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# Projections of Prevalence, Lifetime Risk, and Life Expectancy of Parkinson's Disease (2010-2030) in France

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**ABSTRACT: Background:** Previous studies on the number of Parkinson's disease (PD) patients in the future based on projections of population size underestimated PD burden because they did not take into account the improvement of life expectancy over time.

**Objective:** The objective of this study was to assess PD progression from 2010 to 2030 in France in terms of prevalent patient numbers, prevalence rates, lifetime risk, and life expectancy with PD, accounting for projections of overall mortality and increased risk of death of PD patients.

**Methods:** To provide projections of PD burden, we applied a multistate approach considering age and calendar time to incidence and prevalence rates of PD (France 2010) based on drug claims and national demographic data.

**Results:** The number of PD patients will increase by 65% between 2010 (n = 155,000) and 2030 (n ~ 260,000), mainly for individuals older than 65 years; the

prevalence rate of PD after age 45 will increase from 0.59% in 2010 to ~0.80% in 2030. We project an extension of ~3 years of the life expectancy of PD patients at 65 years between 2010 (women, 14.8 years; men, 13.0 years) and 2030 (women, 17.8 years; men, 16.1 years), and a relative increase of about 10% of the lifetime risk of PD at 45 years between 2010 (women, 5.5%; men, 6.0%) and 2030 (women, 6.3%; men, 7.4%).

**Conclusions:** The number of PD patients is predicted to grow substantially in future years as a consequence of population aging and life expectancy improvement. The assessment of the future PD burden is an important step for planning resources needed for patient care in aging societies.

**Key Words:** Parkinson's disease; projections; prevalence; life expectancy; multistates model

Parkinson's disease (PD) is a neurodegenerative disorder that leads to a progressive deterioration of health and an increased risk of death.<sup>1</sup> Its main risk factor is increasing age. PD is rare before the age of 50 years, and its incidence increases sharply after that age; more than 80% of patients are older than 65 years.<sup>2</sup> In addition, PD is ~1.5 times more frequent in men than women.<sup>3</sup> According to the Global Burden of Disease,

PD was the neurological disease with the largest increase in age-standardized prevalence between 1990 and 2015.<sup>4</sup> As the disease cannot be cured and develops over time, the number of PD patients will increase in years to come as a result of population aging.

A previous study used published PD prevalence estimates from different countries to estimate its burden based on their population size in 2030 and projected that the number of PD patients will increase by 50% between 2005 and 2030 in the most populated countries.<sup>5</sup> However, because prevalence is influenced by the duration of the disease and their approach did not take into account the improvement in life expectancy over time, the burden of PD was likely underestimated.

The main objective of this work is to provide projections of the number of PD patients in France, estimates of life expectancy with PD, and lifetime risk of PD. We

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used a multistate approach that takes into account the competing risk between PD and death and accounts for changes in mortality rates over calendar time and age.

## Methods

### Data

We used two data sources.

First, PD patients were identified in the French National Health Insurance database (SNIIRAM) using a prediction model based on drug claims that allow one to estimate the probability that people who used antiparkinsonian drugs in a given year are being treated for PD.<sup>6</sup> We have previously shown that this approach identifies treated patients with 92.5% sensitivity and 86.4% specificity and yields age- and gender-specific incidences consistent with 22 previously published studies.<sup>3</sup> We applied this prediction model for years 2009 to 2012. In a given year, prevalent PD patients were those predicted by the model as patients and who were alive on December 31 of that year; incident patients were those predicted by the model as patients that year who did not have antiparkinsonian drug reimbursements the previous year. The number of prevalent and incident patients were divided by the corresponding population estimates and number of person-years, respectively (French National Institute of Statistics and Economic Studies, INSEE) to compute prevalence (2009-2011) and incidence (2010-2012) rates by sex and by 5-year age groups. These rates were first corrected for imperfect sensitivity/specificity of the model.<sup>7</sup> We then corrected prevalence and incidence rates for underdiagnosis after age 80; PD is more difficult to diagnose at older ages, and some cases may not be diagnosed or may be institutionalized and not identified through drug claim databases (about 30% of French institutions have internal pharmacies, and the drugs delivered in these institutions are missed in the drug claim databases). This likely explains the deceleration we observed in prevalence/incidence rates after age 80. To correct for underdiagnosis after that age, we first modeled the observed prevalence/incidence rates between 45 and 79 years using the best fitting fractional polynomial of age (*fracpoly* function in Stata 14; StataCorp LP, College Station, Texas) and then projected prevalence/incidence rates after age 80 based on the best fitting fractional polynomial. This was done for each year and for men and women separately (Supporting Information Figures e-1 and e-2). The resulting incidence/prevalence rates were then smoothed by a spline function to obtain continuous functions of age. In the remainder of this paper, we refer to these estimates as “the observed incidence and prevalence.” The observed number of men and women with PD in 2010 was obtained by multiplying these age- and sex-specific smoothed prevalence rates by the corresponding population size.

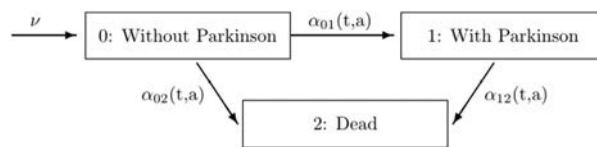


FIG. 1. Illness death model.

Second, we retrieved projections for the overall mortality and size of the population alive by age, sex, and date of birth between years 1950 and 2060 in France (French National Institute of Statistics and Economic Studies). Mortality rates were smoothed using an approximation by a Gompertz-Makeham model to obtain continuous functions of age.

### Model and Assumptions

Figure 1 represents the 3-states model called the “illness-death model.” As input of the model, we define  $\nu$  as the number of individuals alive and free of PD (state ‘0’) at a given age. They can develop PD (state 1) and then die (state 2) or die without developing PD. Three transition intensities are considered:  $\alpha_{01}$  represents PD incidence rates, whereas  $\alpha_{02}$  and  $\alpha_{12}$  denote mortality rates among individuals without and with PD, respectively. Transition intensities depend on calendar time  $t$  and age  $a$  (with  $t$  minus  $a$  being the year of birth).

As PD is rare, mortality among individuals without PD,  $\alpha_{02}(t,a)$ , can be approximated by the overall mortality,  $\alpha_2(t,a)$ . The model relies on the hypotheses that there are no time trends in PD incidence and that incidence is null before age 45 (the number of patients below this age represents less than 2% of the total number and can be neglected). Thus, PD incidence depends on age alone and  $\nu(45, t-a)$  corresponds to the population size at 45 years by sex and year of birth.

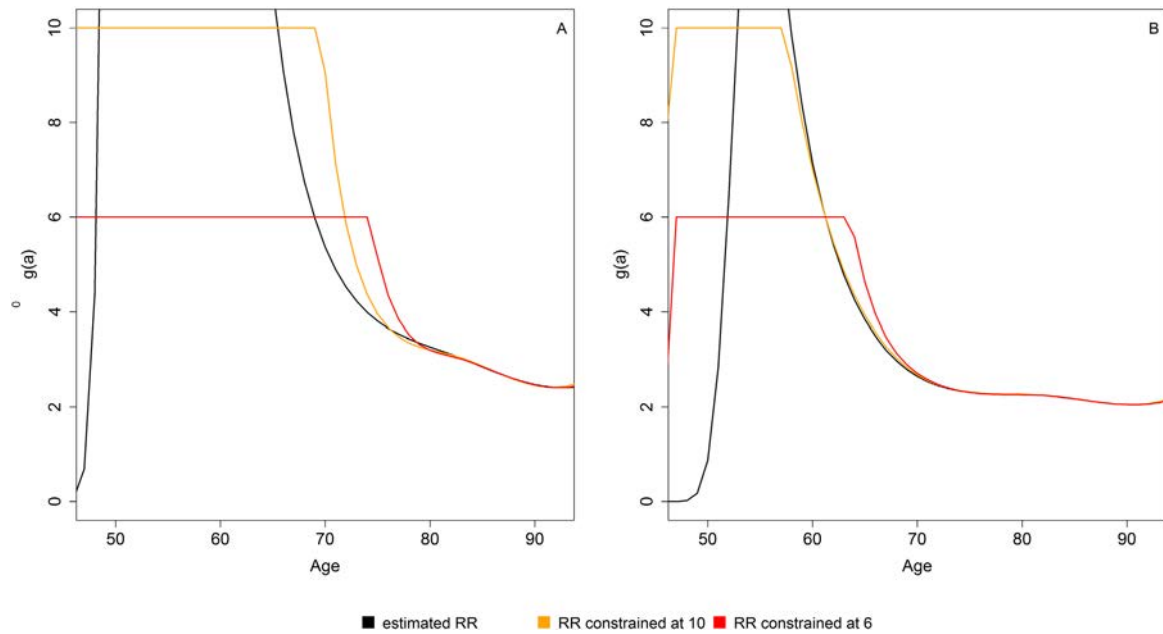
Mortality among patients with PD ( $\alpha_{12}$ ) is flexibly modeled by assuming that it is proportional to the overall mortality ( $\alpha_2$ ) with an age- and sex-specific relative risk (RR) of death ( $g(a)$ ) for those with PD versus those without PD. Thus, mortality among PD follows the same calendar time-trend than the general mortality,

$$\alpha_{12}(t,a) = \alpha_2(t,a) \times g(a) \quad (1)$$

This model corresponds to a nonhomogeneous Markov model.<sup>8</sup>

### Steps of the Method for Computing Projections

The available data are the population at risk at age 45 by sex and year of birth  $\nu(45, t-a)$ , the overall mortality rates  $\alpha_2(t,a)$ , and PD incidence  $\alpha_{01}(a)$ . To compute projections of the number of PD patients and life expectancy with PD, the RR of death  $g(a)$  and mortality among patients with PD,  $\alpha_{12}(t,a)$  are needed. However, these data, in particular age- and sex-specific



**FIG. 2.** Relative risk of death for patients with PD versus those without PD by sex and age. Estimates of the relative risk of death of PD patients  $g(a)$  by sex (A: women; B: men) and age (yellow, constrained at 10; red, constrained at 6) and without constraints (black). RR, relative risk.

estimates, are not readily available from the literature and existing estimates are inconsistent.<sup>1,9</sup> The first step is to estimate these parameters.

### Step 1: Estimation of Mortality Among PD Patients

The number of PD patients at time  $t$  is the sum, over age groups and sex, of the number of individuals in state 1 at time  $t$ . The mortality of PD patients is estimated using PD incidence and prevalence rates as well as the overall mortality and population size as follows:

$$\text{Number of cases at time } t = \sum_{a > 45} \nu(45, t-a) \times P_{01}(45, a|t) \quad (2)$$

where  $\nu(45, t-a)$  is the number of individuals alive and free of PD at age 45 and born on year  $t-a$ , and  $P_{01}(45, a|t)$  is the probability for these individuals to be alive and have PD at age  $a$  and time  $t$ . This probability depends on the incidence rate  $\alpha_{01}$ , the overall mortality rate  $\alpha_2$ , and the RR of death  $g(a)$  (Supporting Information Methods, equation e-1).

Based on Equation 2, we search the  $g(a)$  values that yield estimates of the number of PD patients that fit the observed prevalence numbers in 2009, 2010, and 2011. The least-square method (weighted by the number of patients by age) and a spline approximation are used to estimate  $g(a)$  and mortality of PD patients by age and sex ( $\alpha_{12}$ ).

### Step 2: Projection of Health Indicators

To assess the PD burden in future years, we use PD incidence ( $\alpha_{01}$ ), the projected population size at age

45 ( $\nu(45, t-a)$ ), and the projected mortality among PD ( $\alpha_{12}$ ) and non-PD individuals ( $\alpha_2$ ). We estimate the number of PD patients, the life expectancy for individuals with PD ( $LE_{11}$ ), and the lifetime risk of PD ( $F_{01}$ ) for all ages older than 45 years and each year of birth. The statistical method is described in detail in Wan-  
neveich and colleagues.<sup>10</sup> In this paper, we provide projections for the year  $t = 2030$ ; all analyses are sex stratified.

## Results

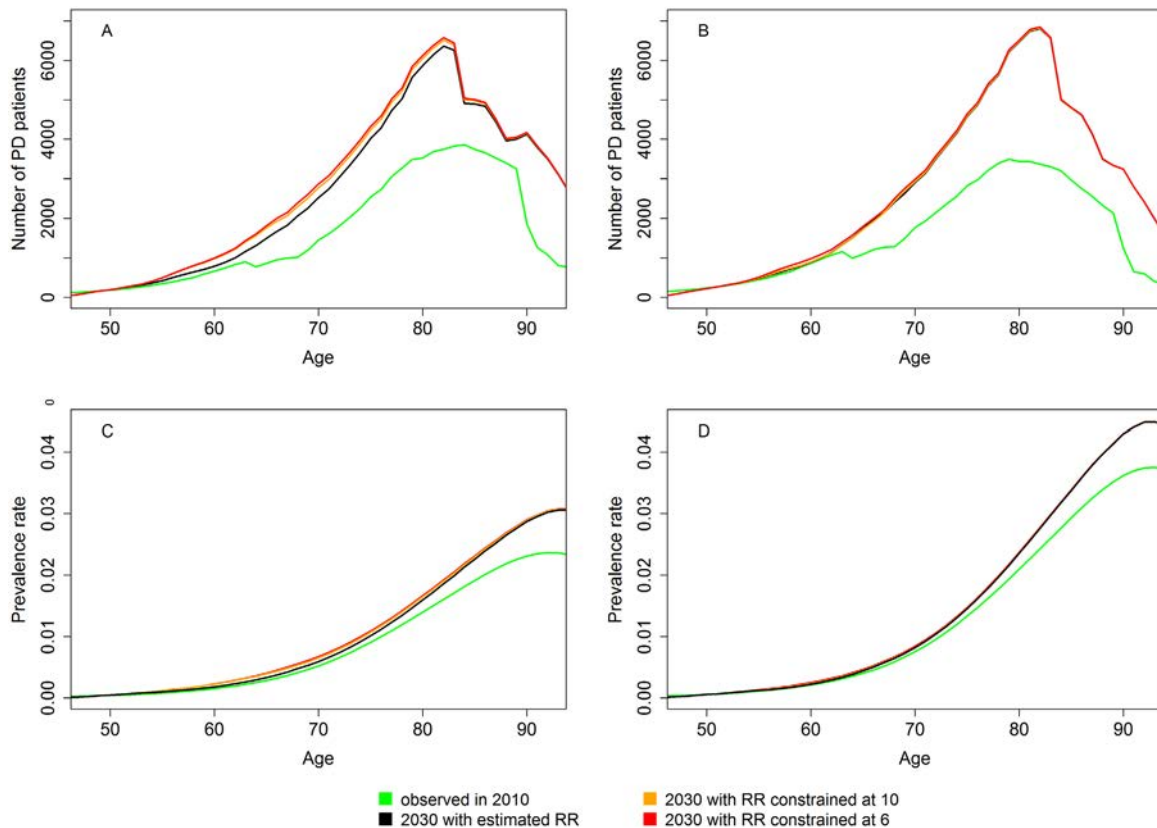
### Estimation of Mortality of PD Patients

Figure 2 shows the estimated RR of death for individuals with PD versus those without,  $g(a)$ . Because of the small number of patients and low overall mortality rates before 65 years, RR estimates are extremely high and unrealistic for the youngest individuals. Thus, we projected the number of PD patients using both crude RR estimates and RR re-estimated with the additional constraints that they must be lower than 10 or 6.

The impact of constraining the RR of death is negligible for men and small after 70 years for women regarding the number of PD patients in 2010; Supporting Information Figure e-3 compares the observed and estimated (equation 2) number of PD patients (2010) based on the 3 different estimates of the RR of death displayed in Figure 2.

### Projections of the Burden of PD in 2030

Figure 3 displays the projected number of men and women with PD and prevalence rates of PD (2030)



**FIG. 3.** Observed (2010) and projected (2030) number of PD patients and prevalence rates by sex and age in France. Number of PD patients and prevalence rates of PD by age and sex (women: A and C; men: B and D) observed in 2010 (green) and estimated in 2030 using the illness death model based on 3 different estimates of the relative risk of death of PD patients  $g(a)$  (unconstrained, black; constrained at 10, yellow; constrained at 6, red). RR, relative risk.

based on 3 estimates of the RR of death in PD patients (equation 2). The number of PD patients increases sharply between 2010 and 2030 after age 60, reaches a maximum around age 80, and decreases thereafter. The prevalence rates of PD in 2030 are higher than in 2010 for older people. Constraints on the RR of death have little impact on these projections.

Table 1 summarizes projections in 2030 of the number of PD patients, according to 3 estimates of the RR of death; Supporting Information Table e-1 provides a description by age groups— $g(a)$  unconstrained—and Supporting Information Figure e-4 shows the annual number of PD patients between 2010 and 2030. From 2010 to 2030, the number of patients is expected to grow by more than 60% for women and 70% for men; the increase will be more pronounced for those aged older than 65 years. The impact of constraints on the RR of death is relatively weak as a result of the small number of patients younger than 70 years.

Table 2 summarizes the projections in 2030 for the life expectancy with PD ( $LE_{11}$ ) and lifetime risk of PD ( $F_{01}$ ) with  $g(a)$  unconstrained. Indeed,  $F_{01}$  does not depend on the RR of death in PD patients, and we observed that this RR had little impact on  $LE_{11}$  estimates. The only difference was for women with PD aged 65 years,

where  $LE_{11}$  was estimated to be 15.3 years in 2010 and 18.2 years in 2030 with  $g(a)$  constrained to 6 compared to 14.8 years in 2010 and 17.8 years in 2030 without constraint. Table 2 shows that  $LE_{11}$  increased between 2010 and 2030; the increase was smaller among the oldest (65 years: + 3 years among women, + 3.1 years among men; 85 years: + 0.8 years among women, + 0.7 years among men).

The lifetime risk of developing PD before death ( $F_{01}$ ) is higher for men than women and increases between 2010 and 2030 (men: + 0.8% at 45 years, + 1.4% at 65 years; women: + 0.6% at 45 years, + 0.8% at 65 years).

## Discussion

We provide projections of the number of PD patients, the life expectancy with PD, and the lifetime risk of PD to help assess its future demographic, economic, and social burden. Between 2010 and 2030, we show a relative increase of ~10% of the lifetime risk of PD at 45 years for men and women. We estimate that there will be around 260,000 PD patients in France in 2030, corresponding to an increase of ~65% compared to

**TABLE 1.** Observed (2010) and estimated (2030) number of PD patients and prevalence rates of PD according to the relative risk of death of PD patients for men and women in France

Health Indicators	Relative risk of death (g(a))	Women		Men		Total	
		2010	2030	2010	2030	2010	2030
Number of PD patients	Unconstrained	79,100 <sup>a</sup>	126,800	75,900 <sup>a</sup>	130,000	155,000 <sup>a</sup>	256,800
	≤10		133,200		130,600		263,800
	≤6		135,100		132,200		267,300
Prevalence rates of PD after 45 years (in %)	Unconstrained	0.55	0.74	0.63	0.89	0.59	0.81
	≤10		0.77		0.90		0.83
	≤6		0.78		0.91		0.84

<sup>a</sup>Number of PD patients observed.

2010. Under our assumptions, in 2030, 1 person of 124 individuals aged older than 45 years will have PD. We also project that the life expectancy of PD patients at 65 years will increase by ~3 years between 2010 and 2030.

If PD incidence remains stable over time and given the projections for the French population,<sup>11</sup> the PD burden will increase sharply between 2010 and 2030. Our projection (260,000 PD patients in France in 2030) is higher than an earlier one by Dorsey and colleagues (190,000 patients).<sup>5</sup> Previous projections calculated the number of PD patients as the product of the country's age-specific prevalence and population structure between 2005 and 2030. For France, the projections relied on prevalence rates from a population-based study (1988-1989) that identified 60 PD-prevalent patients.<sup>12</sup> Our estimates are higher for 2 main reasons. First, in a comparative study of 5 population-based European studies, the French study yielded the lowest prevalence rate;<sup>13</sup> the French screening instrument was the least sensitive, as it was the only study that did not include a neurological examination in the first screening stage, which resulted likely in a higher number of false negatives. Second, the method used to estimate the projected number of PD patients did not take into account the improvement in life expectancy over time (on average, + 0.25 months per year in France in the last 60 years). In a meta-analysis of 10 studies,

those with a later recruitment period showed longer disease duration (+0.25 years per year of recruitment period, 95% confidence interval = 0.11-0.34).<sup>1</sup> Therefore, age-specific prevalence rates are likely to increase over time as a result of the longer life expectancy of PD patients; declining cardiovascular mortality and better care of chronic diseases are likely to contribute to this pattern. The prevalence study used to perform the projections is rather old and likely contributed to underestimations of the number of future patients.

A recent study revised U.S. projections accounting for the potential impact of declining smoking rates.<sup>14</sup> Assuming a causal inverse smoking-PD association and a 10-year lag to account for the temporal effect of smoking on PD incidence, the projected number of PD patients was ~10% higher in 2040 compared to projections without consideration of smoking, whereas there was no difference in 2030. We decided not to take smoking into account in our main analysis for 3 main reasons. First, it is still debated whether the smoking-PD association is truly causal or explained by reverse causation or other biases.<sup>15,16</sup> Second, the 10-year lag time was arbitrary and may actually be longer<sup>17</sup>; if so, the impact of declining smoking rates would be seen even later. Third, in France, the declining time trends for smoking are much less pronounced and clear-cut than in the United States.<sup>18</sup> Although smoking prevalence declined by more than 40% in both men and women in the United States from 1980 to 2006, the overall smoking prevalence in France remained stable (around 30% daily smokers) from 1980 to 2006, with different trends in men (-20%) and women (+44%).<sup>19</sup> In addition, between 2005 and 2014, the prevalence of smoking remained stable in France for both men and women. It is difficult to anticipate the impact of these smoking trends on PD incidence.

Only 2 previous studies provided estimates of the lifetime risk of developing PD.<sup>2,20</sup> Although lifetime risks obtained in different populations are not directly comparable because they are not standardized with respect to mortality, our findings for men (lifetime risk at 65 years, 6.0%) are similar to those obtained in the U.S. Physicians' Health Study (1982-2006; lifetime risk

**TABLE 2.** Estimated life expectancy of a PD patient (LE<sub>11</sub>) and lifetime risk of PD for a healthy individual (F<sub>01</sub>) at different ages in 2010 and 2030 for men and women in France

Health Indicators	Age	Women		Men	
		2010	2030	2010	2030
Lifetime risk of PD (F <sub>01</sub> ), (in %)	45	6.6	7.2	7.1	7.9
	65	5.5	6.3	6.0	7.4
Estimated life expectancy with PD <sup>a</sup> (LE <sub>11</sub> ), (in years)	65	14.8	17.8	13.0	16.1
	75	8.7	10.4	7.5	9.0
	85	4.2	5.0	3.6	4.3

<sup>a</sup>For comparison, the overall life expectancy in 2030 at 65 years, 75 years, and 85 years are respectively estimated at 26.3, 16.5, and 8.6 for women and 22.3, 13.3, and 6.8 for men.

at 65 years: 6.46%).<sup>2</sup> These estimates are higher than those obtained in Minnesota (1976-1990; lifetime risk at 60 years, 2.0%) because of the lower PD incidence in that study when compared with ours and to the Physicians' Health Study, especially after 75 years. Our model predicts that the lifetime risk of PD will increase between 2010 and 2030. One striking finding is that, although PD incidence is about 1.5 times higher in men when compared with women and the male-to-female ratio increases with age,<sup>3</sup> the difference in lifetime risk between men and women was considerably less pronounced (ratio 2030 = 1.17). This is because the longer life expectancy in women counterbalanced the higher PD incidence in men.

Consistent with a previous study, life expectancy in PD patients was predicted to be longer in women than men and in younger patients when compared with older patients.<sup>21</sup> Our model predicts a gain in life expectancy that is also more pronounced in younger patients and women.

An important contribution of our approach is that it takes into account the impact of age and calendar time on mortality among diseased patients. The assumptions of no time trends in incidence and mortality of PD patients could be relaxed if needed, and we could account for changes in PD incidence or in RR of death over calendar time. Regarding incidence, few studies have examined time trends and have reported inconsistent findings. In the United States, a recent study suggested an increase in PD incidence between 1976 and 2005, particularly in men aged 70 or older, whereas no trend was evident for women.<sup>22</sup> The authors argued that declining smoking prevalence may contribute to this pattern. On the contrary, in the Netherlands, the Rotterdam study reported a marked decrease in PD incidence between 1990 and 2011 without any obvious explanation.<sup>23</sup> Two previous U.S. studies and one Canadian study showed no significant time trends.<sup>24</sup> In France, no incidence trend was observed between 2010 and 2015 (unpublished data from the authors), but data over a longer period are not available. Because it is unclear whether PD incidence has changed over time and decreasing trends may be explained by a better recognition of other causes of parkinsonism, we followed a conservative approach by assuming a constant incidence scenario. However, in a sensitivity analysis, we assumed an increasing trend in PD incidence among men of +2% per additional birth year, following the results from Savica and colleagues<sup>22</sup> in the United States. The estimated number of male PD patients in 2030 was 183,700, rather than 130,000 under a constant incidence scenario. Please note, however, that there is no evidence in France supporting the hypothesis of such a large increase (+24% per 10 years) in PD incidence.

Regarding the RR of death of PD patients, there is no clear evidence that the introduction of levodopa and improvements in PD care have allowed to improve the

survival of PD patients when compared with people without PD of similar age and sex.<sup>1</sup> Our model assumes that the time trend in mortality of PD patients is proportional to the overall mortality of the population, but it does not make any particular assumption about the effect of treatment strategies and better care of PD patients; in particular, it does not assume that the RR of death of PD patients has decreased over time. In fact, a meta-analysis showed that the RR of death tended to slightly increase over time (+1% increase, 95% confidence interval = 0.0-2.0, per year of study recruitment), which suggests that life expectancy has increased faster in the general population than in PD patients<sup>1</sup>; however, this finding was not robust in sensitivity analyses. If we imputed an annual 1% increase of the RR of death, both the projected number of PD patients (n = 232,500) and life expectancy with PD at 65 years (men, 14.7 years; women, 16.5 years) would decrease by ~9% compared to our main analysis. When compared with people without PD, the mortality of PD patients was higher at all ages, including among the oldest, with a RR of death of approximately 2.0, similar to a previous report.<sup>25</sup> However, we observed that the RR of death decreased with age, which is consistent with previous studies,<sup>26,27</sup> including in France.<sup>28</sup> Younger PD patients have longer disease duration when compared with older patients,<sup>1</sup> but relative to non-PD individuals, the disease has a stronger impact on mortality at younger ages because of the low mortality rates from other non-PD causes.<sup>21</sup>

One of the limitations of our study is that the effect of disease duration on mortality was not considered.<sup>29</sup> We attempted to account for the impact of age, disease duration, and calendar time on mortality (nonhomogeneous semi-Markov model), and predicted 230,000 PD patients in 2030. However, compared to our main analysis, this approach yielded better prevalence predictions in younger individuals in 2010 (ie, closer to observed prevalence), whereas they were worse in older individuals, especially after age 80, which represents a more important group in terms of the number of patients. Ideally, a solution would consist in using the semi-Markov assumption to model mortality among young patients, in whom disease duration has a stronger effect on death than age, and the Markov assumption among older-onset patients, in whom age has a stronger effect on mortality than disease duration. However, this would considerably complicate the estimation process and would require additional input data that are not available at the present time. Another limitation is that we probably failed to identify some patients (eg, untreated or undiagnosed, in institutions with in-house pharmacies), but we were able to correct our frequency estimates for the sensitivity and specificity of the method used to identify PD patients, and we previously showed that our frequency estimates are consistent with those from other studies.<sup>3</sup> In addition, we took into account the

underestimation in the oldest persons by correcting estimates for underdiagnosis after age 80. Nevertheless, the validity of the clinical diagnosis of PD is not perfect<sup>31</sup>; although this is likely to affect the crude number of patients at any given time, it is less likely to affect the relative change in the number of patients over time.

In conclusion, our approach yields more realistic projections of the number of PD patients in 2030 than previously reported and can be easily adapted for other countries where data on PD incidence as well as population and mortality projections are available. Our conclusion regarding the increase of life expectancy with PD is transposable to most developed countries as it relies only on decreasing mortality trends that are assumed to be similar in PD patients and the rest of the population. The estimated increase of the number of PD patients and lifetime risk of PD rely on both decreasing mortality and the constant PD incidence assumption. As discussed previously, the latter assumption may be debatable for some countries, but our method is able to take into account hypothetical time trends in incidence. The number of patients with PD is predicted to grow substantially as a consequence of population aging and life expectancy improvement. The assessment of the future PD burden is an important step for planning resources needed for patient care in aging societies.

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