[32]; and (iii) an informant interview (CSI-D)[31] for evidence of cognitive and functional decline. Information from participant and informant interviews, cognitive test scores, neurological examination, and the history and etiology questionnaire[33] was used to define dementia diagnosis and subtype.

2.2.2 | Parkinsonism

All participants underwent a comprehensive interview lasting 3 hours, including a structured interview, a physical and neurological examination, and an informant interview.[28] The comprehensive questionnaire on self-reported, non-communicable diseases (e.g., PD, stroke, dementia) and neurological symptoms, together with the comprehensive neurological examination, permitted estimation of the prevalence of Parkinsonism and PD.[26,34] Based on the clinical interview and neurological exam available in 10/66 data, we determined a parkinsonism diagnosis[18,34] and estimated PD diagnosis based on the exclusion of "negative" features (absolute exclusions, red flags) that argue against a diagnosis of PD and "positive" features (supportive criteria) that favor

a PD diagnosis.[18,34] We defined parkinsonism and PD according to the Parkinson's Disease Society Brain Research Centre of the United Kingdom criteria.[35,36] Full details about the parkinsonism/PD diagnosis algorithm and PD prevalence have been published elsewhere.[18,34] Due to limitations on sample size in the analysis, we focused on clinical syndromes and not on clinical diagnosis (e.g., PD, AD, and Lewy body disease [LBD]).

2.2.3 | Neuropsychiatric symptoms

The Neuropsychiatric Inventory (NPI-Q) was used to assess NPSs.[37] The NPI-Q is a structured interview that collects information on the presence of the 12 most common symptoms in patients with dementia: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, and eating and sleep disorders. The NPI-Q is administered to the caregiver or an informant close to the older adult. Each domain is explored with a yes or no question (present/absent). If the respondent answered affirmatively, further questions are asked to rate the symptom in terms of severity and caregiver distress. Thus the maximum score for symptom severity would be 36. Although the NPI was originally developed for research with dementia patients, it has been suggested as an appropriate tool for use in parkinsonism and PD patients by the Movement Disorder Society.[38] In this study, we determined the presence/absence, severity, and associated caregiver distress for the 12 NPSs measured by the NPI-Q. We analyzed their frequency in elders without neurodegenerative syndromes (control group) relative to elders with dementia, parkinsonism, or parkinsonism and dementia combined (PDD). The severity of each NPS was assessed by the caregiver on a scale from 1 to 3 (mild, moderate, and severe). Clinically relevant NPSs were defined according to caregiver-reported distress. Distress scores from 0 to 2 (not distressing, minimal, or mild) were considered not clinically significant and scores 3 to 5 (moderate, severe, and extreme) were considered clinically significant distress. In the clinical setting, domain scores of 3 or more are indicative of clinical relevance and are associated with the need for intervention to manage the symptoms.[39,40] Our final assessment included NPI-Q total score and sub-scores for severity and caregiver distress.

2.2.4 | Caregiver Burden

The Zarit Burden Interview (ZBI) was used to assess caregiver burden.[41–43] The ZBI (22-item) is a self-reported measure and one of the most commonly used instruments to assess caregiving burden in clinical and research settings. The questionnaire covers several areas related to care, including (1) burden in the relationship, (2) psychological well-being, (3) social life, (4) finances, and (5) loss of control over one's life. The ZBI was developed originally to assess the burden among caregivers of community-dwelling persons. Each item on the interview is a statement that the caregiver is asked to endorse using a 5-point scale. Response options ranged from 0 (Never) to 4 (Nearly Always), with the sum of scores ranging between 0 and 88. Higher scores indicate a greater burden.

2.2.5 | Care dependence and caregiver characteristics

We defined care dependence as the need for care that arise from difficulties in performing important tasks and activities related to daily living. Care needs were ascertained via open-ended questions followed by an interviewer's perception of care needs (does not need care; needs care occasionally; or needs care much of the time). This judgment was further guided by an assessment of critical intervals of care (hours per day). Caregiver characteristics, including sex, age, and relation with the participant, were also collected. Details about data collection on care dependence are available in an open-access publication.[44,45]

2.2.6 | Covariates

Age was ascertained using participant or informant reports, documented age, or an event calendar. Education level was ascertained and coded as no education, did not complete primary, completed primary, secondary, or tertiary education. Sex was assessed according to the participant's self-report. Socioeconomic status was assessed according to the number of reported household assets (motor vehicles; television; refrigerator and/or freezer; water and electrical utilities; telephone; plumbed toilet; plumbed bathroom). We assessed physical morbidity through measures of stroke, physical impairments, and main contributors to disability and dependence.[20,46] Physical multimorbidity was defined as having three or more of nine self-reported, limiting physical impairments (arthritis; persistent cough; breathlessness, difficulty breathing or asthma; high blood pressure; heart trouble or angina; stomach or intestine problems; faints or blackouts; paralysis, limb weakness or loss; and skin disorders such as pressure sores, leg ulcers or severe burns). Country of residence and caregiver characteristics, including sex, age, and relation with the participant, were also included as covariates.

2.3 | Analysis

Sample characteristics, NPI-Q score by diagnosis groups, and caregiver characteristics and burden were summarized with descriptive statistics (mean [SD] for continuous variables; frequencies and percentages for categorical variables). In our analysis, elders without neurodegenerative syndromes were considered as the control group. The prevalence of individual NPSs was presented as frequencies and percentages of the total sample of patients with NPI data. The relationship between diagnosis type and the likelihood of reporting a particular NPS was investigated using logistic regression models separately for each NPS. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for crude and adjusted models, which were adjusted for age,

sex, educational level, and number of physical illnesses. In addition, the severity of the NPS and the prevalence of clinically significant caregiver distress were reported as frequencies or percentages with 95% CIs by individual NPS and diagnosis groups. Finally, the odds of having three or more NPS with clinically significant caregiver distress by diagnosis type was assessed using logistic regression model adjusted for age, sex, education level, number of physical illnesses, carer age, carer sex, carer education, carer relationship, and country of residence. The missingness in the demographic and NPS variables was low in the analytic sample (<1%), thus a complete case analysis was carried out in the present paper.

3 | RESULTS

3.1 | Prevalence and severity of NPSs

The total sample was 12,865, but 1097 participants were missing data on parkinsonism or dementia, or both. Details about the 10/66 sample relative to our analytical sample are shown in Table S1. In summary, participants with missing data were more likely to be less educated, have more co-morbidities, and have more disability.

Our final analytical sample included 11,768 participants (4189 men; 7579 women), with a mean age of 74.7 years. Of these participants, 844 were diagnosed with dementia only, 704 had parkinsonism only, 229 had parkinsonism-dementia (PDD), and 9991 were considered elders without neurodegenerative syndromes (control group). Summary statistics including sample size, sex, age, education, and socioeconomic status are shown in Table 1. Across the whole sample, only 40.2% (4663/11581) of the participants were without any symptoms, whereas 59.8% (6918/11,581) presented at least one of the NPSs, and 26.3% (3043/11,581) had three or more NPSs. Overall, the most frequent NPSs, regardless of clinical severity (see Table S2), were depression (n = 3655, 28.8%), sleep disorders (n = 3174, 25.0%), irritability (n = 2939, 23.1%), and agitation (n = 2418, 19.0%). Compared to elders without neurodegenerative syndromes, the individuals with PDD showed higher NPI-Q severity and distress scores, followed by dementia and parkinsonism-only groups, respectively (see Tables S3 and S4).

3.2 | Comparisons of NPSs across diagnosis group

In a subgroup analysis, we sought to explore the prevalence of each NPSs by diagnostic groups relative to elders without neurodegenerative syndromes (control group). On the control group, 43.7% exhibited no NPSs, whereas only 29.9%, 16.4%, and 11.5% of the participants with parkinsonism, dementia, and PDD were NPSs free. About 22.4% of the control group reported three or more NPSs; in contrast, 34.3%, 56.1%, and 61.2% of the participants with parkinsonism, dementia, and PDD exhibited three or more NPSs, respectively. The prevalence of each NPSs by diagnostic group is summarized in Figure 1 and Table S2. Using the control group as a reference, we explored the likelihood of reporting each NPS according to diagnostic group (see Table 2). Compared to the control group, participants with a diagnosis of parkinsonism, dementia, or PDD showed a significant higher association with the presence of almost all 12 NPSs, after adjusting for age, sex, education, and the number of physical illnesses (model 1). A model including caregiver characteristics (model 2) or country of residence (model 3) did not significantly change the results from model 1 (Table 2). Among participants reporting NPSs, the prevalence of clinically significant caregiver distress due to NPSs ranged from 14% (elation) to 30% (irritability) in the control group, from 16% (elation) to 43% (disinhibition) in the parkinsonism group, from 28% (aberrant motor behavior) to 49% (disinhibition) in the dementia group, and from 21% (hallucination) to 46% (irritability) in the PDD group. The frequencies of clinically relevant NPSs by diagnostic groups are shown in Table S4. Compared to controls, participants with parkinsonism (OR, 1.92; 95% CI, 1.43–2.53), dementia (OR, 5.79; 95% CI, 4.78–6.99), and PDD (OR, 5.81; 95% CI, 4.14–8.02) were more likely to show three or more NPS with clinically significant caregiver distress (see Table S5).

3.3 | Influence of NPSs on caregiver burden

In a second analysis, we described the relationship between caregiver burden, represented by the ZBI total score, and NPSs for each diagnostic group. General characteristics of the caregivers by group are shown in Table 3. Mean age of the caregiver group was 53.5 (SD 17.9) years, and the majority were female (71.4%), without statistically significant differences across groups. Caregivers in this sample were predominantly son/daughters (4891, 38.2%) and spouses (n = 3626, 28.3%). Regarding care needs (Table 3), participants with PDD (43.8%) and dementia only (33.2%) showed the highest need for caregiver support relative to those with parkinsonism (8.3%) and the control group (1.5%). Mean ZBI total score was 8.72 (SD 14.41): the PDD group reported the highest caregiver burden (23.43, SD 16.09), followed by dementia (20.26, SD 17.09), parkinsonism (10.61, SD 13.88), and the control group (3.67, SD 9.68). Caregiver burden was substantially higher among individuals with three or more NPSs (18.94, SD 17.82) compared to those with less than three NPSs (4.18, SD 9.58) regardless of clinical diagnosis. In general, severe NPSs in the care recipient (as rated by the caregiver) were associated with moderate to severe distress in the care partner.

4 | DISCUSSION

This study presents the frequency of NPSs in the largest sample of community-dwelling Hispanic participants, including elders without neurodegenerative syndromes (considered as control group), dementia, parkinsonism, and PDD reported to date. In addition, this constitutes the first study to report NPSs data from multiple countries in Latin America using the same methodology. In summary, at least one NPS was present in nearly 60% of the participants. In the whole sample, the most common symptoms were depression, sleep disorders,

TABLE 1 Participant's sociodemographic and health characteristics.

Mean (SD) or n (%)	Control N = 9991	Parkinsonism N = 704	Dementia N = 844	Parkinsonism and dementia N = 229	Total N = 11,768
Age (years), mean (SD)	73.8 (6.6)	78.2 (7.3)	80.7 (8.2)	82.2 (7.2)	74.7 (7.2)
Sex, male, n (%)	3570 (35.8)	280 (39.8)	253 (30.0)	86 (37.6)	4568 (35.5)
Education, n (%)					
None	974 (9.8)	99 (14.1)	171 (20.6)	49 (22.6)	1370 (10.7)
Primary or less	2740 (27.5)	234 (33.2)	255 (30.8)	60 (27.6)	3606 (28.2)
Primary	2940 (29.5)	201 (28.6)	241 (29.1)	61 (28.1)	3807 (29.8)
High School	2044 (20.5)	97 (13.8)	99 (11.9)	35 (16.1)	2483 (19.4)
College	1257 (12.6)	73 (10.4)	62 (7.5)	11 (5.1)	1504 (11.8)
No. of assets (0-7), n (%)					
1st quartile	1626 (16.3)	155 (22.0)	212 (25.1)	43 (18.8)	2226 (17.3)
2nd quartile	3520 (35.3)	277 (39.4)	282 (33.5)	93 (40.6)	4596 (35.8)
3rd quartile	2857 (28.6)	161 (22.9)	229 (27.2)	53 (23.1)	3608 (28.1)
4th quartile	1978 (19.8)	110 (15.6)	120 (14.2)	40 (17.5)	2422 (18.8)
Rural, n (%)	1335 (13.4)	94 (13.4)	103 (12.2)	18 (7.9)	1552 (12.1)
Physical multimorbidity, n (%)					
No illnesses	4233 (42.4)	180 (25.6)	273 (32.6)	58 (26.0)	5066 (39.5)
One to two illnesses	4227 (42.4)	330 (46.9)	376 (44.9)	100 (44.8)	5467 (42.7)
Three or more illnesses	1519 (15.2)	194 (27.6)	188 (22.5)	65 (29.1)	2282 (17.8)
Disability score, mean (SD)	0.54 (1.23)	1.57 (1.94)	3.01 (2.83)	3.56 (2.68)	0.89 (1.75)

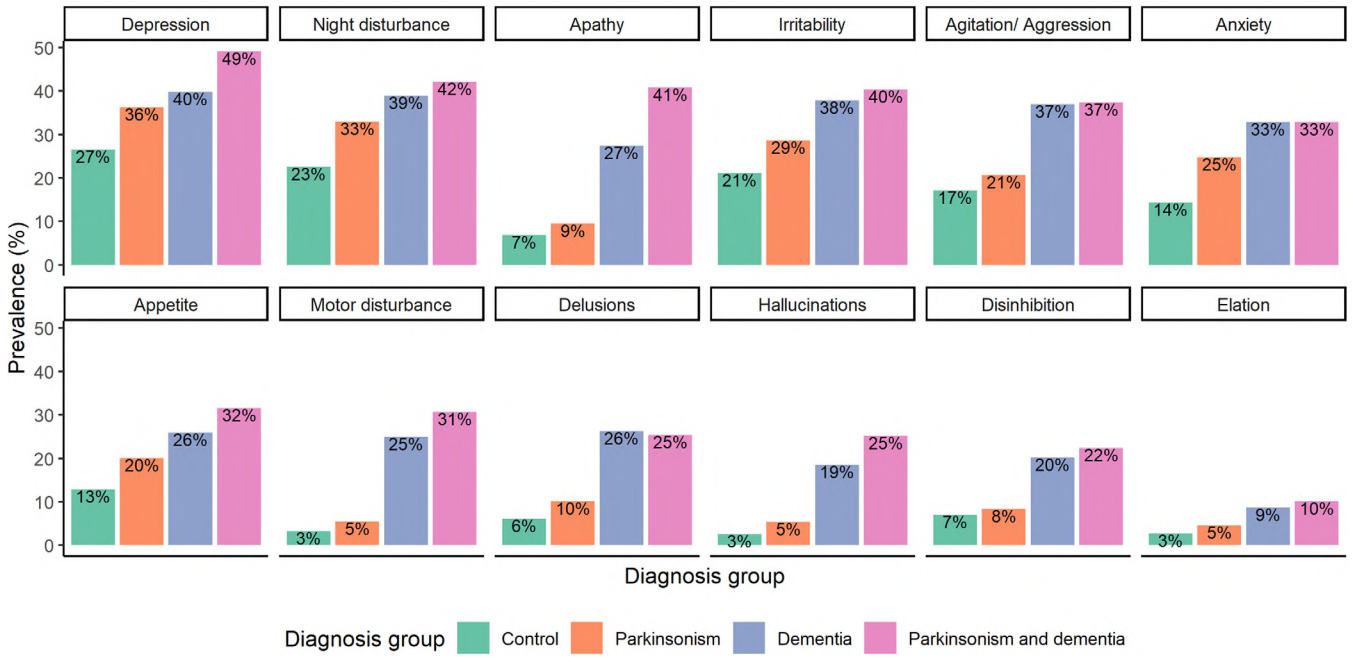

FIGURE 1 Frequency of neuropsychiatric symptoms by diagnosis.

TABLE 2 Odds ratios (95% Cis) for the association between diagnosis and presence of individual neuropsychiatric symptoms.

		Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Delusions	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.71 (1.31–2.20)	1.43 (1.09–1.86)	1.43 (1.09–1.86)	1.42 (1.07–1.84)
	Dementia	5.43 (4.56–6.46)	4.58 (3.78–5.54)	4.44 (3.65–5.39)	4.59 (3.77–5.58)
	Parkinsonism and dementia	5.21 (3.79–7.05)	4.03 (2.85–5.61)	4.12 (2.91–5.76)	4.03 (2.84–5.65)
Hallucinations	Control	Reference	Reference	Reference	Reference
	Parkinsonism	2.10 (1.45–2.95)	1.71 (1.17–2.42)	1.63 (1.11–2.32)	1.58 (1.07–2.25)
	Dementia	8.51 (6.87-10.52)	6.91 (5.44–8.75)	6.77 (5.31–8.61)	6.97 (5.46–8.88)
	Parkinsonism and dementia	12.51 (8.99-17.21)	10.06 (7.01-14.26)	10.34 (7.18-14.73)	10.15 (7.04-14.48)
Agitation/ aggression	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.26 (1.04–1.52)	1.03 (0.84–1.25)	1.03 (0.84–1.25)	1.01 (0.82–1.23)
	Dementia	2.82 (2.43–3.27)	2.37 (2.01–2.77)	2.34 (1.99–2.75)	2.35 (1.99–2.78)
	Parkinsonism and dementia	2.88 (2.19–3.78)	2.17 (1.62–2.90)	2.20 (1.63–2.94)	2.08 (1.53–2.80)
Depression	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.57 (1.34–1.85)	1.44 (1.22–1.70)	1.44 (1.22–1.71)	1.45 (1.22–1.71)
	Dementia	1.82 (1.58–2.11)	1.76 (1.51–2.06)	1.70 (1.45–1.99)	1.70 (1.45–1.99)
	Parkinsonism and dementia	2.66 (2.05–3.47)	2.53 (1.91–3.36)	2.46 (1.85–3.26)	2.46 (1.85–3.28)
Anxiety	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.96 (1.63–2.34)	1.80 (1.49–2.16)	1.84 (1.52–2.22)	1.86 (1.53–2.24)
	Dementia	2.92 (2.50–3.40)	2.91 (2.46–3.43)	2.83 (2.39–3.35)	2.75 (2.32–3.26)
	Parkinsonism and dementia	2.92 (2.19–3.86)	2.82 (2.08–3.79)	2.72 (2.00–3.67)	2.69 (1.97–3.63)
Elation/ euphoria	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.73 (1.17–2.48)	1.58 (1.06–2.29)	1.53 (1.02–2.23)	1.44 (0.95–2.11)
	Dementia	3.41 (2.59–4.44)	3.36 (2.48–4.50)	3.40 (2.50–4.58)	3.65 (2.67–4.96)
	Parkinsonism and dementia	4.02 (2.51–6.17)	3.90 (2.33–6.24)	4.20 (2.50–6.75)	3.88 (2.28–6.32)
Apathy/ indifference	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.44 (1.09–1.86)	1.26 (0.96–1.65)	1.24 (0.94–1.62)	1.21 (0.91–1.58)
	Dementia	5.18 (4.37–6.14)	4.92 (4.08–5.93)	4.87 (4.03–5.89)	5.12 (4.22–6.20)
	Parkinsonism and dementia	9.43 (7.14-12.40)	7.81 (5.76-10.55)	7.94 (5.84-10.76)	7.85 (5.76-10.67)
Disinhibition	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.21 (0.91–1.59)	1.11 (0.82–1.46)	1.09 (0.81–1.44)	1.06 (0.78–1.42)
	Dementia	3.36 (2.78–4.03)	3.33 (2.71–4.07)	3.17 (2.58–3.88)	3.69 (2.98–4.56)
	Parkinsonism and dementia	3.82 (2.75–5.23)	3.41 (2.37–4.81)	3.36 (2.33–4.75)	3.65 (2.50–5.24)
Irritability/ lability	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.50 (1.27–1.78)	1.36 (1.14–1.62)	1.37 (1.15–1.64)	1.38 (1.15–1.65)
	Dementia	2.28 (1.97–2.64)	2.30 (1.96–2.69)	2.19 (1.86–2.57)	2.19 (1.86–2.57)
	Parkinsonism and dementia	2.53 (1.93–3.31)	2.42 (1.81–3.22)	2.34 (1.75–3.12)	2.32 (1.73–3.09)
Aberrant motor behavior	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.72 (1.20–2.40)	1.41 (0.98–1.99)	1.36 (0.93–1.92)	1.27 (0.87–1.81)
	Dementia	9.86 (8.13-11.93)	8.30 (6.70-10.26)	8.37 (6.74-10.38)	9.30 (7.44-11.62)
	Parkinsonism and dementia	13.15 (9.67-17.72)	9.74 (6.92-13.57)	10.17 (7.21-14.22)	10.19 (7.16-14.37)
Nighttime behaviors	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.69 (1.43–1.99)	1.46 (1.23–1.74)	1.46 (1.22–1.73)	1.45 (1.21–1.73)
	Dementia	2.19 (1.89–2.53)	2.01 (1.71–2.35)	1.91 (1.63–2.25)	1.97 (1.68–2.32)
	Parkinsonism and dementia	2.49 (1.91–3.25)	2.08 (1.56–2.77)	2.03 (1.51–2.71)	1.95 (1.44–2.61)

(Continues)

TABLE 2 (Continued)

		Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Appetite/ eating	Control	Reference	Reference	Reference	Reference
	Parkinsonism	1.71 (1.40–2.07)	1.44 (1.18–1.76)	1.45 (1.18–1.78)	1.39 (1.12–1.71)
	Dementia	2.38 (2.01–2.80)	2.11 (1.76–2.52)	2.06 (1.71–2.46)	2.25 (1.87–2.71)
	Parkinsonism and dementia	3.14 (2.35–4.16)	2.60 (1.90–3.53)	2.62 (1.91–3.56)	2.58 (1.87–3.54)

Note: Logistic regression model adjustments: Model 1: age, sex, education level, and number of physical illnesses (0, 1, 2, or 3+); Model 2 = Model 1 + carer age, carer sex, carer education, and carer relationship; Model 3 = Model 2 + country of residence.

TABLE 3 Caregivers' characteristics.

Characteristic	Control *N* = 9,991	Parkinsonism *N* = 704	Dementia *N* = 844	Parkinsonism and dementia *N* = 229	Total *N* = 11,768
Age (years), mean (SD)	53.3 (18.1)	54.0 (17.8)	53.0 (16.0)	55.1 (16.4)	53.5 (17.9)
Sex, male, n(%)	3013 (30.3)	163 (23.3)	161 (19.1)	47 (20.5)	3658 (28.6)
Education, n(%)					
None	228 (2.3)	14 (2.0)	22 (2.6)	7 (3.1)	297 (2.3)
Primary or less	991 (10.0)	100 (14.3)	91 (10.8)	26 (11.4)	1308 (10.2)
Primary	2168 (21.8)	154 (22.1)	170 (20.2)	55 (24.0)	2832 (22.1)
High School	3811 (38.3)	238 (34.1)	327 (38.8)	82 (35.8)	4871 (38.1)
College	2747 (27.6)	192 (27.5)	232 (27.6)	59 (25.8)	3487 (27.3)
Relationship with care-recipient, n(%)					
Spouse	2986 (30.0)	156 (22.3)	138 (16.4)	52 (22.7)	3626 (28.3)
Child	3650 (36.7)	287 (41.0)	423 (50.1)	115 (50.2)	4891 (38.2)
Son/daughter-in-law	423 (4.3)	32 (4.6)	39 (4.6)	9 (3.9)	527 (4.1)
Sibling	508 (5.1)	30 (4.3)	44 (5.2)	8 (3.5)	646 (5.0)
Other relative	1152 (11.6)	96 (13.7)	115 (13.6)	25 (10.9)	1512 (11.8)
Friend	533 (5.4)	34 (4.9)	30 (3.6)	3 (1.3)	665 (5.2)
Neighbor	526 (5.3)	47 (6.7)	23 (2.7)	4 (1.7)	673 (5.3)
Other	173 (1.7)	18 (2.6)	32 (3.8)	13 (5.7)	265 (2.1)
Care need, n(%)					
Much of the time	141 (1.5)	57 (8.3)	274 (33.2)	98 (43.8)	763 (6.1)
Occasionally	274 (2.8)	75 (10.9)	129 (15.6)	40 (17.9)	589 (4.7)
Does not need care	9269 (95.7)	553 (80.7)	423 (51.2)	86 (38.4)	11150 (89.2)
Zarit score, mean (SD)					
Overall	3.67 (9.68)	10.61 (13.88)	20.26 (17.09)	23.43 (16.09)	8.72 (14.41)
<3 NPI symptoms	1.99 (6.55)	6.94 (11.23)	14.29 (14.88)	14.67 (13.93)	4.18 (9.58)
≥3 NPI symptoms	10.65 (15.69)	17.52 (15.71)	24.52 (17.31)	27.72 (15.38)	18.94 (17.82)

irritability, and agitation. In the control group, NPSs were predominantly mild and not clinically significant. Overall, our results confirm that NPSs are more frequently encountered among individuals with parkinsonism and/or dementia and that the severity and clinical significance are higher than in the control groups. In addition, our findings highlight the relevance of NPSs in caregiver burden. NPSs explained a substantial proportion of the variance in global caregiver burden (CB), having the largest effect sizes on CB and emphasizing the strong contribution of NPSs to caregiver burden.

Frequency estimates and clinical features of NPSs in parkinsonism and dementia vary across studies due to methodological differences and a lack of uniform diagnostic criteria.[47] In our study, we captured the frequency of NPSs in a population-based cohort, which is 15% to 20% lower than the frequency reported using clinic-based registries.

The prevalence of NPSs in clinical settings ranges from 85% to 92%, and up to 75% of those are considered clinically relevant.[11,14,39,48] Studies conducted in the clinical setting are subject to referral bias that might overestimate the true prevalence of NPSs at a population level. In addition, we found a relatively high frequency of NPSs in the control group, which may be explained by the advanced age of the sample. This finding is consistent with previous reports in similar age groups.[10,22,23] In addition, there is the potential of early/prodromal NPSs in "healthy individuals" due to underlying pathology but not yet meeting clinical diagnosis criteria.

Regarding the prevalence of NPSs in parkinsonism, there are multiple prevalence estimates ranging from 14% to 81%, depending on the disease stage and study methodology.[12,49–55] Our study adds to the existing literature by reporting the frequency of NPSs in a population-based cohort of Hispanic participants with parkinsonism. In addition, although the frequency of NPSs in parkinsonism was lower than in PPD and dementia, parkinsonism participants had a higher frequency of NPSs relative to the control group, suggesting that NPSs are not necessarily restricted to those with dementia and reflect the wider-spread pathology in other clinical syndromes.

Similar to previous reports,[48,14,56–60] our study found a higher frequency and severity of NPSs in the PDD group than in parkinsonism and dementia only groups. At a group level, the likelihood of developing mood symptoms, delusions, and appetite disorders was similar among patients with dementia and PDD; however, patients with PDD were more likely to develop hallucinations and apathy. The cause for this difference may lie in the differential pathology for both diseases. Brain changes underlying psychosis in Alzheimer's dementia may differ from those in PDD, as has been shown previously for dementia with Lewy bodies and AD.[61,62] There is an ongoing controversy with the underlying pathology of PDD, which is likely to include diffuse Lewy body distribution in the cortical areas as well as AD pathology.[11,63] As a population-based cohort without evidence of disease biomarkers, we cannot rule out the possible co-existence of AD pathology in the PDD cohort; however, the differential likelihood of hallucinations in the PPD group, a symptom strongly correlated with Lewy body pathology, suggests that dementia in participants with parkinsonism was not only due to concomitant AD.

In summary, our study described prevalence estimates of NPSs that are comparable with prior population-based reports and studies using similar methodology.[10,57,64,65]

NPSs contributed in a significant way to caregiver burden. This is consistent with previous data where the presence of NPS is associated with higher levels of depression among caregivers of older Hispanics with cognitive impairment. As NPSs are a potentially modifiable contributor to caregiver burden, clinicians should screen for the presence of NPSs in older patients with neurodegenerative diseases, as well as inquire about the presence of caregiver stress in the setting of NPSs.[66]

The present study must be interpreted within the context of its potential limitations. First, the cross-sectional design does not allow us to infer causality but rather associations between NPSs, parkinsonism, dementia, and PDD. Second, it is well known that medications can have an impact on NPS; however, our study did not collect the use of antipsychotic, anxiolytic, or PD medications systematically, and so the relationship between certain NPSs and different diagnoses could be mitigated by medication use. A third concern involves our reliance on survey data and that the parkinsonism, dementia, and PPD diagnoses were not made by movement disorders or dementia specialists, which may create case underreporting, especially in participants at earlier stages of the disease. This may increase the frequency of NPSs in the control group due to a diagnosis bias. Alternatively, missing those cases at earlier stages of the disease may overestimate the frequency of NPSs in the more advanced cases.

Despite previous limitations, it is worth noting that there are several advantages to the current approach. This is the largest study to date exploring the frequency of NPSs in Hispanic populations using a population-based cohort from multiple countries in LatAm. Population-based registries are not standard in LatAm, and clinic-based registries cannot be assumed to be representative because underdiagnosis is common and there is a relative lack of access to health care. In addition, this is the first study to directly explore and report the effect of NPSs on caregiver burden living in LatAm. Using a population-based approach involving participants' direct contact to assess disease status diminishes the possibility of prevalence underestimation. Therefore, this study is particularly well suited to estimate the prevalence of NPSs in neurodegenerative diseases, related caregiver needs, and disease burden in LatAm. Future studies will be required to explore cross-population differences in PD prevalence and risk, especially between HICs and low- to middle-income countries (LMICs). If differences are observed between these studies, we may find valuable clues about the determinants of NPSs in neurodegeneration.

5 | CONCLUSIONS

We demonstrated that NPSs are highly prevalent in Hispanic populations with neurodegenerative disease, significantly impacting caregiver burden. Therefore, healthcare professionals involved in the care of elders should proactively screen for the presence of NPS, particularly in patients with parkinsonism, dementia, and PPD. From a public policy point of view, LatAm countries may need to develop intervention plans to support families and caregivers dealing with NPSs.

AUTHOR CONTRIBUTIONS

All authors worked collectively to develop the protocols and methods described in this article. Ana Rodriguez Salgado and Jorge J Llibre-Guerra had full access to all the data in the study and take responsibility for the integrity and accuracy of the data analysis. (1) **Acquisition of data**: Jorge J Llibre-Guerra, Ana Luisa Sosa, Daisy Acosta, Ivonne Z. Jimenez-Velasquez, Mariella Guerra, Aquiles Salas, Juan C Llibre-Guerra, Isaac Acosta, and Juan J. Llibre Rodriguez. **(2) Research project: A. Conception**: Ana Rodriguez Salgado, Jorge J Llibre-Guerra, and Juan J Llibre Rodriguez. **B. Organization and project administration**: Ana Rodriguez Salgado and Jorge J Llibre-Guerra. **C. Execution**: Ana Rodriguez Salgado. **(3) Statistical Analysis: A. Design**: Matthew Prina and Dani J Kim. **B. Execution**: Dani Kim. **C. Review and Critique**: All authors. **(4) Manuscript: A. Writing of the first draft**: Ana Rodriguez

Salgado, Issac Acosta, Dani Kim, and Jorge J Llibre-Guerra. **B. Review and Critique**: All authors.

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CONFLICT OF INTEREST STATEMENT

Rodriguez-Salgado AM, Acosta I, Kim D, Zitser J, Sosa AL, Acosta D, Jiménez-Velázquez IZ, Guerra M, Salas A, Valvuerdi A, Llibre-Guerra JC, Jeyachandran C, López Contreras R, Hesse H, Tanner C, Llibre-Rodríguez J, Prina M, and Llibre-Guerra JJ report no conflict of interest or relevant financial disclosure related to this manuscript. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT STATEMENT

Written informed consent was obtained from all participants and their study partners. This project was approved by local institutional review boards and the King's College London Research Ethics Committee. The full protocol for the 10/66 population-based surveys is available in an open-access publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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