Parkinson's disease prevalence, age distribution and staging in Colombia

Jorge Luis Orozco,[1,2] Jaime Andrés Valderrama-Chaparro,[1,2] Gabriel David Pinilla-Monsalve,[1,3] María Isabel Molina-Echeverry,[3] Ana Melissa Pérez Castaño,[4] Yoseth Ariza-Araújo,[3] Sergio I. Prada,[2,4] Yuri Takeuchi[1,3]

[1]Departamento de Neurología, Fundación Valle del Lili, Cali; [2]Centro de Investigaciones Clínicas, Fundación Valle del Lili, Cali; [3]Facultad de Ciencias de la Salud, Universidad Icesi, Cali; [4]PROESA, Universidad Icesi, Cali, Colombia

Abstract

Parkinson's disease (PD) has the second highest prevalence among neurodegenerative diseases. In Colombia, PD population dynamics are currently unknown. Health records offer a unique resource to study frequency and multi-morbidity of chronic diseases. The aim of this research is to estimate prevalence and staging using administrative data (AD) provided by Health Maintenance Organizations (HMOs). A cross-sectional study was conducted using 2015 AD from two Colombian HMOs (4.312.928 beneficiaries, 9.01% of the affiliated Colombian population). PD prevalence and severity was estimated by age and sex. Prevalence was adjusted to WHO demographics. Age-adjusted PD prevalence was 205.89 per 100.000 inhabitants. Prevalence increment of 62.13% was found between those aged ≥40 years and those aged ≥50 years. Similarly, each extra decade (50-80+) represented an increment of 83.65%, 80.95%, and 35.10%. Between 40 and 89 years, males exhibited a significantly higher PD prevalence compared to females. Advanced PD was more frequent as age increased from 3.77% in the group between 40 to 49 years to 25.86% in those older than 89 years. More common related comorbidities were arterial hypertension, diabetes, and psychiatric disorders; the first two increased their frequency with age, and the last one maintained its prevalence across all age groups. AD sets are useful to estimate the prevalence and staging of PD. Prevalence of PD in Colombia is higher in men and increases with age, as well as disease severity.

Introduction

Neurological disorders produce a considerable epidemiological burden associated with high rates of disability. Parkinson's disease (PD) has the second highest prevalence among neurodegenerative diseases. Due to the world population´s aging, PD prevalence and incidence are dramatically increasing, even surpassing the growth of Alzheimer's disease. According to the Global Burden of Disease study, 6.2 million patients live with PD and this frequency will double by 2040. Being a chronic and disabling illness, especially in elders, it imposes great financial burden to PD patients, their families, and the healthcare system.[1-3]

Epidemiological data on PD are highly variable across countries.[4,5] These differences can be explained by the variability in the diagnostic criteria, changes in population age distribution and the access to health care services, including the opportunity to consult with trained doctors or specialists.[6] To achieve more accurate estimates and understand the distribution of the disease, epidemiological studies should include large and representative samples of the population.[7] Increasing the sample size is usually problematic because it implies an increase in the costs of the entire research, especially if the population is large and the economic resources are limited.

Due to its cost-effectiveness, standardization and high coverage (all-inclusive for the population enrolled in a health system or health care plan), administrative datasets seem useful for calculating the frequency of non-communicable diseases.[8] In fact, these datasets facilitate the study of incidence, prevalence, mortality, and multi-morbidity of diseases. For PD this kind of studies have already been conducted in countries like Argentina and Israel.[9,10]

In South America, Colombia is a country in epidemiological transition where there has been a continuous increase in elderly population, with a rise of chronic non-infectious illnesses.[11] The EPINEURO studies conducted between 1995 and 1996, are the only experiences involving a nationally representative sample to estimate PD epidemiological data. According to its results, PD prevalence was 4.7 per 1.000 inhabitants over fifty years (95% CI 2.2-8.9). Although their results were promising, the study methodology, a population-based survey of a stratified random sample, has several limitations and the observed PD occurrence of only nine cases in the whole country, was debatable.[12]

Correspondence: Yuri Takeuchi Tan, Facultad de Ciencias de la Salud, Universidad Icesi, Calle 18 No. 122-135 Pance, Cali 760031, Colombia.
Tel.: +57.2.5552334 (Ext: 8032).
E-mail: yuri.takeuchi@fvl.org.co

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The objective of this research is to estimate the prevalence and stage of PD using HMO (Health Management Organizations) data, based on an adapted algorithm that includes ICD-10 diagnostic codes and pharmacy records (Anatomical Therapeutic Chemical Classification System codes, ATC).

Materials and Methods

The Colombian national healthcare system is a mandatory policy based on the principles of solidarity and managed competition with universal coverage. There

are two schemes, one financed by employee-employer contributions and one financed by general taxes that subsidizes healthcare for poor people. Funds are distributed among Health Management Organizations (HMOs) using an age-sex and region adjusted capita. There are HMOs in both schemes, and each one is responsible for contracting healthcare providers (*e.g.* hospitals, laboratories, outpatient services) and creating a healthcare network based on the needs of its users. People are free to choose their HMOs, and HMOs are free to choose their providers. There is a mandatory benefits package by law that all HMOs must provide. Lastly, there is private supplemental health insurance.

Characteristics of the administrative data used for the study

We conducted an observational study to determine PD prevalence based on administrative de-identified data from two Colombian HMOs using claims from 2015. Access was obtained in the settings of a research agreement with Icesi University (Cali). According to national records from 2015, 97.6% of the Colombian population is insured by the National Healthcare System.[13] The two HMOs that provided us with claims data have 4,312,928 beneficiaries (9.01% of the affiliated Colombian population in 2015) distributed across different regions of the country, mainly in the southwest. These claims are filled only by physicians certified by the government and other regulatory entities. The information is compiled by the institutions providing health services (*e.g.* hospitals), and is prepared annually and submitted to the national government for regulatory purposes.

The analyzed data include individual records of all services provided to each affiliate: medical consultation, pharmacy, laboratory, medical props (*e.g.* walking aids), and surgical procedures. These records are encoded through a complete, expandable and standardized system called CUPS (Universal Code of Supply Point). CUPS are defined by a decision-making group composed by medical scientific societies of the country and are used universally by all HMOs. Since each patient may use the HMO more than once per year or receive more than one service per visit, claims were grouped using a randomly assigned ID number to obtain the total patients per year and period.

Parkinson disease case definition

To define probable PD cases, we built an algorithm taking into account the clinical diagnoses (ICD-10: G20X, F02.3) and the pharmacological prescriptions (ATC: N04BA01, N04BA02, N04BA03) of each subject. Selection of diagnostic codes was made by a neurologist trained in movement disorders taking into account previous works on administrative data in PD.[14] According to the ICD-10 manual, G20X code is applicable to hemi-parkinsonism, idiopathic parkinsonism, primary parkinsonism, and paralysis agitans. These terms are defined as "progressive, degenerative diseases of the central nervous system characterized by tremor, rigidity, postural instability, bradykinesia, and gait disturbances", which is consistent with the commonly accepted criteria for diagnosing PD.[15] Based on previous studies, we chose levodopa (LD) as an inclusion criterion. This medication, also known as L-3,4-dihydroxyphenylalanine, represents the standard of treatment for most PD cases, regardless of clinical stage, because of its efficacy.

From all "probable PD cases", patients aged ≤30 years were excluded due to the very-low relative frequency of the disease in young adults.[16-18] To improve the accuracy of the defined criteria, probable cases were classified in two arms. In the first group, patients were considered if the diagnostic code was registered in their record with the prescription of drugs according to the ATC codes previously mentioned; for guaranteeing an adequate true negative rate, patients that were not prescribed levodopa, must have one or more specific diagnosis (G20X, F02.3) that were continuously registered over time (at least twice over the year). Subjects were only included if they were not repeatedly prescribed medications associated with pharmacological parkinsonism (DIPP: antipsychotics, dopamine depleters, antiemetics, calcium-channel blocker).[19] Figure 1A clarifies the percentage of subjects excluded. In the second group, the inclusion criteria were fulfilled in patients who were prescribed LD at least twice,[10] for an unspecified diagnosis, and not for other conditions such as dystonia or restless legs syndrome. Finally, patients taking this antiparkinsonian drug for "off label" diagnoses were also excluded (Figure 1B). This algorithm has been previously published by our Group elsewhere.[19]

Parkinson's disease stage assessment

To determine disease stage (advanced PD vs. non-advanced PD), we adapted items from clinical and functional scales and translated them into ICD-10 conditions and ATC drug codes as follows: dementia (ICD-10: F00, F01, F02, F03, F05; ATC: N06DA02, N06DA03, N06DA04, N06DX01), tracheostomy (ICD-10: Z930, Z430; CUPS 311300, 311301, 965500), gastrostomy (ICD-10: Z931; CUPS: 431100, 431200, 100031, 431001-03), jejunostomy (CUPS: 437100, 460102, 463200), falls and fractures (ICD-10: W0, S52, S62, S72, T10, T12) and deep brain stimulation (CUPS: 028301, 028302). Due to inherent limitations of the used dataset, disease duration and motor complications were not taken into

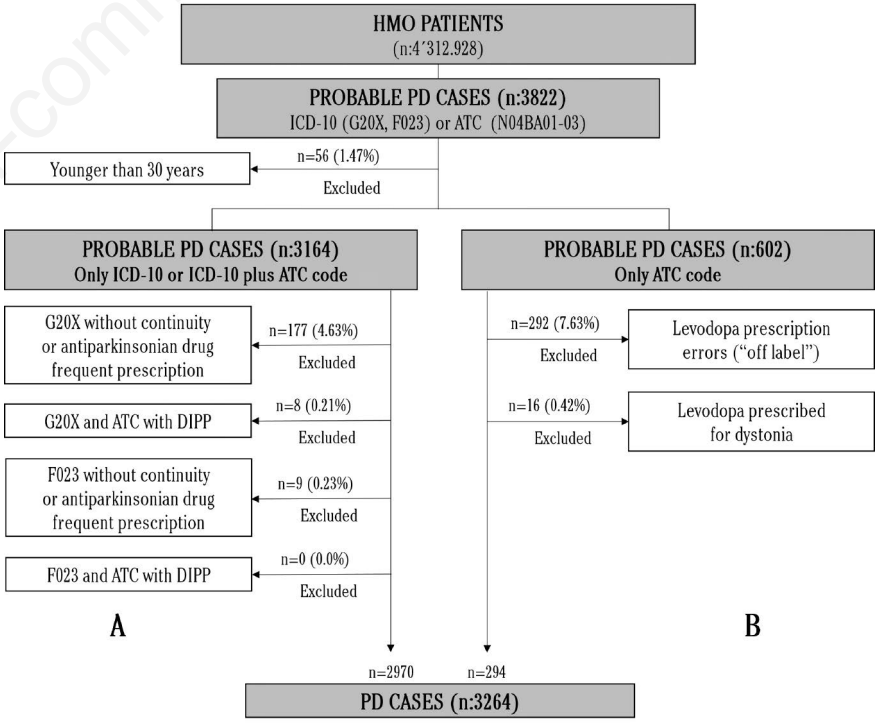


Figure 1. PD cases selection algorithm.

account in the staging classification.

Statistical analysis

Age and comorbidity count (as previously defined by Macleod and colleagues)[20] were assessed with median and interquartile range based on non-normal distribution determined by Shapiro Wilk's test. Subsequently, age was classified by deciles. Categorical characteristics are expressed with relative frequencies and total counts. Bivariate analysis according to sex and disease stage was therefore based on Mann Whitney's U and Chi X^2 or Fisher's exact test according to the distribution in the contingency table.

Prevalence estimates for PD were calculated by age group and sex, then prevalence was adjusted by sex and age according to Colombian demographics and the World Health Organization (WHO) standardized population. Estimates are presented with 95% confidence intervals (CIs). To estimate the agreement between the patients selected by our algorithm and the assessment and follow-up by specialists in movement disorders, we compared a subsample of the database provided by our algorithm with the registry of patients from an outpatient neurology service that uses electronic clinical records and standardized coding processes. This registry comprised patients with PD diagnosis that was confirmed by multiple clinical evaluations. The statistical analysis was performed using STATA® 13.0 software (StataCorp, Texas USA).

Results

From 4,312,928 HMO affiliates, 3822 met at least one of the inclusion criteria for 'probable PD'. A total of 558 patients (14.59%) were excluded. Of these, 56 patients (1.47%) were under 30 years, 292 (7.64%) had levodopa prescription errors ("off-label"), 177 (4.63%) had no G20X diagnostic code continuity or frequent antiparkinsonian drug prescriptions, 16 (0.42%) had levodopa prescribed for dystonia, and 8 (0.21%) had a G20X diagnostic code and frequent levodopa use but frequent DIPP prescriptions (Figure 1).

PD patient characteristics

After applying the exclusion criteria, 3264 PD patients (85.40%) were included. 1750 (53.62%) were men, the median age was 73 (IQR 64–80) years. 2825 (86.55%) took at least one antiparkinsonian drug (Table 1). Regarding comorbidities, 2142 (65.62%) had arterial hypertension, 717 (21.97%) psychiatric disorders and 552 (16.91%) diabetes. 512 patients (15.69%) were classified as advanced PD, the most common reason for being classified as such was dementia (313, 9.59%) followed by fractures (120, 3.68%) and gastrostomy or jejunostomy requirement (68, 2.08%) (Table 2).

Age differences in PD

Regarding the age group distribution, between 30 and 79 years PD was more frequent in men. Levodopa prescription increased from 57.14% in the group between 30-39 years to 82.03% in the group between 70-79 years, then decreased to 81.03% in those older than 89 years. Other antiparkinsonian drug prescriptions were more common in those between 50 and 69 years. Frequency of comorbidities such as arterial hypertension, diabetes and COPD increased with age. Advanced PD was more frequent as age increased from 3.77% in the group between 40 to 49 years to 25.86% in those older than 89 years (Supplementary Table S1).

Sex differences in PD

Median age was significantly higher in women (p<0.001), PD total number of cases was higher in men from 30 to 69 years. Levodopa and other antiparkinsonian drug prescriptions were significantly higher in men (p=0.001). In contrast, comorbidities such as hypertension, diabetes, dyslipidemia and psychiatric disorders were more common in females. Advanced PD (p<0.001), and fractures (p<0.001) were more frequent in women as well. Age distribution, drug prescriptions, and comorbidities are exhibited in Tables 1 and 2.

Advanced and Non-Advanced PD

Among the advanced PD patients, there was a higher proportion of women (54.69% *vs.* 44.84%; p<0.001). Levodopa prescription was slightly higher in the advanced group (81.84% *vs.* 80.20%; p=0.390), and other antiparkinsonian drug prescriptions were more common in non-advanced patients (47.13% *vs.* 41.12%; p=0.014). Except for dyslipidemia, all comorbidities were more frequent in the advanced disease group. Comorbidity count tended to be statistically higher as well (Supplementary Table S2).

Prevalence estimates

In our sample, PD crude prevalence was 157.92 (95% CI 152.25-163.43) per 100.000

Table 1. PD patient characteristics.

Sample characteristics	PD patients (n:3264)	Male (n:1750)	Female (n:1514)	p
Median age in years (IQR) N (%)	73 (64–80)	72 (63-79)	74 (66-81)	<0.001
30–39	21 (0.64)	14 (0.80)	7 (0.46)	-
40–49	106 (3.25%	69 (3.94)	37 (2.44)	-
50–59	384 (11.76)	231 (13.20)	153 (10.11)	-
60–69	780 (23.90)	445 (25.43)	335 (22.13)	-
70–79	1113 (34.10)	592 (33.83)	521 (34.41)	-
80–89	744 (22.79)	355 (20.29)	389 (25.69)	-
90 years or older	116 (3.55)	44 (2.51)	72 (4.76)	-
Antiparkinsonian drug prescriptions (%)				
At least one antiparkinsonian drug	2825 (86.55)	1534 (87.66)	1291 (85.27)	0.046
Levodopa	2626 (80.45)	1447 (82.69)	1179 (77.87)	0.001

Table 2. PD patient comorbidities and staging.

Sample characteristics	PD patients (n:3264)	Male (n:1750)	Female (n:1514)	p
Comorbidities (%)				
Median comorbidity count (IQR)	1 (1-2)	1 (1-2)	1 (0-2)	<0.001
Arterial hypertension	2142 (65.62)	1099 (62.80)	1043 (68.89)	<0.001
Diabetes	552 (16.91)	293 (16.74)	259 (17.11)	0.782
Dyslipidemia	314 (9.62)	154 (8.80)	160 (10.57)	0.088
COPD	342 (10.48)	172 (9.83)	170 (11.23)	0.193
Minimal cognitive impairment	50 (1.53)	30 (1.71)	20 (1.32)	0.362
Psychiatric disorders	717 (21.97)	333 (19.03)	384 (25.36)	<0.001
Sleep disorders	79 (2.42)	37 (2.11)	42 (2.77)	0.221
Stage (%)				
Advanced PD	512 (15.69)	232 (13.26)	280 (18.49)	<0.001
Dementia	313 (9.59)	144 (8.23)	169 (11.16)	0.005
Tracheostomy	12 (0.37)	8 (0.46)	4 (0.26)	0.364
Gastrostomy/jejunostomy	68 (2.08)	29 (1.66)	39 (2.58)	0.067
Fractures	120 (3.68)	45 (2.57)	75 (4.95)	<0.001
Deep brain stimulator	52 (1.59)	29 (1.66)	23 (1.52)	0.754

inhabitants. After age-adjustment according to Colombian demographics and WHO standardized population, estimated prevalence increased to 207.12 and 212.23, respectively. Sex-adjustment did not exhibit significant changes, with a variation of less than 1 case per 100.000 inhabitants.

Prevalence by age group

In subjects between 30 and 89 years old, our data revealed a rising prevalence of PD with age: 2.9 (95% CI 1.80-4.45) in those aged 30-39, 19.5 (95% CI 15.99-23.63) in those aged 40-49, 91.6 (95% CI 82.71-101.29) in those aged 50-59, 336.8 (95% CI 313.57-361.28) in those aged 60-69, 1081.9 (95% CI 1019.27-1147.38) in those aged 70-79 and 1786.7 (95% CI 1660.05-1919.19) per 100.000 inhabitants in those aged 80-89. PD prevalence decreased in the group older than 89 years to 1579.7 (95% CI 1305.37-1894.74) (Table 3). A prevalence increment of 62.13% was found between those aged ≥40 years and those aged ≥50 years. Similarly, each extra decade (50-80+) represented an increment of 83.65%, 80.95%, and 35.10%. A prevalence decrease of 9.99% was found comparing those 80 years or older and those 90 years or older (Supplementary Table S3).

Prevalence by sex

The effect of sex on PD prevalence was also analyzed and stratified by age group. In our sample, PD crude prevalence was 175.00 (95% CI 166.69-183.40) in males and 141.91 (95% CI 134.85-149.24) in females. After the age adjustment according to Colombian and WHO standardized populations, estimated prevalence increased to 236.67 and 235.37 in males, and 181.78 and 192.03 in females, respectively. According to our deciles age-distribution in the groups between 40 and 89 years, males exhibited a significantly higher PD prevalence compared to females. A slight, non-significant male preponderance was also found in the 30−39 and over 89 years groups (Table 3).

Algorithm testing

The registry of our outpatient neurology service contained information on 81 PD patients insured by the HMO that provided the administrative data for this study. To evaluate the algorithm, we compared PD cases in the hospital registry with the final database filtered by our algorithm. 75 (92.60%) patients were found in both databases. The medical records of the six patients who did not match were reviewed. Of these, five had other types of parkinsonism and one was confirmed with diagnosis of progressive supranuclear palsy (PSP).

Discussion

Information on the magnitude of a health event in a population is indispensable for planning healthcare services, formulating public policies and identifying new areas of research aimed at generating useful knowledge for the decision-making process. Epidemiological information about neurodegenerative diseases is especially valuable for populations in demographic transition. However, obtaining accurate estimates involves methodological challenges that affect validity and precision. Based on administrative data, this study calculated the prevalence of PD by age and sex. As an additional contribution, disease staging was estimated using a data categorization strategy proposed by the authors.

According to Global Burden of Disease data, provided by the Institute for Health Metrics and Evaluation. in 2015 the country with the highest age-adjusted PD prevalence was China (136.34, 95% CI 111.56-165.55), and that with the lowest was Tanzania (72.19, 95% CI 59.86-87.82). In this classification, Colombia occupied an intermediate-low position with 98.51 (95% CI 80.92-120.77) PD cases per 100.000 inhabitants. In our sample, crude PD prevalence was higher (157.92; 95% CI 152.25-163.43) and even increased to 212.23 after adjustment to world WHO demographics. This is expected based on the different relative frequencies of each age group in our sample compared to those from Colombia and the World; in fact, our sample included a smaller proportion of adults older than 50 years (Figure 2A).

PD prevalence in Colombia

Comparing our prevalence with other countries in South America, Colombia has a higher PD rate than the estimated in 2015 by GBD for Latin America and the Caribbean (94.93, 95% CI 77.73-115.29) and other countries from the region like Venezuela (98.08, 95% CI 80.00-118.52), Mexico (100.8, 95% CI 81.89-122.91), Brazil (101.04, 95% CI 82.17-123.22), Peru (101.36, 95% CI 82.23-122.80) and Argentina (116.03, 95% CI 93.79-142.96). Nonetheless it is important to clarify that GBD estimates are calculated using meta-regression analyses which could lead to an underestimation of the event frequency.

In our sample, PD prevalence among individuals over 40 years old was 241.1 (95% CI 232.88-249.55), lower than the reported in Argentina by Bauso and colleagues in 2012 (394 per 100.000).[9] It could be argued that our prevalence might be higher than the one calculated by Bauso because of a chronological (2012 vs. 2015) rather than a geographical difference, but this is not supported by the GBD data which reported a prevalence rate change of only 0.57% in the aforementioned period. In this case, for instance, there is also a prevalence overestimation of more than three times when compared with GBD results from that country and year (115.36, 95% CI 93.05-141.84). Besides, this Argentinian study used different diagnostic and prescription codes as inclusion criteria for their case definition, which suggests greater sensitivity but not specificity. However, their study did not filter by frequency of prescription, which may have increased the proportion of false positives. Our study considered the consistent repetition of diagnostic codes, the relationships with associated diagnoses and the formulation of levodopa, criteria that probably increase the specificity of the algorithm. Unfortunately, due to access limitation to information on other antiparkinsonian drugs, it was not possible to include them for our case definition.

Regarding previous rates adjusted to Colombian population, our PD prevalence was 207.12 per 100.000, lower to that reported 20 years ago by EPINEURO (470, 95% CI 220−890). This study used the WHO neuroepidemiology protocol and estimated standardized prevalence with a small number of cases (9 PD patients), which may overestimate the frequency of the disease.[12] Interestingly, the increase of prevalence

Table 3. PD prevalence sex and age distribution.

Age (2015)	Prevalence estimates per 100.000		
	Global	Male	Female
30-39	2.9 (95% CI 1.8-4.45)	3.9 (95% CI 2.14-6.56)	1.9 (95% CI 0.73-3.96)
40-49	19.5 (95% CI 15.99-23.63)	25.7 (95% CI 19.98-32.51)	13.5 (95% CI 9.51-18.62)
50-59	91.6 (95% CI 82.71-101.29)	115.0 (95% CI 100.66-130.85)	70.1 (95% CI 59.46-82.16)
60-69	336.8 (95% CI 313.57-361.28)	408.8 (95% CI 371.70-448.61)	272.9 (95% CI 244.48-303.78)
70-79	1081.9 (95% CI 1019.27-1147.38)	1303.9 (95% CI 1200.95-1413.27)	906.5 (95% CI 830.36-987.84)
80-89	1786.1 (95% CI 1660.05-1919.19)	2236.9 (95% CI 2010.26-2482.16)	1508.6 (95% CI 1362.42-1666.26)
90+	1579.7 (95% CI 1305.37-1894.74)	1747.4 (95% CI 1269.68-2345.83)	1492.2 (95% CI 1167.58-1879.21)
All ages	157.92 (95% CI 152.25-163.43)	175.00 (95% CI 166.69-183.40)	141.91 (95% CI 134.85-149.24)

between 1995 and 2015 according to GBD is 47.2% while comparing EPINEURO with our study would be -144.04%. About their sampling methodology, participation of inhabitants over 50 years old was favored, and PD was only found in those older than 60. On the other hand, our study excluded those patients who did not seek medical care, probably decreasing the estimated proportion. According to our findings, age-adjusted PD prevalence is higher in men than women (235.37 vs. 192.03 per 100.000) this is consistent with previous studies in Asia and Europe,[20-23] but contrary to EPINEURO. In our sample, prevalence tends to increase with every 10 years of age, as could be expected and have been proved by previous literature. Nevertheless, there was a small reduction of prevalence (~10%) when comparing those inhabitants 80-89 years old with those aged 90+ (Figure 2B). This could be related to the increase in deaths, especially in men where the frequency of PD is higher.

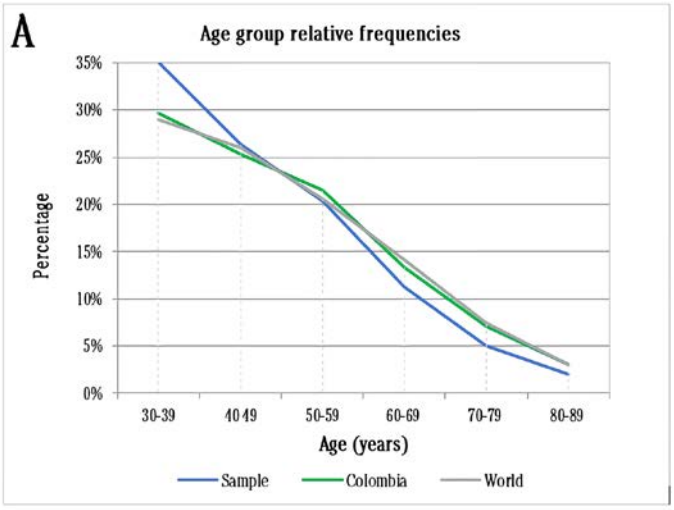
PD staging in Colombia

Taking into account disease stage, patients with advanced PD were older than their mild counterparts ($p<0.001$). Furthermore, all considered comorbidities except dyslipidemia ($p=0.020$) were more frequent in the advanced PD group. Although we cannot determine disease duration in our sample, our results confirm that PD severity increases with age (Figure 3); this is probably due to the longer history of the disease. The use of levodopa was slightly higher in the advanced PD group, but this difference was not significant ($p=0.390$). The use of other antiparkinsonian agents was higher in the non-advanced group ($p=0.014$), which could be explained by the recommendation to delay, at least in some cases, the use of levodopa in early stages in favor of other antiparkinsonian drugs. However, due to its effectiveness, levodopa is the most widely used medicine in all stages of the disease, and tends to be used as monotherapy in advanced stages because it has fewer adverse effects.[24]

As expected, dementia and fractures frequency increased with age,[25,26] these two conditions were more prevalent in females which is coherent with previous studies,[27] and related to the greater frequency of advanced PD in this sex group. Chronic conditions such as arterial hypertension, diabetes, and COPD also increased with age. Psychiatric disorders maintained their frequency across all age groups.

Limitations

As we discussed previously,[19] this kind of research has multiple limitations that are



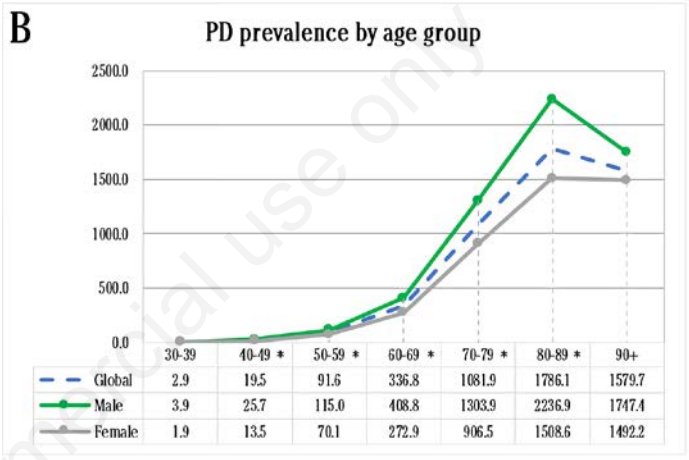


Figure 2. A) Distribution of Colombian and WHO age groups; B) PD prevalence according to age group distribution).

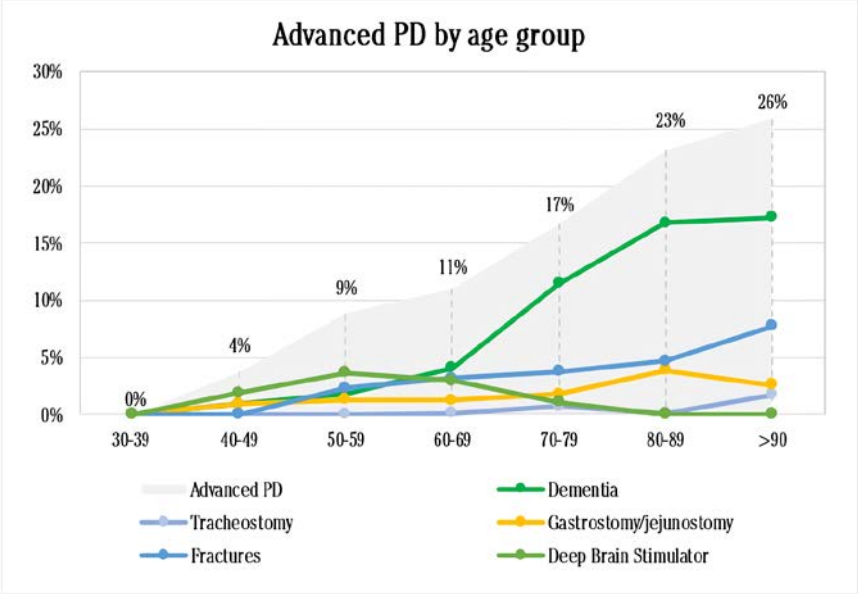


Figure 3. Distribution of PD advance stage according to age group distribution.

mainly based on its design. Unfortunately, we could not control for diagnostic errors when assigning ICD-10 codes and there is uncertainty about the training level of healthcare providers who registered PD diagnosis for our sample (*i.e.* neurologists or general practitioners). Likewise, calculating the exact PD frequency is difficult as the diagnosis is built under the fulfillment of clinical criteria, and no paraclinical test (including neuroimaging) can be used for confirmation.[28] From a pharmacovigilance perspective, we were not able to include other antiparkinsonian drugs as part of the inclusion criteria due to the restricted variables collected by HMOs. Levodopa prescription in the context of experimental research was not considered. Hence, we tried to reduce false positives by proposing a strict algorithm with multiple steps for inclusion (age, frequency of diagnosis allocation and prescription of LD, DIPP). Our study presents a basic test of the internal performance of our algorithm compared to a clinical source generated based on the PD diagnosis gold standard (movement disorders neurologist) but external validation is pending as results might not be applicable to other populations and healthcare policies.[19]

Conclusions

Administrative data sets are useful to estimate the prevalence and staging of PD, applying filters by frequency of diagnosis and drug prescription can be useful to reduce the sources of error in this type of studies. The prevalence of PD in Colombia is higher in men and increases with age, as well as disease severity. More common related comorbidities were arterial hypertension, diabetes, and psychiatric disorders; the first two increased their frequency with age, and the last one maintained its prevalence across all age groups.

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