

## ORIGINAL ARTICLE

# Mortality rates for Parkinson's disease are increasing in Spain. An age-period-cohort and joinpoint analysis of mortality rates from 1981 to 2020



C. García-Muñoz<sup>a,c</sup>, J.C. Hernández-Rodríguez<sup>b,\*</sup>, J.J. Pereyra-Rodríguez<sup>b</sup>

<sup>a</sup> Universidad Loyola de Andalucía, Sevilla, Spain.

<sup>b</sup> Departamento de Medicina, Facultad de Medicina, Universidad de Sevilla, Sevilla, Spain

<sup>c</sup> Uncertainty, Mindfulness, Self, Spirituality (UMSS) Research Group, Sevilla, Spain.

## KEYWORDS

Mortality rate;  
Parkinson's disease;  
Joinpoint;  
Age-Period-Cohort;  
Potential years of life  
lost

## Abstract

**Background:** Mortality in Parkinson's disease is increasing worldwide, but Spanish data need further study.

**Objective:** To analyse the mortality trends of Parkinson's disease in Spain between 1981 and 2020.

**Methods:** This observational retrospective study assessed the Parkinson's disease mortality data from 1981 to 2020 collected from the National Statistics Institute of Spain. Age-standardised mortality rates were analysed by age and sex groups, detecting significant mortality trends through a joinpoint analysis. Age-period-cohort effect and potential years of life lost analyses were conducted. The European standard population of 2013 was considered for the analyses.

**Results:** A total of 88 034 deaths were assessed. The overall age-standardised mortality rate rose throughout the period from 3.67 to 8.57 per 100 000 inhabitants. Mortality rates in men were higher than in women, 11.63 versus 6.57 deaths per 100 000 inhabitants. The sex ratio showed an increase in premature mortality in men during 2020. The overall joinpoint analysis recorded a rise in mortality, primarily since the 20th century, mainly in male and older groups, that matched with a period effect. The age effect was detected, confirming higher mortality at an older age. The analysis of potential years of life lost detected a growth in this rate, changing from 0.66 in 1981 to 1.06 in 2020.

DOI of refers to article: <https://doi.org/10.1016/j.nrleng.2023.06.003>.

**Abbreviations:** AAPC, average annual percent change; AIC, Akaike information criterion; APC, age-period-cohort; ASMR, age-standardised mortality rate; COVID-19, coronavirus disease 2019 pandemic; ICD, International Classification of Diseases; PD, Parkinson's disease; PYLL, potential years of life lost analysis; SD, standard deviation.

\* Corresponding author.

E-mail address: [jhernandez7@us.es](mailto:jhernandez7@us.es) (J.C. Hernández-Rodríguez).

<https://doi.org/10.1016/j.nrl.2023.05.002>

0213-4853/© 2023 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la CC BY-NC-ND licencia (<http://creativecommons.org/licencias/by-nc-nd/4.0/>).

**PALABRAS CLAVE**

Tasas de mortalidad;  
Enfermedad de  
Parkinson;  
Joinpoint;  
Edad-Periodo-  
Cohorte;  
Años potenciales de  
vida perdido

**Conclusions:** Mortality data for Parkinson's disease in Spain rose significantly in forty years. Mortality rate was higher in the male and age group above 75 years of age. The sex ratio showed premature mortality in men in 2020, which will need further study.

© 2023 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Las tasas de mortalidad para la Enfermedad de Parkinson están incrementando en España. Un análisis Edad-Periodo-Cohorte y Joinpoints en las tasas de mortalidad desde 1981 a 2020

**Resumen**

**Introducción:** La mortalidad de la Enfermedad de Parkinson está incrementando a nivel mundial, pero los datos españoles necesitan ser estudiados en profundidad.

**Objetivo:** Analizar las tendencias de mortalidad de la Enfermedad de Parkinson en España entre 1981 y 2020.

**Métodos:** Este estudio observacional retrospectivo analizó los datos de mortalidad de la Enfermedad de Parkinson extraídos desde 1981 a 2020 del Instituto Nacional de Estadística de España. Las tasas de mortalidad estandarizada por edad fueron analizadas por grupos de edad y sexo, detectando cambios de tendencia de mortalidad significativos mediante un análisis de joinpoint. Se llevaron a cabo análisis de Edad-Periodo-Cohorte y años potenciales de vida perdidos. La población estándar europea fue considerada para el análisis.

**Resultados:** Un total de 88.034 defunciones fueron examinadas. La tasa global de mortalidad estandarizada por edad creció a lo largo del periodo estudiado desde 3,67 a 8,47 por cada 100.000 habitantes. Las tasas de mortalidad fueron mayores en hombre que en mujeres, 11,63 frente a 6,57 fallecimientos por cada 100.000 habitantes. La proporción de sexo mostró un incremento en la mortalidad prematura en hombre durante 2020. El análisis de joinpoint global reportó un aumento de mortalidad, principalmente desde el siglo XX, siendo más notable en hombre y grupos de edad avanzada, que coincidió con un efecto periodo. Se detectó un efecto de edad confirmando una mayor mortalidad a edad más avanzada. El análisis de años potenciales de vida perdidos detectó un crecimiento en esta tasa, cambiando de un 0,66 en 1981 a 1,06 en 2020.

**Conclusiones:** Los datos de mortalidad para la Enfermedad de Parkinson en España ha incrementado significativamente durante cuarenta años. La tasa de mortalidad fue mayor en hombre y en grupos de edad mayores de 75 años de edad. La proporción de sexo mostró una mortalidad prematura en hombres en 2020, que necesitará ser estudiado en mayor profundidad.

© 2023 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la CC BY-NC-ND licencia (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Introduction**

Parkinson's disease (PD) is the second most common neurological disease worldwide and is expected to double its prevalence in the next 3 decades.<sup>1</sup> PD is a neurodegenerative disease characterised by cell loss of the substantia nigra and other central areas, but the primary aetiology is still unknown.<sup>2</sup> The first PD denomination was made in 1817 by James Parkinson,<sup>3</sup> so the first registries of mortality started after this date. Diagnostic criteria for PD have changed over the years, until the MDS criteria were established in 2015 by the Movement Disorders Society.<sup>4</sup> The main diagnostic criteria for PD, based on motor symptoms, are bradykinesia plus resting tremor or rigidity.<sup>4</sup>

A recent study analysed PD mortality trends worldwide using the World Health Organization mortality database, assessing data from a 25-year period, specifically from 1994 to 2019.<sup>5</sup> The worldwide standardised mortality rate was 5.67 per 100 000 inhabitants in 2019, while the Spanish rate

reached 3.9 per 100 000 inhabitants.<sup>5,6</sup> In recent decades, without explained reasons, a striking rise in mortality rates worldwide has been recorded, as well as an exponential increase in incidence and prevalence.<sup>1,5</sup>

The study of PD mortality trends is important for patient information, disease management, and design of future clinical trials.<sup>7</sup> Regarding the epidemiological context of mortality, it is essential to examine the effects of age, period, and cohort effects (APC) to assess how temporal trends of mortality of PD could be affected.<sup>8</sup> Although the study by Lampropoulos et al.<sup>5</sup> analysed the worldwide mortality rate, no previous literature on mortality trends has focused on the Spanish population with PD. Also, to the best of our knowledge no previous studies on PD had analysed the effects on mortality of age, period, and birth cohorts. Therefore, this study aims to assess the standardised mortality trends and age-period-cohort effects adjusted by age and sex for PD mortality in Spain over a 40-year period.

## Materials and methods

### Data source and data extraction

In this observational retrospective study, we assessed data on mortality caused by PD in the Spanish population from the period between 1981 and 2020. We selected this specific period due to the reliability of the data available in the institutional database. We consulted and collected all mortality data from the Spanish National Statistics Institute (<http://www.ine.es>). To ensure the veracity and reliability of the data, we based our analysis on death certificates coded with the International Classification of the Diseases (ICD). We only included cases in which the cause of mortality was PD. In ICD-8 and ICD-9 PD was classified as paralysis agitans under codes 342.0 and 332.0, respectively. After that, the PD denomination was recognised in the ICD-10 with the code G20. The code G21 was not considered because it was related to secondary parkinsonism. In our analysis, we also excluded the diagnosis of dementia with parkinsonism (ICD-10 G31.83), to focus only on primary PD.

Although this study did not report global mortality data, to carry out good practice, we followed the Guidelines for Accurate and Transparent Health Estimates Reporting standards statements (GATHER).<sup>9</sup> The STROBE guideline for observational studies were also considered. No institutional or ethical approval was required for this study.

### Statistical analysis

#### Standardised mortality rates

To manage and analyse mortality data, we used EPI-DAT (v.4.2; <https://www.sergas.es/Saude-publica/EPIDAT>), Microsoft Excel (Microsoft Corp.; Redmond, WA, USA), and SPSS Statistics (v.25; IBM SPSS; Armonk, NY, USA) statistical software. This study calculated the age-specific mortality rate in 5-year age groups, as well as the annual age-standardised mortality rate (ASMR) stratified by sex and age (35–54, 55–74 and  $\geq 75$  years old). We estimated the sex ratio for all ages as the proportion of male relative to female mortality. In this study, the rates were displayed as 100 000 inhabitants. All analyses were carried out using the direct method and adjusted for the European Standard Population of 2013.<sup>10</sup>

We identified significant trend changes in mortality stratified by sex and age using a joinpoint analysis. To conduct this analysis, the Joinpoint Regression program, developed by the Surveillance Research Program of the US National Cancer Institute, was used (V4.8.0.1; <https://surveillance.cancer.gov/joinpoint>). The statistical significance for a mortality trend was established as  $P < .05$ . The maximum number of joinpoints allowed in the analysis was 5, while the number of periods was one more than the number of registered joinpoints. The joinpoint was equal to zero when no joinpoint was registered. Additionally, the annual average percent change (AAPC) was computed by sex and age group using the mentioned method.

#### Age-period-cohort model

To examine the effect of age, period, and birth cohort on mortality rate fluctuation, an APC analysis was conducted. The age effect refers to the change in mortality

caused by the ageing process detected by varying rates over age groups. Period effects refer to an external factor that affects all ages in a concrete calendar period. The birth cohort effect refers to changes derived from factors, experiences, or exposures that involve a group of subjects with a common birth year.<sup>11</sup> The APC model was performed using the penalty function proposed by Decarli and La Vecchia.<sup>12</sup> To run the analysis and generate the graphic representation of the results, we used the R studio software (v.4.1.2). The authors<sup>13</sup> kindly provided the generalised linear interactive modelling (GLIM) macros to perform the analyses using the APC package (v.1.3., 3; [https://cloud.r-project.org/web/packages/APCtools/vignettes/main\\_functionality.html](https://cloud.r-project.org/web/packages/APCtools/vignettes/main_functionality.html)). Assuming a Poisson distribution, all joinpoints would represent a significant change in mortality trends. Data were divided into 5-year periods and 5-year age groups to make these estimates. The goodness of fit of the possible APC models was also compared, showing a better fit with a lower Akaike information criterion (AIC) and a narrower deviation.

### Potential years of life lost

In order to assess the burden of PD mortality and quantify premature mortality, we carried out a potential years of life lost (PYLL) analysis. We calculated the crude and standardised PYLL for each study year and the sex group.

## Results

A total of 88 034 deaths due to PD were identified between 1981 and 2020, with a mean age of mortality of 81.70 and a standard deviation (SD) of 7.74. Of the total number, 43 108 deaths were women with a mean age of 82.75 (7.71) and 44 926 men with a mean age of 80.70 (7.64).

### Standardised mortality rate

The total ASMR in PD between 1981 and 1985 was 3.67 per 100 000 inhabitants, rising to 8.57 per 100 000 in the period between 2016 and 2020. For males, the ASMR reached 8.84 per 100 000 between 1981 and 1985, changing to 11.63 per 100 000 inhabitants for 2016 to 2020. Female ASMR increased from 2.94 to 6.57 per 100 000 inhabitants from 1981–1985 to 2016–2020 (Table 1). The ASMR for each year of study can be found in Table A1 of the Supplementary Material.

### Joinpoint analysis

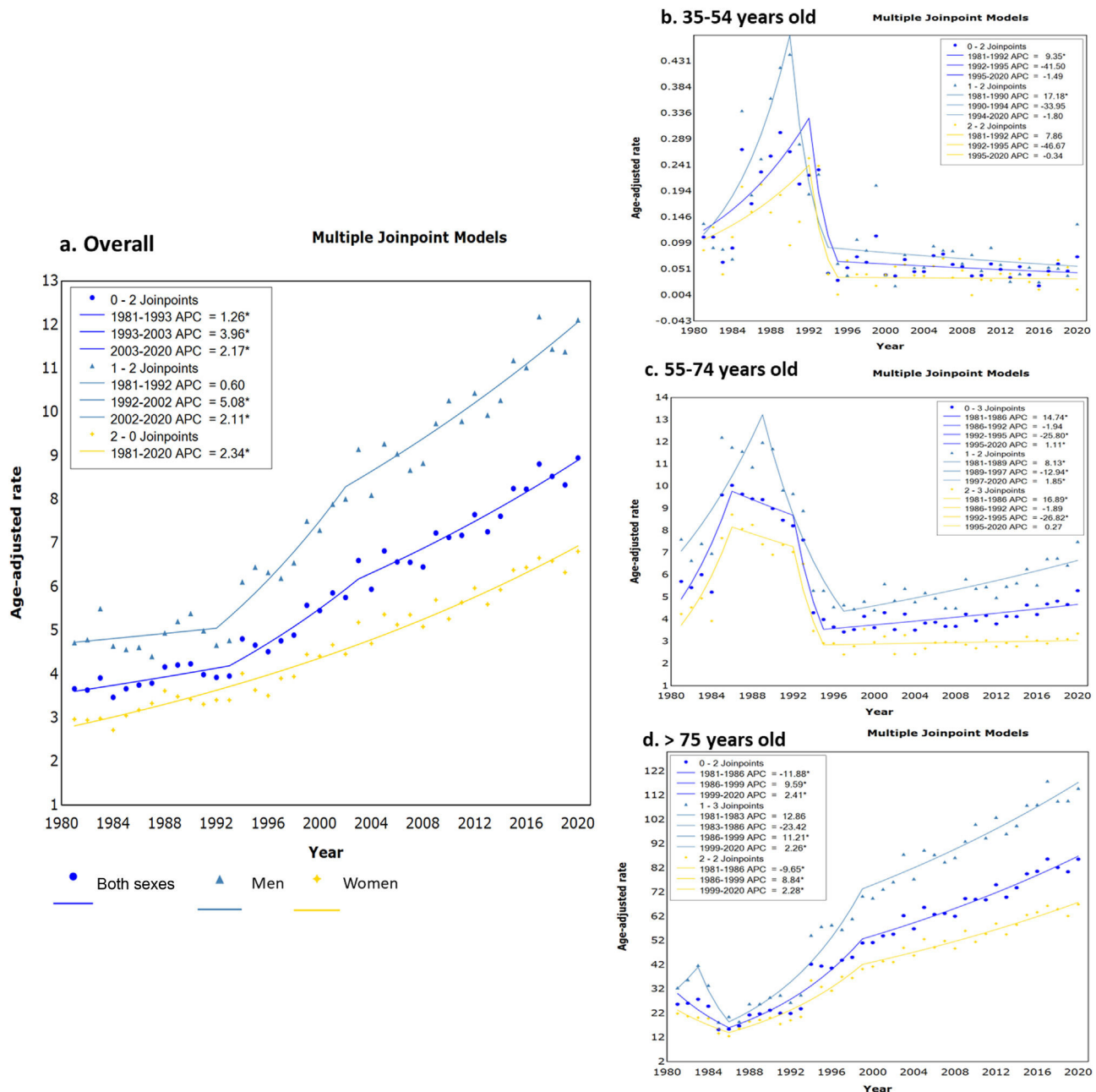
The results of ASMR by age group are shown in Table 1 and mortality trends by age group are presented in Fig. 1. The overall population and the male curve underwent 2 changes in the mortality trend over 3 periods (Fig. 1a). All mortality trends in PD were significant, but it is necessary to highlight the growth of death cases during the last period of 2003 and 2020 with a global AAPC of 2.17%; this was more noticeable in men, as reflected in Fig. 1a. In the case of females, no mortality trend was detected (without joinpoints), but a steady ascent of ASMR was observed. A similar curve compared to the one of the 2 sexes was obtained in people older than 75 years of age (Fig. 1d). The main difference was that in the first period, from 1980 to 1986, the ASMR significantly dropped (AAPC = −11.88%) and later continued to rise until 2020 in the 3 curves. For the age group 35 to 54 and 54 to

**Table 1** Age-standardised mortality rates of Parkinson's disease in Spain per 100 000 inhabitants and trend analysis of annual average percentage change according to age and sex.

	1981–1985	2016–2020	Total 1981–2020	JP	Periods	
	ASMR (95% CI)	ASMR (95% CI)	AAPC (95% CI)		Years	AAPC (95% CI)
Both sexes						
All ages	3.67 (3.40-3.96)	8.57 (8.32-8.83)	2.3 (1.9-2.8)	2	1981-1993 1993-2003 2003-2020	1.26* (0.21-2.44) 3.96* (2.72-5.31) 2.17* (1.77-2.53)
35-54 years old	0.13 (0.05-0.26)	0.05 (0.00-0.13)	−2.5 (−9.4-4.9)	2	1981-1992 1992-1995 1995-2020	9.35* (4.50-14.41) −41.50 (−77.49-52.09) −1.49 (−3.79-0.9)
55-74 years old	6.40 (5.77-7.07)	4.74 (4.32-5.18)	−0.1 (−2.4-2.2)	3	1981-1986 1986-1992 1992-1995 1995-2020	14.74* (8.09-21.75) −1.94 (−6.77-3.18) −25.80* (−43.35 to −2.71) 1.11* (0.52-1.74)
≥ 75 years old	23.98 (21.68-26.57)	82.96 (80.39-85.61)	2.7 (1.3-4.2)	2	1981-1986 1986-1999 1999-2020	−11.88* (−20.33 to −2.60) 9.59* (7.42-11.81) 2.41* (2.01-2.92)
Men						
All ages	4.84 (4.35-5.41)	11.63 (11.16-12.12)	2.4 (1.8-3.1)	2	1981-1992 1992-2002 2002-2020	0.60 (−0.98-2.20) 5.08* (3.33-6.88) 2.11* (1.74-2.53)
35-54 years old	0.14 (0.05-0.33)	0.06 (0.01-0.16)	−1.8 (−7.7-4.5)	2	1981-1990 1990-1994 1994-2020	17.18* (5.89-29.71) −33.95 (−62.13-15) −1.80 (−4.68-1.20)
55-74 years old	8.18 (7.11-9.34)	6.60 (5.88-7.38)	−0.2 (−1.4-1.1)	2	1981-1989 1989-1997 1997-2020	8.13* (4.33-12.19) −12.94* (−16.78 to −8.91) 1.85* (1.10-2.57)
≥ 75 years old	32.44 (27.91-37.96)	112.15 (107.23-117.26)	3.4 (−1.1-8.1)	3	1981-1983 1983-1986 1986-1999 1999-2020	12.86 (−29.68-81.15) −23.42 (−53.69-26.61) 11.21* (8.78-13.73) 2.26* (1.76-2.74)
Women						
All ages	2.94 (2.65-3.27)	6.57 (6.28-6.87)	2.3 (2.2-2.50)	0	1981-2020	2.34* (2.20-2.49)
35-54 years old	0.11 (0.03-0.27)	0.04 (0.0-0.13)	−2.9 (−13.2 5-8.6)	2	1981-1992 1992-1995 1995-2020	7.86 (−1.48-18.10) −46.67 (−87.47-127.05) −0.34 (−3.69-3.18)
55-74 years old	5.06 (4.34-5.86)	3.11 (2.64-3.63)	−0.5 (−3.0-2.0)	3	1981-1986 1986-1992 1992-1995 1995-2020	16.89* (9.22-25.10) −1.89 (−7.10-3.60) −26.82* (−45.91 to −0.88) 0.27 (−0.36-1.00)
≥ 75 years old	19.28 (16.73-22.24)	64.89 (62.03-67.87)	2.8 (1.4-4.2)	2	1981-1986 1986-1999 1999-2020	−9.65* (−17.91 to −0.59) 8.84* (6.77-10.89) 2.28* (1.82-2.68)

95% CI: 95% confidence interval; AAPC average annual percent change; ASMR: age standardised mortality rate; JP: joinpoint.

\**P* < .05.



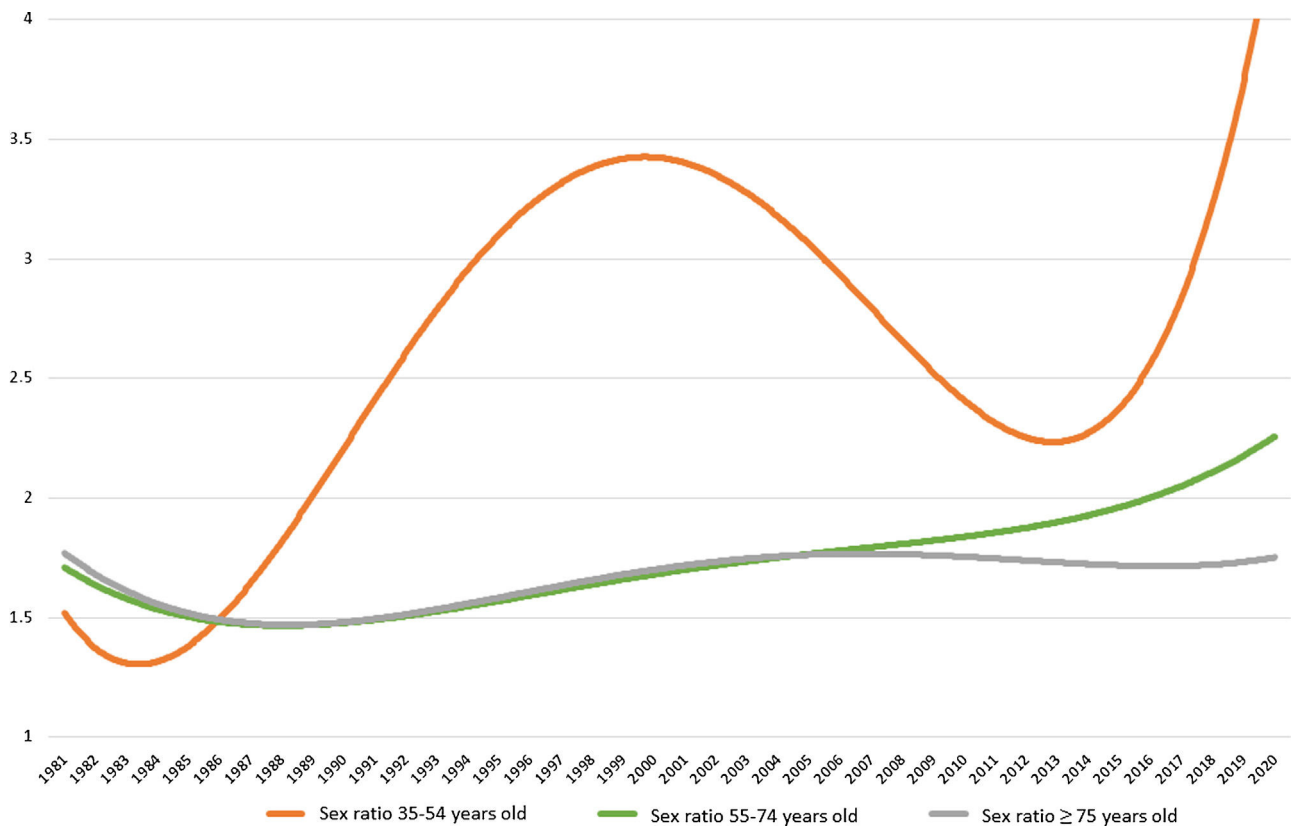
**Figure 1** Joinpoint regression analysis of mortality rates of Parkinson's disease in Spain between 1981 and 2020 for a) all ages, b) 35 to 54 years old, c) 55 to 74 years old, and d)  $\geq 75$  years old. APC: Average percent change; \*Indicates a significant mortality trend change; spot mark: overall data; triangle mark: men data; star mark: women data. The number that appears before the joinpoint results are the number of periods.

74 years in both sexes, a notable mortality trend registered an increase in the AAPC recorded during the periods 1981 to 1992 for the younger group (AAPC = 9.35%), and in 1981 to 1986 in the group between 55 and 74 years (AAPC = 14.74%) (Fig. 1b and c). The latter group displayed a rise in mortality for both sexes in the last periods of the 3 curves. In contrast to all previous age groups between 35 and 54 years old, underwent a steady descent in mortality since the year 1994 in men and 1995 for the overall and women curves (Fig. 1b). However, we observed in 2020 an increase of mortality in men with PD between 35 and 54 years of age, this fact being confirmed by the results of the sex ratio.

### Sex ratio

In the group older than 75 years of age, the sex ratio (male/female) slightly ascend throughout the study period. The sex ratio for group between 55 and 74 years of age ascent more markedly from 2007. The younger group (35-54 years old) doubled the sex ratio from the inception of the study period until 2000 when started decreasing until 2014. From this year, the male/female ratio experienced a drastic increase in 2020, achieving a sex ratio of 9.94, compared to the previous ratio of 0.74 obtained in 2019 (Fig. 2).





**Figure 2** Mortality trend in Parkinson's disease of the sex ratio (men/women) over the years 1981 to 2020 in Spain, sorted by age group. Note: Y-axis refers to sex ratio (men/women); X-axis refers to the studied years.

### Age-period-cohort model

Regarding the age effect, a marked increase in mortality is observed for both sexes after 70 years of age. It is remarkable that the period effect observed in PD since the beginning of the 21st century, when the mortality rate started to rise, has been remarkable until the end of the study. This period effect was more notable in men. Related to birth cohort effect, an increase in mortality was recorded in the cohort born before 1920; from this moment on, a drop was observed. This fall ended with an increase in the relative risk of death of PD, which is more notable in men in birth cohorts since 1960. Fig. 3 illustrates the results of the APC analysis. The data for the goodness of fit of the different APC models are reported in Table A1 in the Supplementary Material. The APC effect was the model that better fit for both sexes, male and female showing the lower AIC and the narrower deviance.

### Potential years of life lost

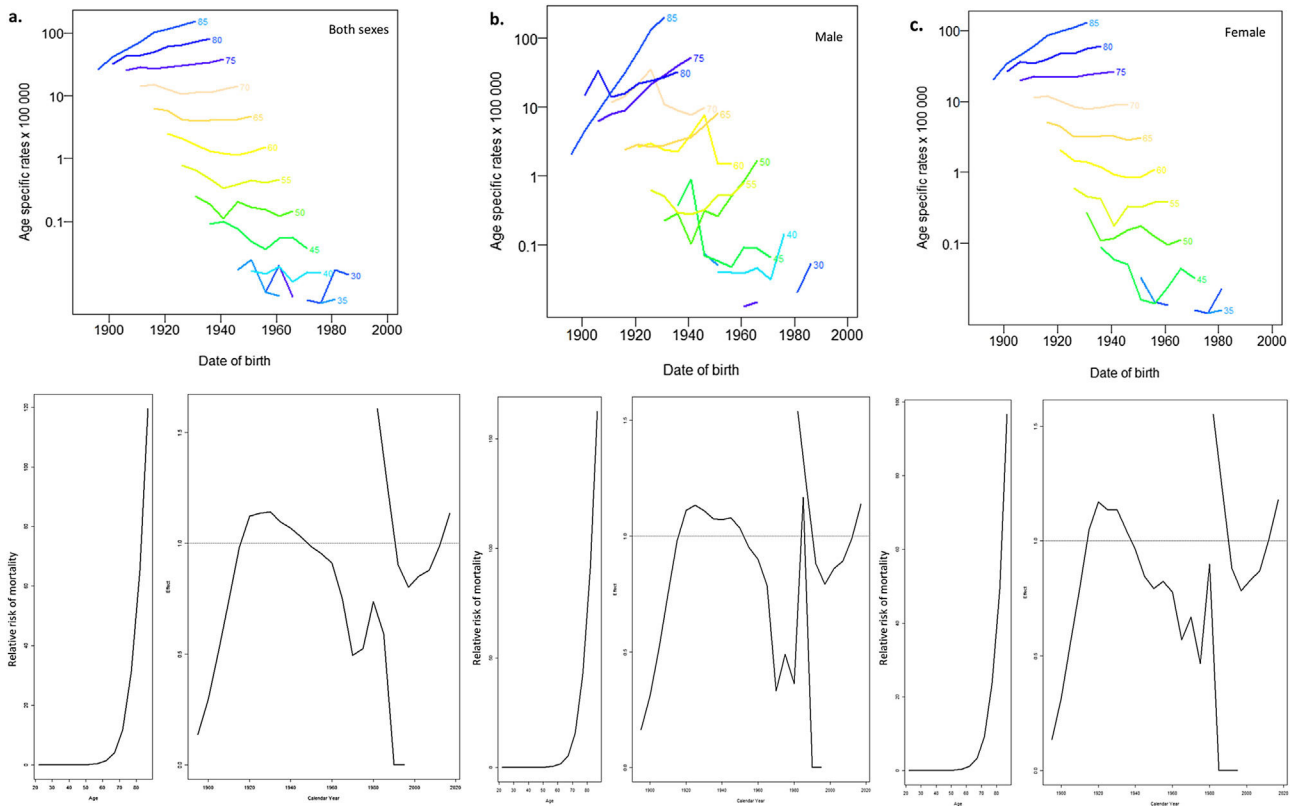
A total of 1 183 932 potential years of life were lost in the 40 years of study. The 3 curves illustrated in Fig. 4 showed a rise in the PYLL rate as the years go by, resulting from data for both sexes, an adjusted rate of 0.66 in 1981 and 1.06 in 2020. Men had the highest PYLL rate during the entire period, changing from an adjusted PYLL rate of 0.86 in 1981 to 1.47 in 2020. All data and rates of PYLL can be found in Table A2 of the Supplementary Material.

### Discussion

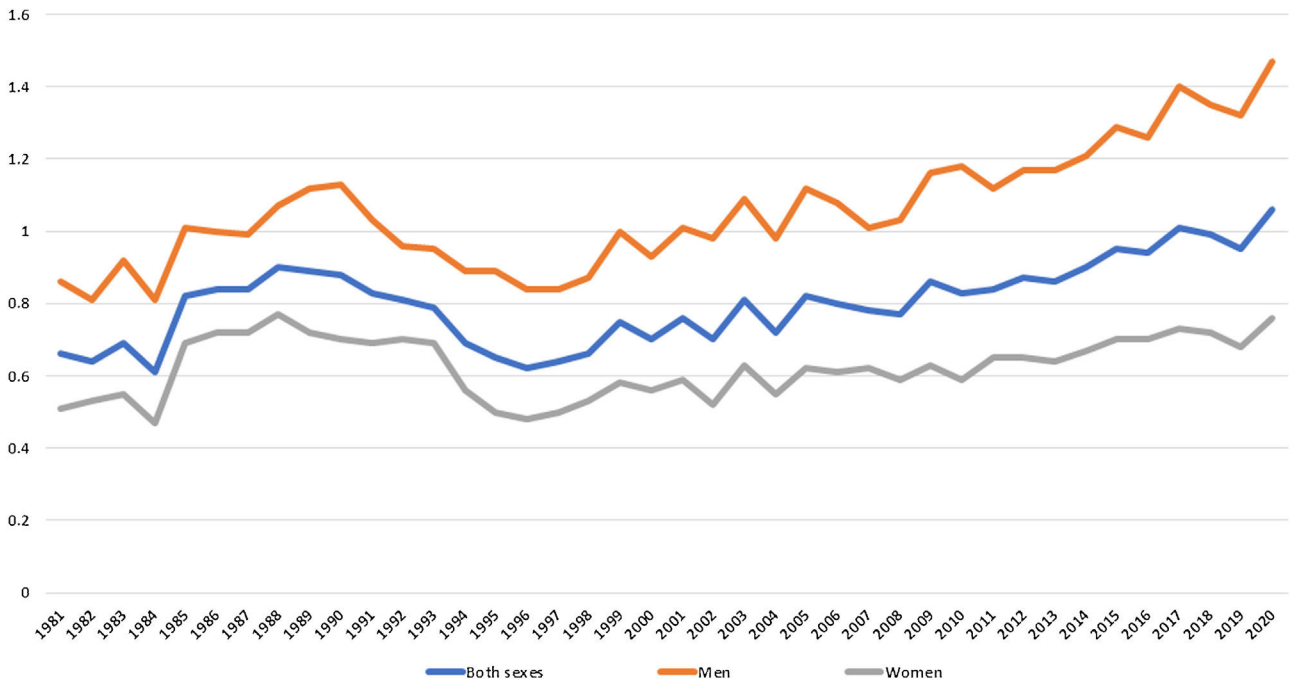
This study presents the widest study period (40 years) assessed in the mortality of PD in Spain. The analysis showed a general trend of increased mortality throughout the period for both sexes and the age group 55 to 74 years and older than 75 years. Only the group between 35 and 54 years of age showed a steady decline in PD mortality since the 1990s, increasing again only in the curve of both sexes and in the male curve in 2020. Mortality rates in men were higher than in women regardless of age group.

Our results are in line with recent literature that reported a considerable increase in PD mortality rates worldwide<sup>5</sup> or in specific territories like the United States of America,<sup>14</sup> the United Kingdom,<sup>15</sup> and Italy.<sup>16</sup>

No specific reasons could be directly attributed to this mortality increase, highlighting the last 2 decades.<sup>5,17</sup> However, the rise in PD mortality in the 21st century could be related to several factors such as the increased incidence and prevalence registered on the disease,<sup>18</sup> even in Spain.<sup>19</sup> This fact could be translated into an exponential increment of mortality rates in both sexes as we recorded in our analysis. Furthermore, environmental factors such as pollution, herbicides, or health behaviours such as smoking appear to be related to a higher incidence and mortality in PD.<sup>20,21</sup> Other factors that could model epidemiology in PD are the increase in life expectancy. An older population is more likely to be diagnosed with PD, as well as a greater possibility of presenting comorbidities.<sup>22</sup> Our analysis showed that death cases were strikingly higher in the group over 75



**Figure 3** Analysis of the age-period-cohort effect of Parkinson's disease in Spain for a) both sexes, b) males and c) females. Note: The upper graphs are related to age effect and show the mortality rates for each 5-year age. Age-specific rates are given per 100 000 inhabitants. The lower graph shows the variation of the relative risk of mortality for the different age (left-pictures in the second row) cohorts (first part of right-picture in the second row) and period effects (second part of right-picture in the second row).



**Figure 4** Rates of potential years lost per 100 000 persons-year of Parkinson's disease in Spain. Note: Y-axis: potential years of life lost rates. X-axis: studied period.

years old than in younger groups, as occurred in previous researches.<sup>5,14,15</sup> Another factor is increased awareness of the disease among healthcare professionals and more accurate registries based on death certificates coded by the ICD.<sup>23</sup> In addition, diagnostic criteria tended to be more precise, leading to an early detection of the disease and diagnosis,<sup>24</sup> so all this may influence PD mortality data.

Our results did not only show differences in mortality rates with respect to age, but also sex variability was found. According to the previous literature on PD, mortality was higher in males than females<sup>25</sup>; only the study focused in Estonian population with PD reported similar rates for both sexes.<sup>26</sup> Within our results of the sex ratio (male/female), we have to underline the increase in male mortality compared to female mortality in the group between 35 and 54 years of age. This pointed to premature mortality in men compared to women with PD that occurred between 1986 and 2000, which later increased again from 2014 until 2020. In our results, the number of men versus women deceased was much higher in 2020 concurring with the coronavirus disease 2019 pandemic (COVID-19). Recent studies confirmed that COVID-19 augmented the death cases in people with PD compared to the general population with a higher number of deaths in males than females.<sup>27</sup> A Spanish cross-sectional survey of 568 patients with PD during the COVID-19 pandemic reported a worsening of disease symptoms in 65.7% of the cases.<sup>28</sup> A worsening of motor and nonmotor symptoms in PD and comorbidities (primarily pneumonia) were described as mortality predictors by Bugalho et al.<sup>29</sup> During the pandemic, young people were more affected by COVID-19 than older people with PD, and the main comorbidity was pneumonia.<sup>30</sup> Comorbidities seem to affect in early stages of PD,<sup>31</sup> that could be related to premature mortality. Taking into account the information mentioned and the results obtained, we stated the need for future studies that assessed mortality trends during pandemic years not only in Spain, but also in other countries and worldwide. The study of Fedeli et al.<sup>27</sup> stated the need for further studies focused on PD mortality during the COVID-19 pandemic and claimed a correct practice on death certification for not underestimating or biasing future mortality trends studies. We also considered it of interest to perform an APC analysis to know if there will be a period effect on PD mortality, due to COVID-19 being exposed to the entire PD population for a concrete period of time.

Our APC analysis showed age and period effects on mortality during the studied period, but no effect on the birth cohort was found. The age effect only shows the natural course of the disease, presenting a higher mortality at an older age. The period effects could be related to the use of levodopa treatment. Although pharmacological therapy for PD has not been proven to promote changes in mortality trends, some authors reported that levodopa delayed death in people diagnosed with PD; but real effects of levodopa on mortality trends remains controversial.<sup>32</sup> Around 1980 first side effects of long-term administration which involve a worsening on disease symptoms.<sup>33</sup> After our analysis of APC, the period effect observed in the Spanish population appears to be concordant with the beginning of levodopa prescription in the decade of the 1960s to 70s. However, after 2000 mortality started to increase strikingly, which could be related to awareness of levodopa side effects and the search for new therapy options. This could also be related to the slight ascent of mortality and the descent in mortality in the group above 75 years observed in the joinpoint analysis before the beginning of the 20th century, with a later mortality ascent. This idea was supported by Ulivelli et al.<sup>16</sup> who stated a descent in Italian mortality rates in the PD pop-

ulation associated with levodopa, followed by a later rise in mortality. Regarding other therapeutic options, recently Tvete et al.<sup>34</sup> reported that dopamine-agonists presented lower risk of mortality compared to monoamine oxidase B (MAO-B). However, we must point out that because of the study design used, no relational causes could be established, so the hypothesis under the period effect should be taken with caution.

Finally, our PYLL analysis supported the known and stated reduction in life expectancy of the disease, being higher in male.<sup>35</sup>

## Clinical implications

One of the main clinical implications that could be extracted from our findings is the need to strengthen health measures to manage the disease, due to the remarkable increase in the mortality from PD between 1981 and 2020. In order to achieve this goal, the PARKINSON 2030 Delphi project has been proposed in the Spanish territory, to pave the road toward an accurate diagnostic and a proper therapeutic management of PD.<sup>36</sup> Additionally, recognition of the increase in mortality in PD in 2020 could enable the identification of risk factors (such as comorbidities) and be the first step to plan health care programmes that would impact the survival of people diagnosed with PD.<sup>7</sup>

## Strengths and limitations

This study has strengths. To our knowledge, we provided the largest period assessed in Spain (40 years) to analyse mortality trends in the PD population. Another strength of our study is the use of the APC model to know how these factors could influence mortality throughout the analysis period. To our knowledge, this is the first study to use this model to examine Spanish mortality trends in PD. The use of the European Standard Population of 2013 will allow comparison with future studies. The use of a national mortality register ensured data reliability and allowed for the analysis of large death cases.

The main limitation of this study was the inability of APC methods to explain the reasons under changes in mortality trends. One example of this, is that we could hypothesise that the increase in mortality data could be caused by an underdiagnosis during first years of study, or the ageing of Spanish population during the studied period, but further research is needed to support these ideas. Regarding the ageing of population, it seems to be a risk factor for underdiagnosis or overdiagnosis in degenerative diseases, like PD,<sup>37</sup> so this issue should be considered when interpreting our mortality rates results. We used data based on death certificates which could present bias, for example in PD mortality studies the attribution of death cause could change depending on the health care professional (eg, neurologist, internist, cardiologist). Even within the group of neurologists the fact that this professional is an expert or not in PD, it could condition the cause of death registered in death certificates, possibly leading to additional bias. These issues and the likely sticky-diagnosis bias could have conditioned our results.<sup>38</sup> In addition, the number of neurologists since 1981 has grown exponentially in Spain and so the diagnostic precision; being possible that initial cases from 1981 could be diagnosed like only PD not identifying atypical parkinsonism cases. This could not only influence diagnosis, but also death certificates registries or mortality data. Changes in the ICD between 1981 and 2020 could



have influenced our findings. However, there is no evidence of major changes associated with successive ICD revisions. Furthermore, data about comorbidities and clinical management were not available and could not be considered during the analysis.

## Conclusions

## Ethic approval

The study received authorisation of Spanish National Statistics Institute to conduct this research (21 January 2020; reference no. ES002/2020). Informed consent not applicable.

## Funding

The authors did not receive support from any organisation for the submitted work.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Conflicts of interest

None.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.nrl.2023.05.002>.

## References

1. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. *Lancet Neurol*. 2021;20(5):385–97, [http://dx.doi.org/10.1016/S1474-4422\(21\)00030-2](http://dx.doi.org/10.1016/S1474-4422(21)00030-2).
2. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet*. 2021;397(10291):2284–303, [http://dx.doi.org/10.1016/S0140-6736\(21\)00218-X](http://dx.doi.org/10.1016/S0140-6736(21)00218-X).
3. McDonald C, Gordon G, Hand A, Walker RW, Fisher JM. 200 Years of Parkinson's disease: what have we learnt from James Parkinson? *Age Ageing*. 2018;47(2):209–14, <http://dx.doi.org/10.1093/ageing/afx196>.
4. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591–601, <http://dx.doi.org/10.1002/mds.26424>.
5. Lampropoulos IC, Malli F, Sinani O, Gourgoulanis KI, Xiromerisiou G. Worldwide trends in mortality related to Parkinson's disease in the period of 1994–2019: analysis of vital registration data from the WHO Mortality Database. *Front Neurol*. 2022;13, <http://dx.doi.org/10.3389/fneur.2022.956440>.
6. Ministerio de Sanidad. [https://www.sanidad.gob.es/estadEstudios/estadisticas/estMinisterio/mortalidad/docs/Patrones\\_Mortalidad\\_2019.pdf](https://www.sanidad.gob.es/estadEstudios/estadisticas/estMinisterio/mortalidad/docs/Patrones_Mortalidad_2019.pdf), 2022.
7. Gonzalez MC, Dalen I, Maple-Grødem J, Tysnes O-B, Alves G. Parkinson's disease clinical milestones and mortality. *npj Park Dis*. 2022;8(1):58, <http://dx.doi.org/10.1038/s41531-022-00320-z>.
8. Dobson A, Hockey R, Chan H-W, Mishra G. Flexible age-period-cohort modelling illustrated using obesity prevalence data. *BMC Med Res Methodol*. 2020;20(1):16, <http://dx.doi.org/10.1186/s12874-020-0904-8>.
9. Stevens GA, Alkema L, Black RE, Boerna JT, Collins GS, Ezzati M, et al. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. *Lancet*. 2016;388(10062):e19–23, [http://dx.doi.org/10.1016/S0140-6736\(16\)30388-9](http://dx.doi.org/10.1016/S0140-6736(16)30388-9).
10. Monica P, Lanzieri G, Glickman M, Grande E, Zupanec T, Wojtyniak B, et al. Revision of the European Standard Population: report of Eurostat's task force: 2013 edition. *Publ Off*. Published online. 2013, <http://dx.doi.org/10.2785/11470>.
11. Bell A. Age period cohort analysis: a review of what we should and shouldn't do. *Ann Hum Biol*. 2020;47(2):208–17, <http://dx.doi.org/10.1080/03014460.2019.1707872>.
12. Decarli A, La Vecchia C. An R package for fitting age, period and cohort models. *Epidemiol Biostat Public Heal*. 2014;11(4):e9977, <http://dx.doi.org/10.2427/9977>.
13. Decarli A, La Vecchia C, Malvezzi M, Micciolo R. An R package for fitting age, period and cohort models. *Epidemiol Biostat Public Heal*. 2014;11(4):1–12, <http://dx.doi.org/10.2427/9977>.
14. Rong S, Xu G, Liu B, Sun Y, Snetselaar LG, Wallace RB, et al. Trends in mortality from Parkinson disease in the United States, 1999–2019. *Neurology*. 2021;97(20):e1986–93, <http://dx.doi.org/10.1212/WNL.00000000000012826>.
15. Okunoye O, Horsfall L, Marston L, Walters K, Schrag A. Mortality of people with Parkinson's disease in a large UK -Based Cohort Study: time trends and relationship to disease duration. *Mov Disord*. 2021;36(12):2811–20, <http://dx.doi.org/10.1002/mds.28727>.
16. Olivelli M, Bezzini D, Kundisova L, Grazi I, Battaglia MA, Nante N, et al. Mortality of Parkinson's disease in Italy from 1980 to 2015. *Neurol Sci*. 2022;43(6):3603–11, <http://dx.doi.org/10.1007/s10072-021-05854-3>.
17. Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis*. 2018;8(s1):S3–8, <http://dx.doi.org/10.3233/JPD-181474>.
18. Ou Z, Pan J, Tang S, Duan D, Yu D, Nong H, et al. Global trends in the incidence, prevalence, and years lived with disability of Parkinson's disease in 204 countries/territories from 1990 to 2019. *Front Public Heal*. 2021;9:9, <http://dx.doi.org/10.3389/fpubh.2021.776847>.
19. García-Ramos R, López Valdés E, Ballesteros L, Jesús S, Mir P. The social impact of Parkinson's disease in Spain: report by the Spanish Foundation for the Brain. *Neurol (English Ed)*. 2016;31(6):401–13, <http://dx.doi.org/10.1016/j.nrleng.2013.04.008>.
20. Marras C, Canning CG, Goldman SM. Environment, lifestyle, and Parkinson's disease: implications for prevention in the next decade. *Mov Disord*. 2019;34(6):801–11, <http://dx.doi.org/10.1002/mds.27720>.
21. Paul KC, Chuang YH, Shih I, Keener A, Bordelon Y, Bronstein JM, et al. The association between lifestyle factors and Parkinson's disease progression and mortality. *Mov Disord*. 2019;34(1):58–66, <http://dx.doi.org/10.1002/mds.27577>.
22. McMillan JM, Michalchuk Q, Goodarzi Z. Frailty in Parkinson's disease: a systematic review and meta-analysis. *Clin Park Relat Disord*. 2021;4:100095, <http://dx.doi.org/10.1016/j.prdoa.2021.100095>.
23. McGivern L, Shulman L, Carney JK, Shapiro S, Bundock E. Death certification errors and the effect on mortality statistics. *Public Health Rep*. 2017;132(6):669–75, <http://dx.doi.org/10.1177/0033354917736514>.

24. Virameteekul S, Revesz T, Jaunmuktane Z, Warner TT, De Pablo-Fernández E. Clinical diagnostic accuracy of Parkinson's disease: where do we stand? *Mov Disord.* 2023; <http://dx.doi.org/10.1002/mds.29317>. Published online January 5.
25. Fedeli U, Schievano E. Increase in Parkinson's disease-related mortality among males in Northern Italy. *Parkinsonism Relat Disord.* 2017;40:47–50, <http://dx.doi.org/10.1016/j.parkreldis.2017.04.008>.
26. Kadastik-Eerme L, Taba N, Asser T, Taba P. Incidence and Mortality of Parkinson's Disease in Estonia. *Neuroepidemiology.* 2019;53(1-2):63–72, <http://dx.doi.org/10.1159/000499756>.
27. Fedeli U, Casotto V, Barbiellini Amidei C, Saia M, Tiozzo SN, Basso C, et al. Parkinson's disease related mortality: Long-term trends and impact of COVID-19 pandemic waves. *Parkinsonism Relat Disord.* 2022;98:75–7, <http://dx.doi.org/10.1016/j.parkreldis.2022.04.011>.
28. Santos-García D, Oreiro M, Pérez P, Fanjul G, González, M.J.F. Paineiras, JMP, et al. Impact of coronavirus disease 2019 pandemic on Parkinson's disease: a cross-sectional survey of 568 Spanish patients. *Mov Disord.* 1712–1716;35(10):2020, <http://dx.doi.org/10.1002/mds.28261>.
29. Bugalho P, Ladeira F, Barbosa R, Marto JP, Borbinha C, Salavisa M, et al. Motor and non-motor function predictors of mortality in Parkinson's disease. *J Neural Transm.* 2019;126(11):1409–15, <http://dx.doi.org/10.1007/s00702-019-02055-3>.
30. Putri C, Hariyanto TI, Hananto JE, Christian K, Situmeang RFV, Kurniawan A. Parkinson's disease may worsen outcomes from coronavirus disease 2019 (COVID-19) pneumonia in hospitalized patients: a systematic review, meta-analysis, and meta-regression. *Parkinsonism Relat Disord.* 2021;87:155–61, <http://dx.doi.org/10.1016/j.parkreldis.2021.04.019>.
31. Santos-García S, Suárez-Castro E, Hernandez J, Expósito-Ruiz I, Tuñas-Gesto C, Aneiros-Díaz M, et al. Predictors of mortality in nondemented patients with Parkinson disease: motor symptoms versus nonmotor symptoms. *J Geriatr Psychiatry Neurol.* 2018;31(1):19–26, <http://dx.doi.org/10.1177/0891988717743589>.
32. Morgan JC, Currie LJ, Harrison MB, Bennett JP, Trugman JM, Wooten GF. Mortality in levodopa-treated Parkinson's disease. *Parkinsons Dis.* 2014;2014:1–8, <http://dx.doi.org/10.1155/2014/426976>.
33. Binde CD, Tvette IF, Klemp M. Time until need for levodopa among new users of dopamine agonists or MAO-B inhibitors. *Parkinsons Dis.* 2021;2021:1–7, <http://dx.doi.org/10.1155/2021/9952743>.
34. Tvette IF, Klemp M. Parkinson's disease, treatment choice and survival over time. *Clin Park Relat Disord.* 2022;6:100136, <http://dx.doi.org/10.1016/j.prdoa.2022.100136>.
35. Bäckström D, Granåsen G, Domellöf ME, Linder J, Mo SJ, Riklund K, et al. Early predictors of mortality in parkinsonism and Parkinson disease. *Neurology.* 2018;91(22):e2045–56, <http://dx.doi.org/10.1212/WNL.0000000000006576>.
36. Santos García D, Blázquez-Estrada M, Calopa M, Escamilla-Sevilla F, Freire E, Ruiz PJG, et al. Present and future of Parkinson's disease in Spain: PARKINSON-2030 Delphi project. *Brain Sci.* 2021;11(8):1027, <http://dx.doi.org/10.3390/brainsci11081027>.
37. Skinner T, Scott I, Martin J. Diagnostic errors in older patients: a systematic review of incidence and potential causes in seven prevalent diseases. *Int J Gen Med.* 2016;137, <http://dx.doi.org/10.2147/IJGM.S96741>. Published online May.
38. Moscovich M, Boschetti G, Moro A, Teive HAG, Hassan A, Munhoz RP. Death certificate data and causes of death in patients with parkinsonism. *Parkinsonism Relat Disord.* 2017;41:99–103, <http://dx.doi.org/10.1016/j.parkreldis.2017.05.022>.