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

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Abstract

Background: Neuro-psychiatric symptoms (NPSs) are a common occurrence in neurodegenerative diseases; however, little is known about the prevalence of NPSs in Hispanics populations.

Methods: Using data from community-dwelling participants aged 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 normal cognitive 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 3 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 the occurrence of NPSs, especially in patients with parkinsonism, dementia and PPD and develop intervention plans to support families and caregivers.

Keywords

Neuropsychiatric symptoms; Hispanics; dementia; parkinsonism and parkinsonism-dementia

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1. Background:

The upcoming demographic shifts toward older populations have prompted efforts to estimate healthcare 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, which promotes cognitive decline.[3–9] Several studies have estimated the prevalence of NPSs. Depending on the methodology and disease stage, it has been estimated that NPS affects 32% to 75% of people with PD and 50% to 80% of those 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 neuropsychiatric symptoms in PD.[13,14] Similarly, although dementia, including dementia due to Alzheimer's disease, 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 neuropsychiatric symptoms 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 (HIC) in rather homogeneous populations (predominantly non-Hispanic whites)[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 neuropsychiatric symptoms 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).

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 aged 65 years 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=2,944), Dominican Republic (Santo Domingo, n=2,011), Puerto Rico (Bayamon, n=2,009), Venezuela (Caracas, n=1,965), Peru (Lima, n=1,381), and Mexico (Mexico City, n=1,003). Rural sites, remote from major population centers with low-density population and agriculture and related trades as the primary local employment, were located in Peru (Canete Province, n=552) and Mexico (Morelos State, n=1,000). The response rate in the 10/66 range from 80 % to 95%, and 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 a 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.

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 diagnoses was established following: (i) a structured clinical interview; (ii) a cognitive test battery including a) the Community Screening Instrument for Dementia (CSI-D)[31] b) a verbal fluency task, and c) the modified 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] were used to define dementia diagnosis and subtype.

Parkinsonism: All participants underwent a comprehensive interview lasting three 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 the small sample size in this analysis we focused on clinical syndromes and not on clinical diagnosis (e.g., PD, AD, Lewy Body Disease (LBD) etc).

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 use in research with dementia patients, it has been suggested as an appropriate tool for use in parkinsonism and PD patients to assess by the Movement Disorder Society.[38] In this study, we determined the presence/absence, severity, and associated caregiver distress for each 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 NPSs was assessed by the caregiver on a scale from 1–3 (mild, moderate, and severe). Clinically relevant NPSs were defined according to caregiver-reported distress. Distress scores from 0–2 (not distressing, minimal, or mild) were considered not clinically significant and scores 3–5 (moderate, severe, and extreme) were considered clinically significant distress. In the clinical setting, domains scores of 3 or more are indicative of clinical relevance and are associated with 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.

Caregiver Burden: The Zarit Burden Interview was used to assess caregiver burden. [41–43] The Zarit Burden Interview (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 originally developed to assess the burden among caregivers of community-dwelling persons. Each item on the interview is a statement which 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 0–88. Higher scores indicate a greater burden.

Care dependence and caregiver characteristics: We defined care dependence as the needs 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 needs for care (does not need care; needs care occasionally; or needs care much of the time). This judgment wass 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]

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 percentage of the total sample of those 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 and 95% confidence intervals (CI) were reported for crude and adjusted models, which were adjusted for age, sex, educational level, and number of physical illnesses. Additionally, the severity of the NPS symptom and the prevalence of clinically significant caregiver distress were reported as frequencies or percentages with 95% CIs by individual NPS and diagnosis group. Lastly, the odds of having 3 or more NPS with clinically significant caregiver distress by diagnosis type was assessed using logistic regression model adjusted for age, sex, education level, and 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 1,097 participants were missing data on parkinsonism or dementia, or both. Details about the 10/66 sample relative to our analytical sample are shown in Supplemental Table 1. In summary, participants with missing data were more likely to be less educated, have more co-morbidities and more disability.

Our final analytical sample included 11,768 participants (4,189 men; 7,579 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 9,991 were

considered elders without neurodegenerative syndromes (control group). Summary statistics, including sample size, sex, age, education, and socio-economic status, are shown in Table 1. Across the whole sample, only 40.2% (4,663/11,581) of the participants were without any symptoms, whereas 59.8% (6,918/11,581) presented at least one of the NPSs, and 26.3% (3043/11,581) had 3 or more NPSs. Overall, the most frequent NPSs, regardless of clinical severity, (See supplemental Table 2), were depression (n=3,655, 28.8%), sleep disorders (n=3,174, 25.0%), irritability (n=2,939, 23.1%), and agitation (n=2,418, 19.0%). Compared to elders without neurodegenerative syndromes, the individuals with PDD showed higher NPI severity and distress scores, followed by dementia and parkinsonism-only groups, respectively (See supplemental Tables 3 and 4).

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 healthy elders. 43.7% of the healthy elders exhibited no NPSs; while 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 3 or more NPSs; in contrast approximately 34.3%, 56.1%, and 61.2% of the participants with parkinsonism, dementia, and PDD exhibited 3 or more NPSs respectively. The prevalence of each NPSs by diagnostic group is summarized in Figure 1 and Supplemental Table 2. Using the control group as a reference, we explored the likelihood of reporting each NPSs according to diagnostic group (see Table 2). Compared to elders without neurodegenerative syndromes, a diagnosis of parkinsonism, dementia, or PDD was statistically significantly associated 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. The frequency of clinically relevant NPSs by diagnostic groups are shown in Supplemental Table 4. Compared to controls, participants with parkinsonism (95% CI, 1.92 [1.43–2.53]), dementia (95% CI, 5.79 [4.78–6.99]), and PDD (95% CI, 5.81 [4.14–8.02]) were more likely to show 3 or more NPS with clinically significant caregiver distress (see Supplemental Table 5).

3.3- Influence of Neuropsychiatric Symptoms on caregiver burden:

In a second analysis, we described the relationship between caregiver burden, represented by the Zarit total score, and NPSs was described 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%) and without statistically significant differences across groups. Caregivers in this sample were predominantly son/daughters (4,891, 38.2%) and spouses (n=3,626, 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 Zarit 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 symptoms in the care recipient (as rated by the CPD) were associated with moderate to severe distress in the care partner, but some also reported severe distress from mild symptoms or mild distress even with severe symptoms.

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 neuropsychiatric symptom was present in nearly 60% of the included participants. In the whole sample, the most common symptoms were depression, sleep disorders, irritability, and agitation. In the healthy population, NPSs were predominantly mild and not clinically significant. Overall, our results confirm that NPS are more frequently encountered among individuals with parkinsonism and/or dementia and that the severity and clinical significance is significantly higher relative to the control group. 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 NPSs to caregiver burden.

Frequency estimates and clinical features of neuropsychiatric symptoms 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 in 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] Also, 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, [48,56–61] our study found a higher frequency and severity of NPSs in the PDD group than in parkinsonism and dementia. At a group level, the likelihood of developing mood symptoms, delusions and appetite disorders was similar among those with dementia and PDD, however those with PDD were more likely to develop hallucinations and apathy. The cause for this difference may lie in differential pathology for both diseases. Brain changes underlying psychosis in Alzheimer's dementia may differ from those in PDD, as has previously been shown for dementia with Lewy bodies and Alzheimer's disease.[62,63] There is an ongoing controversy on the underlying pathology of PDD, which is likely to include diffuse Lewy body distribution in the cortical areas as well as Alzheimer's disease pathology.[11,64] As a population-based cohort without evidence of disease biomarkers, we can't 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 pathology, suggests that dementia in people living with parkinsonism was not only due to concomitant Alzheimer's disease.

In summary, our study described NPSs prevalence estimates that are comparable with prior population-based reports and studies using similar methodology. [10,57,65,66]

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 well as of those with dementia. As NPSs are a potentially modifiable contributor to caregiver stress and burden, clinicians should screen for the presence of NPSs in older patients with neurodegenerative diseases, as well as inquiring about the presence of caregiver stress in the setting of NPSs. [67]

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 usage. 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 those 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's worth noting that there are several advantages of the current approach. This is the largest study to date in 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 as underdiagnosis is common and there is a relative lack of access to health care. In addition, this is the first study to directly assess the effect of NPSs in caregiver burden living in Latin America. Therefore, 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 aimed to explore cross-population differences in PD prevalence and risk, especially between HIC and LMIC. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

References:

[1]. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Movement Disorders 2014;29:1583–90. 10.1002/mds.25945. [PubMed: 24976103]

[2]. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007;68:384–6. 10.1212/01.wnl.0000247740.47667.03. [PubMed: 17082464]

[3]. Allegri RF, Sarasola D, Serrano CM, Taragano FE, Arizaga RL, Butman J, et al. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. Neuropsychiatr Dis Treat 2006;2:105. [PubMed: 19412452]

[4]. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. MENTAL SYMPTOMS IN PARKINSON'S DISEASE ARE IMPORTANT CONTRIBUTORS TO CAREGIVER DISTRESS n.d. 10.1002/(SICI)1099-1166(199910)14:10.

[5]. Gómez-Esteban JC, Tijero B, Somme J, Ciordia R, Berganzo K, Rouco I, et al. Impact of psychiatric symptoms and sleep disorders on the quality of life of patients with Parkinson's disease. J Neurol 2011;258:494–9. 10.1007/S00415-010-5786-Y. [PubMed: 20957384]

[6]. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 2000;48:938–42. 10.1111/J.1532-5415.2000.TB06891.X. [PubMed: 10968298]

[7]. Lyketsos CG, Steele C, Baker L, Galik E, Kopunek S, Steinberg M, et al. Major and minor depression in Alzheimer's disease: prevalence and impact. J Neuropsychiatry Clin Neurosci 1997;9:556–61. 10.1176/JNP.9.4.556. [PubMed: 9447496]

[8]. Stern Y, Tang M-X, Albert MS, Brandt J, Jacobs DM, Bell K, et al. Predicting Time to Nursing Home Care and Death in Individuals With Alzheimer Disease. JAMA 1997;277:806–12. 10.1001/JAMA.1997.03540340040030. [PubMed: 9052710]

[9]. Steele C, Rovner B, Chase GA, Folstein M. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. Am J Psychiatry 1990;147:1049–51. 10.1176/AJP.147.8.1049. [PubMed: 2375439]

[10]. Geda YE, Roberts RO, Knopman DS, Petersen RC, Christianson TJH, Pankratz VS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. Arch Gen Psychiatry 2008;65:1193–8. 10.1001/ARCHPSYC.65.10.1193. [PubMed: 18838636]

[11]. Hommel ALAJ, Meinders MJ, Lorenzl S, Dodel R, Coelho M, Ferreira JJ, et al. The Prevalence and Determinants of Neuropsychiatric Symptoms in Late-Stage Parkinsonism. Mov Disord Clin Pract 2020;7:531. 10.1002/MDC3.12968. [PubMed: 32626798]

[12]. Kulisevsky J, Pagonbarraga J, Pascual-Sedano B, García-Sánchez C, Gironell A. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. Mov Disord 2008;23:1889–96. 10.1002/MDS.22246. [PubMed: 18709682]

[13]. Marras C, Chaudhuri KR. Nonmotor features of Parkinson's disease subtypes. Movement Disorders 2016;31:1095–102. 10.1002/mds.26510. [PubMed: 26861861]

[14]. Weerkamp NJ, Tissingh G, Poels PJE, Zuidema SU, Munneke M, Koopmans RTCM, et al. Nonmotor Symptoms in Nursing Home Residents with Parkinson's Disease: Prevalence and Effect on Quality of Life. J Am Geriatr Soc 2013;61:1714–21. 10.1111/JGS.12458. [PubMed: 24117286]

[15]. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, et al. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimer's & Dementia 2011;7:532–9. 10.1016/j.jalz.2011.05.2410.

[16]. Troiano AR, Micheli FE, Alarcón F, Teive HAG. Movement disorders in Latin America. Parkinsonism Relat Disord 2006;12:125–38. 10.1016/J.PARKRELDIS.2005.08.009. [PubMed: 16503410]

[17]. GBD 2016 Parkinson's Disease Collaborators ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016:

a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:939–53. 10.1016/S1474-4422(18)30295-3. [PubMed: 30287051]

[18]. Llibre-Guerra JJ, Prina M, Sosa AL, Acosta D, Jimenez-Velazquez IZ, Guerra M, et al. Prevalence of parkinsonism and Parkinson disease in urban and rural populations from Latin America: A community based study. The Lancet Regional Health - Americas 2022;7:100136. 10.1016/J.LANA.2021.100136/ATTACHMENT/0D729B60-E37E-4420-BC41-669A91CBCD92/MMC1.DOC. [PubMed: 35300390]

[19]. Stephan BCM, Pakpahan E, Siervo M, Licher S, Muniz-Terrera G, Mohan D, et al. Prediction of dementia risk in low-income and middle-income countries (the 10/66 Study): an independent external validation of existing models. Lancet Glob Health 2020;8:e524–35. 10.1016/S2214-109X(20)30062-0. [PubMed: 32199121]

[20]. Sousa RM, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob K, et al. The contribution of chronic diseases to the prevalence of dependence among older people in Latin America, China and India: a 10/66 Dementia Research Group population-based survey. BMC Geriatr 2010;10:53. 10.1186/1471-2318-10-53. [PubMed: 20691064]

[21]. Nitrini R, Bottino CMC, Albala C, Custodio Capuñay NS, Ketzoian C, Llibre Rodriguez JJ, et al. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. Int Psychogeriatr 2009;21:622–30. 10.1017/S1041610209009430. [PubMed: 19505354]

[22]. Gil M, Alliey-Rodriguez N, Lopez-Alvarenga JC, Diego V, Gaona CA, Mata L, et al. Neuropsychiatric Symptoms Among Hispanics: Results of the Maracaibo Aging Study. J Alzheimers Dis 2021;82:S251–61. 10.3233/JAD-201144. [PubMed: 33612541]

[23]. Milani SA, Cantu PA, Berenson AB, Kuo YF, Markides KS, Raji MA. Gender Differences in Neuropsychiatric Symptoms Among Community-Dwelling Mexican Americans Aged 80 and Older. Am J Alzheimers Dis Other Demen 2021;36. 10.1177/15333175211042958.

[24]. Ortiz F, Fitten LJ, Cummings JL, Hwang S, Fonseca M. Neuropsychiatric and behavioral symptoms in a community sample of Hispanics with Alzheimer's disease. Am J Alzheimers Dis Other Demen 2006;21:263–73. 10.1177/1533317506289350. [PubMed: 16948291]

[25]. DI Luca DG, Sambursky JA, Margolesky J, Cordeiro JG, DIaz A, Shpiner DS, et al. Minority Enrollment in Parkinson's Disease Clinical Trials: Meta-Analysis and Systematic Review of Studies Evaluating Treatment of Neuropsychiatric Symptoms. J Parkinsons Dis 2020;10:1709–16. 10.3233/JPD-202045. [PubMed: 32894250]

[26]. Prina AM, Acosta D, Acostas I, Guerra M, Huang Y, Jotheeswaran AT, et al. Cohort Profile: The 10/66 study. Int J Epidemiol 2016;46:dyw056. 10.1093/ije/dyw056.

[27]. Prina AM, Mayston R, Wu Y-T, Prince M. A review of the 10/66 dementia research group. Soc Psychiatry Psychiatr Epidemiol 2018:1–10. 10.1007/s00127-018-1626-7.

[28]. Prince M, Ferri CP, Acosta D, Albanese E, Arizaga R, Dewey M, et al. The protocols for the 10/66 dementia research group population-based research programme. BMC Public Health 2007;7:165. 10.1186/1471-2458-7-165. [PubMed: 17659078]

[29]. Prince M, Acosta D, Chiu H, Scazufca M, Varghese M. Dementia diagnosis in developing countries: A cross-cultural validation study. Lancet 2003. 10.1016/S0140-6736(03)12772-9.

[30]. Prince MJ, De Rodriguez JL, Noriega L, Lopez A, Acosta D, Albanese E, et al. The 10/66 Dementia Research Group's fully operationalised DSM-IV dementia computerized diagnostic algorithm, compared with the 10/66 dementia algorithm and a clinician diagnosis: A population validation study. BMC Public Health 2008. 10.1186/1471-2458-8-219.

[31]. Hall KS, Hendrie HC, Rodgers DD, Osuntokun BO, Brittain HM, Norton JA, et al. The development of a dementia screening interview in two distinct languages. International Journal of Methods in Psychiatry 1993.

[32]. Sosa AL, Albanese E, Prince M, Acosta D, Ferri CP, Guerra M, et al. Population normative data for the 10/66 Dementia Research Group cognitive test battery from Latin America, India and China: a cross-sectional survey. BMC Neurol 2009;9:48. 10.1186/1471-2377-9-48. [PubMed: 19709405]

[33]. Dewey ME, Copeland JRM. Diagnosis of dementia from the history and aetiology schedule. Int J Geriatr Psychiatry 2001. 10.1002/gps.446.

[34]. Pasquini L, Llibre Guerra J, Prince M, Chua K-C, Prina AM. Neurological signs as early determinants of dementia and predictors of mortality among older adults in Latin America: a 10/66 study using the NEUROEX assessment. BMC Neurol 2018;18:163. 10.1186/s12883-018-1167-4. [PubMed: 30285663]

[35]. Quinn N Fortnightly Review: Parkinsonism—recognition and differential diagnosis. BMJ 1995;310:447. 10.1136/bmj.310.6977.447. [PubMed: 7646647]

[36]. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson ' s disease : a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4. 10.1136/jnnp.55.3.181. [PubMed: 1564476]

[37]. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 2000;12:233–9. 10.1176/JNP.12.2.233. [PubMed: 11001602]

[38]. Martinez-Martin P, Leentjens AFG, de Pedro-Cuesta J, Chaudhuri KR, Schrag AE, Weintraub D. Accuracy of screening instruments for detection of neuropsychiatric syndromes in Parkinson's disease. Mov Disord 2016;31:270–9. 10.1002/MDS.26522. [PubMed: 26695691]

[39]. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, Dekosky S. Prevalence of Neuropsychiatric Symptoms in Dementia and Mild Cognitive Impairment: Results From the Cardiovascular Health Study. JAMA 2002;288:1475–83. 10.1001/JAMA.288.12.1475. [PubMed: 12243634]

[40]. Schneider LS, Ismail MS, Dagerman K, Davis S, Olin J, McManus D, et al. Clinical antipsychotic trials of intervention effectiveness (CATIE): Alzheimer's disease trial. Schizophr Bull 2003;29:57–72. 10.1093/oxfordjournals.schbul.a006991. [PubMed: 12908661]

[41]. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist 1980;20:649–55. 10.1093/GERONT/20.6.649. [PubMed: 7203086]

[42]. Bachner YG, O'Rourke N. Reliability generalization of responses by care providers to the Zarit Burden Interview. Aging Ment Health 2007;11:678–85. 10.1080/13607860701529965. [PubMed: 18074255]

[43]. Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'donnell M. The Zarit Burden Interview: a new short version and screening version. Gerontologist 2001;41:652–7. 10.1093/GERONT/41.5.652. [PubMed: 11574710]

[44]. Prina AM, Wu YT, Kralj C, Acosta D, Acosta I, Guerra M, et al. Dependence- and Disability-Free Life Expectancy Across Eight Low- and Middle-Income Countries: A 10/66 Study. J Aging Health 2020;32:401–9. 10.1177/0898264319825767/ASSET/IMAGES/LARGE/10.1177_0898264319825767-FIG2.JPEG. [PubMed: 30698491]

[45]. Mayston R, Guerra M, Huang Y, Sosa AL, Uwakwe R, Acosta I, et al. Exploring the economic and social effects of care dependence in later life: Protocol for the 10/66 research group INDEP study. Springerplus 2014;3:1–13. 10.1186/2193-1801-3-379/FIGURES/1. [PubMed: 24422185]

[46]. Sousa RM, Ferri CP, Acosta D, Albanese E, Guerra M, Huang Y, et al. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. The Lancet 2009;374:1821–30. 10.1016/S0140-6736(09)61829-8.

[47]. Geurtsen GJ, Hoogland J, Goldman JG, Schmand Ba, Burn DJ, Litvan, et al. Parkinson's Disease Mild Cognitive Impairment: Application and Validation of the Criteria 2015;4:131–7. 10.3233/JPD-130304.Parkinson.

[48]. Aarsland D, Brønnick K, Ehrt U, De Deyn PP, Tekin S, Emre M, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. J Neurol Neurosurg Psychiatry 2007;78:36–42. 10.1136/JNNP.2005.083113. [PubMed: 16820421]

[49]. Antonini A, Barone P, Bonuccelli U, Annoni K, Asgharnejad M, Stanzione P. ICARUS study: prevalence and clinical features of impulse control disorders in Parkinson's disease. J Neurol Neurosurg Psychiatry 2017;88:317–24. 10.1136/JNNP-2016-315277. [PubMed: 28315845]

[50]. Weintraub D, Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Siderowf A, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. Mov Disord 2015;30:919–27. 10.1002/MDS.26170. [PubMed: 25737166]

[51]. Aarsland D, Larsen JP, Cummings JL, Laake K. Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. Arch Neurol 1999;56:595–601. 10.1001/ARCHNEUR.56.5.595. [PubMed: 10328255]

[52]. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003;60:387–92. 10.1001/ARCHNEUR.60.3.387. [PubMed: 12633150]

[53]. Lauterbach EC, Freeman A, Vogel RL. Differential DSM-III psychiatric disorder prevalence profiles in dystonia and Parkinson's disease. J Neuropsychiatry Clin Neurosci 2004;16:29–36. 10.1176/JNP.16.1.29. [PubMed: 14990756]

[54]. Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. Movement Disorders 2009;24:2175–86. 10.1002/mds.22589. [PubMed: 19768724]

[55]. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. Movement Disorders 2008;23:837–44. 10.1002/MDS.21956. [PubMed: 18307261]

[56]. Bougea A, Stefanis L, Paraskevas GP, Emmanouilidou E, Efthymiopoulou E, Vekrelis K, et al. Neuropsychiatric symptoms and α-Synuclein profile of patients with Parkinson's disease dementia, dementia with Lewy bodies and Alzheimer's disease. J Neurol 2018;265:2295–301. 10.1007/s00415-018-8992-7. [PubMed: 30083953]

[57]. Lyketsos CG, Steinberg M, Tschanz JAT, Norton MC, Steffens DC, Breitner JCS. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry 2000;157:708–14. 10.1176/APPI.AJP.157.5.708. [PubMed: 10784462]

[58]. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 2000;54:2269–76. 10.1212/WNL.54.12.2269. [PubMed: 10881251]

[59]. Coelho M, Ferreira JJ. Late-stage Parkinson disease. Nature Reviews Neurology 2012 8:8 2012;8:435–42. 10.1038/nrneurol.2012.126. [PubMed: 22777251]

[60]. Coelho M, Marti MJ, Sampaio C, Ferreira JJ, Valldeoriola F, Rosa MM, et al. Dementia and severity of parkinsonism determines the handicap of patients in late-stage Parkinson's disease: the Barcelona-Lisbon cohort. Eur J Neurol 2015;22:305–12. 10.1111/ENE.12567. [PubMed: 25220687]

[61]. Weerkamp NJ, Tissingh G, Poels PJE, Zuidema SU, Munneke M, Koopmans RTCM, et al. Nonmotor symptoms in nursing home residents with Parkinson's disease: prevalence and effect on quality of life. J Am Geriatr Soc 2013;61:1714–21. 10.1111/JGS.12458. [PubMed: 24117286]

[62]. Aarsland D, Ballard CG, Halliday G. Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? J Geriatr Psychiatry Neurol 2004;17:137–45. 10.1177/0891988704267470. [PubMed: 15312277]

[63]. Ballard CG, Jacoby R, del Ser T, Khan MN, Munoz DG, Holmes C, et al. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with lewy bodies. Am J Psychiatry 2004;161:843–9. 10.1176/APPI.AJP.161.5.843. [PubMed: 15121649]

[64]. Jellinger KA, Korczyn AD. Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? BMC Med 2018;16. 10.1186/S12916-018-1016-8.

[65]. Salazar R, Royall DR, Palmer RF. 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 2015;30:300–7. 10.1002/GPS.4141. [PubMed: 24838594]

[66]. Steinberg M, Tschanz JAT, Corcoran C, Steffens DC, Norton MC, Lyketsos CG, et al. The persistence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry 2004;19:19–26. 10.1002/GPS.1025. [PubMed: 14716695]

[67]. Hinton L, Haan M, Geller S, Mungas D. Neuropsychiatric Symptoms in Latino Elders With Dementia or Cognitive Impairment Without Dementia and Factors That Modify Their Association With Caregiver Depression. Gerontologist 2003;43:669–77. 10.1093/GERONT/43.5.669. [PubMed: 14570963]

Highlights:

- NPSs are highly prevalent in Hispanic populations with neurodegenerative disease.

- In healthy Hispanics 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.
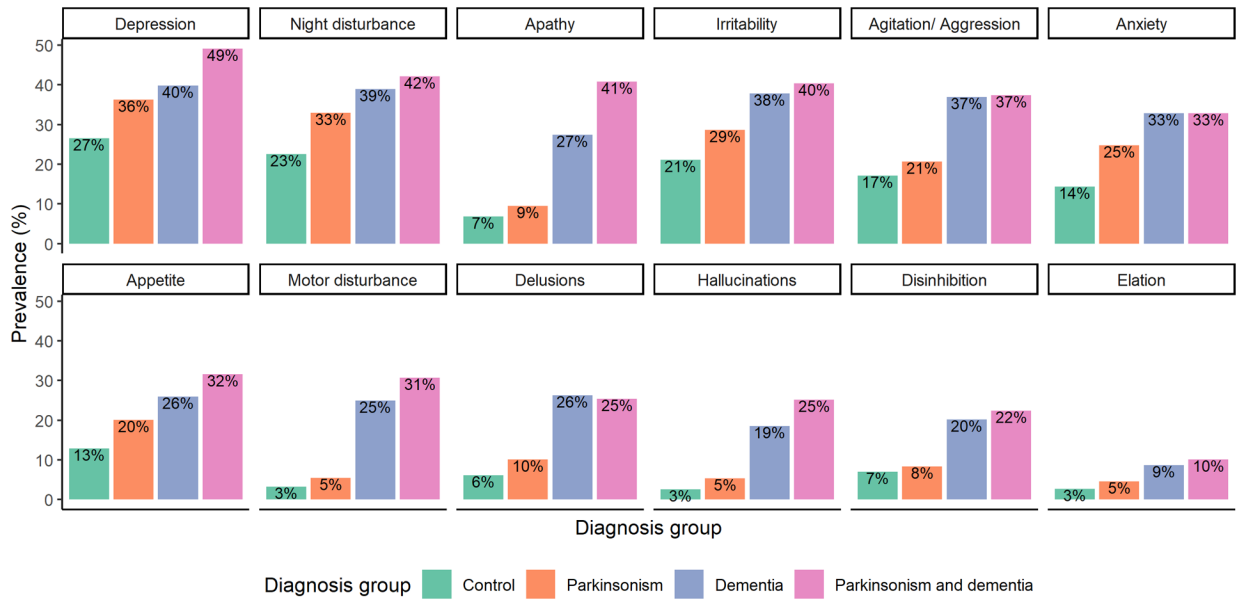
Figure 1:
Frequency of neuropsychiatric symptoms by diagnosis

Table 1:

Participant's Sociodemographic and Health Characteristics.

Mean (SD) or n (%)	Control N=9,991	Parkinsonism N=704	Dementia N=844	Parkinsonism and dementia N=229	Total N=11,768
Age (years)	73.8 (6.6)	78.2 (7.3)	80.7 (8.2)	82.2 (7.2)	74.7 (7.2)
Sex, male	3570 (35.8)	280 (39.8)	253 (30.0)	86 (37.6)	4568 (35.5)
Education					
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					
1stquartile	1626 (16.3)	155 (22.0)	212 (25.1)	43 (18.8)	2226 (17.3)
2ndquartile	3520 (35.3)	277 (39.4)	282 (33.5)	93 (40.6)	4596 (35.8)
3rdquartile	2857 (28.6)	161 (22.9)	229 (27.2)	53 (23.1)	3608 (28.1)
4thquartile	1978 (19.8)	110 (15.6)	120 (14.2)	40 (17.5)	2422 (18.8)
Rural	1335 (13.4)	94 (13.4)	103 (12.2)	18 (7.9)	1552 (12.1)
Physical multimorbidity					
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	0.54 (1.23)	1.57 (1.94)	3.01 (2.83)	3.56 (2.68)	0.89 (1.75)

Table 2:

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

		Crude ORs (95% CI)	Model 1 ORs (95% CI)	Model 2 ORs (95% CI)	Model 3 ORs (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)

	Crude ORs (95% CI)	Model 1 ORs (95% CI)	Model 2 ORs (95% CI)	Model 3 ORs (95% CI)
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)
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)

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:

Caregiver's characteristics

Mean (SD) or n (%)	Control N=9,991	Parkinsonism N=704	Dementia N=844	Parkinsonism and dementia N=229	Total N=11,768
Age (years)	53.3 (18.1)	54.0 (17.8)	53.0 (16.0)	55.1 (16.4)	53.5 (17.9)
Sex, male	3013 (30.3)	163 (23.3)	161 (19.1)	47 (20.5)	3658 (28.6)
Education					
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					
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					
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					
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)