Movement Disorders
CLINICAL PRACTICE
REVIEW

Age Cutoff for Early-Onset Parkinson's Disease: Recommendations from the International Parkinson and Movement Disorder Society Task Force on Early Onset Parkinson's Disease

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ABSTRACT: Background: Early-onset Parkinson's disease (EOPD)/young-onset Parkinson's disease (YOPD) is defined as Parkinson's disease (PD) with an age at onset (AAO) after age 21 years but before the usual AAO for PD. Consensus is lacking, and the reported maximal age for EOPD/YOPD has varied from 40 to 60 years, leading to a lack of uniformity in published studies and difficulty in harmonization of data. EOPD and YOPD have both been used in the literature, somewhat interchangeably.

Objective: To define the nomenclature and AAO cutoff for EOPD/YOPD.

Methods: An extensive review of the literature and task force meetings were conducted. Conclusions were reached by consensus.

Results: First, the literature has seen a shift from the use of YOPD toward EOPD. This seems motivated by an attempt to avoid age-related stigmatization of patients. Second, in defining EOPD, 56% of the countries use 50 or 51 years as the cutoff age. Third, the majority of international genetic studies in PD use an age cutoff of younger than 50 years to define EOPD. Fourth, many studies suggest that changes in the estrogen level can affect the predisposition to develop PD, making the average age at menopause of 50 years an important factor to consider when defining EOPD. Fifth, considering the differential impact of the AAO of PD on professional and social life, using 50 years as the upper cutoff for the definition of EOPD seems reasonable.

Conclusions: This task force recommends the use of EOPD rather than YOPD. It defines EOPD as PD with AAO after 21 years but before 50 years.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a number of defined clinical features such as bradykinesia with either 1 or both of rest tremor and rigidity as well as a variety of nonmotor symptoms.[1-4] Early-onset PD (EOPD), also referred

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to as young-onset PD (YOPD), has been defined as PD with an onset of motor symptoms after age 21 but before what is considered the usual age at onset (AAO) for PD. However, consensus is lacking, and the reported maximal age for EOPD/YOPD has varied from 40 to 60,[5-15] whereas onset at or before age 21 defines juvenile PD.[11,16] Because of the effect of PD symptoms earlier in life, the interaction of symptoms with potentially more active roles in society, and the longer time horizon of disease, people with EOPD/YOPD face unique challenges compared with those with late-onset PD.[17,18] International Parkinson and Movement Disorder Society (MDS) commissioned the Early Onset Parkinson Disease Task Force with the objectives of defining the best nomenclature for EOPD/YOPD and the AAO cutoff defining this condition as well as identifying unmet needs and unique challenges in patients with EOPD/YOPD to guide the harmonization of research and other initiatives. The task force recommendations were based on the nomenclature, epidemiology, geographic differences, genetics, role of sexual hormones, clinical features, impact, and social perceptions. All conclusions were reached by consensus.

Search Strategies and Selection Criteria

The task force chair was appointed by the MDS. The members of the task force, who are also the authors of the present publication, are PD specialists who were selected based on expertise in EOPD/YOPD, and were appointed by the task force chair. A systematic review of available literature was performed in PubMed up to January 2022 with the search terms early onset OR young onset OR early OR young AND Parkinson AND each of the following: definition, hormon*, menopause, social, and genetic. Articles were included if reporting on EOPD and written in English. Articles were excluded from this review if not available in English or published as editorials or letters. All abstracts were reviewed for relevance to the topic. Of the 2677 abstracts reviewed, 2625 were not considered relevant as the search terms were vague to capture the most abstracts possible and minimize the risk of missing a relevant study. A total of 52 abstracts were retained, and the corresponding full articles were carefully reviewed. Of these, 43 full articles were considered relevant and were included. PubMed links and references from these articles were also scrutinized to identify other relevant studies as suggested by the references' titles. Similar to the initial search, abstracts of potentially relevant references were reviewed and, if considered relevant, the corresponding full articles were reviewed. Thus, an additional 63 studies were included in this article, bringing the total of articles included to 106.

In addition, for the geographic differences section, a list of all countries was created, and then a systematic search in the PubMed and Web of Science databases was conducted using the following search terms: early onset Parkinson* disease AND/OR young onset Parkinson* disease AND age AND the country's name. Articles in English were included. Of the 971 abstracts reviewed, 51 were retained, and the corresponding full articles were carefully reviewed.

Because 12 articles were redundant in both research strategies noted previously, the total number of articles included in this review was 145 (Fig. 1).

Nomenclature

Authors who have first developed an interest in, and published on, this subgroup of PD have preferred the use of YOPD.[5-8,19,20] However, there has been a shift toward the use of EOPD in the past 2 decades.[9,11,15,21,22] The are no clear publications detailing the rationale behind this shift, but it seems motivated by an attempt to avoid age-related stigmatization (Table 1). Thus, the recommendation of the Early Onset Parkinson Disease Task Force of the MDS is to use the term *EOPD* to designate PD with an onset of motor symptoms before the specific age that was agreed on.

Epidemiology

The prevalence of PD increases sharply with age, reaching 2.6% in people aged 85 to 89 years,[23–26] with a mean age of onset in the early to mid-60s in the Western hemisphere.[27] EOPD represents 3% to 7% of PD.[17,28] The incidence of EOPD has been reported between 0.29 and 3.3 per 100,000 person-years.[15,20–22,29]

Geographical Differences

The age cutoff for the definition of EOPD varies from 1 country to another. An extensive review of the literature on this topic is presented in Table 2. Among the countries with a published age cutoff, 38% (n = 20) used a cutoff of 40 to 45 years, 56% (n = 29) used a cutoff of 50 or 51 years, and 6% (n = 3) used a cutoff of 55 years or older. More than 1 age cutoff has been used in some countries in different publications.

Genetics

It is beyond the scope of this article to comprehensively review the genetics of PD; however, it has been well recognized that the risk of genetic predisposition may increase with the younger AAO.[71] Indeed, a family history of PD is reported in 20% of patients with EOPD versus 6.9% of patients with later onset PD, and the age-specific risk of PD is 7.8-fold higher in the relatives of patients with EOPD compared with 2.9-fold among the relatives of patients with later onset PD.[14,72] Most frequent genetic mutations associated with EOPD are located on parkin (PARK2), *PINK1* (PARK 6), *DJ-1* (PARK7), *ATP13A2* (PARK9), and *PLA2G6* (PARK14).[17] Although some genetic

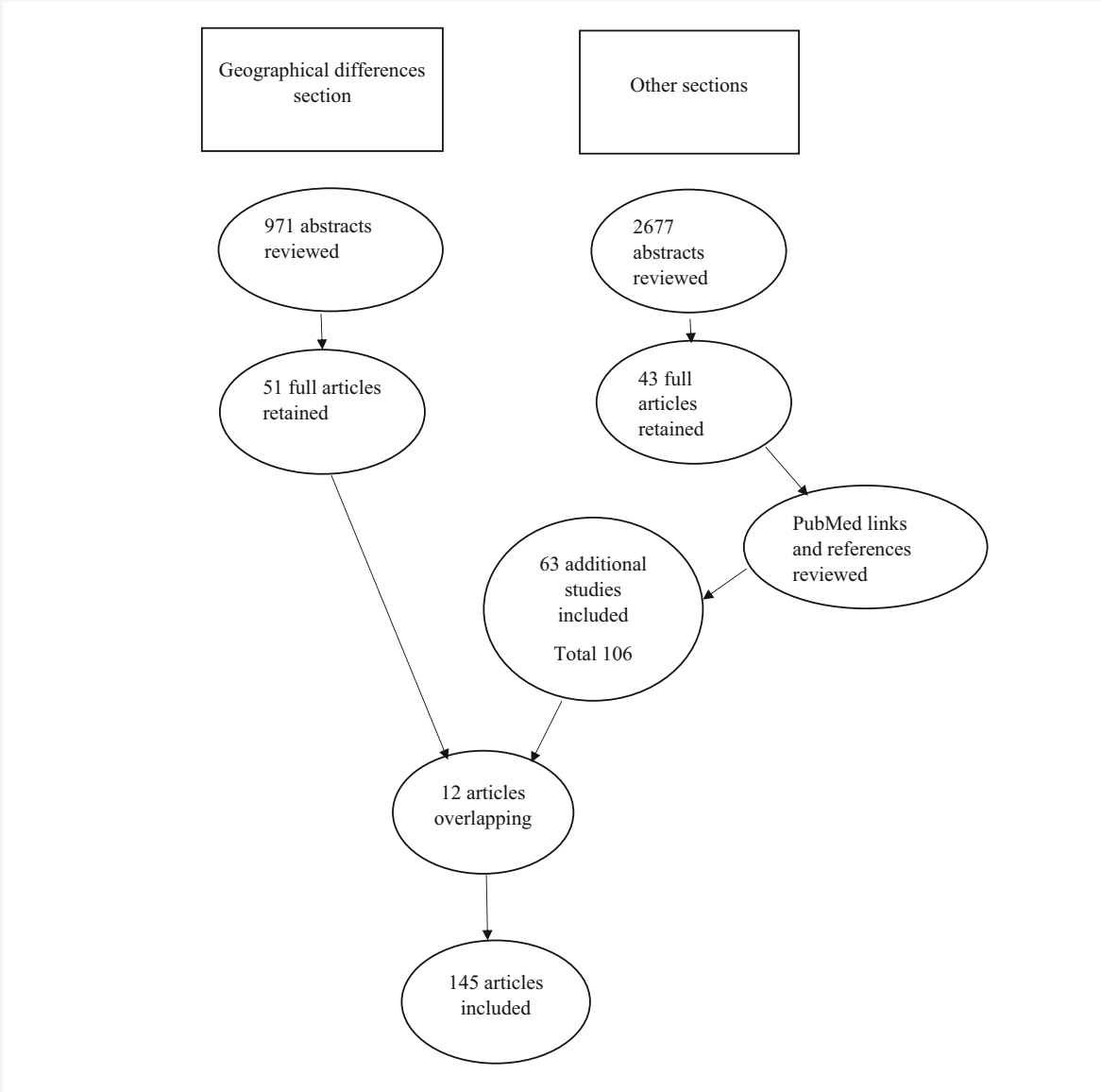

FIG. 1. Search strategy.

TABLE 1 *Considerations for nomenclature*

Young-onset Parkinson's disease (YOPD)
• Might stigmatize younger patients further as being "too young" to develop Parkinson's disease.
• Might stigmatize patients who are older than the age cutoff as being old, while many are still in their 50s or early 60s, with the definition of "old" being constantly revised with the progress of medical care and increase in life expectation.
Early-onset Parkinson's disease (EOPD)
• Delineates that Parkinson's disease developed earlier than average, without stigmatizing patients one way or the other.

studies use a cutoff of 40 years[73] or 45 years,[74] the vast majority of genetic studies in PD from various parts of the world use the age cutoff of younger than 50 years to define EOPD,[38,40,67,75,76,77–82] supporting the recommendation to use that age cutoff for the definition of EOPD.

Role of Sexual Hormones

The incidence of PD is 1.5 to 2.0 times higher in men than in women,[83,84] with women being less susceptible[85,86] to the disease and developing it later in life.[86,87] In addition, the incidence

TABLE 2 *EOPD age cutoff (in years) by country*

Country	Age cutoff for EOPD
Europe	
Belarus	40[30]
Belgium	50[31]
Croatia	40
Czech Republic	40–45[32–34]
Finland	55[21]
Germany	50[35]
Greece	50
Hungary	50[36]
Iceland	50[37]
Ireland	50[38]
Italy	40–50[22,39]
Kazakhstan	50[40]
Luxembourg	50[41]
Netherlands	40–50[18]
Norway	45[42]
Poland	40[43]
Portugal	50[44]
Russia	40[45,46]
Serbia	50[47]
Slovakia	40[48,49]
Spain	50[50]
Sweden	50[51]
United Kingdom	40–50[11]
Americas	
Argentina	40[52]
Brazil	20–45[53,54]
Canada	40[55]
Colombia	50[56]
Ecuador	50[56]
Mexico	45[57]
United States	40–55[14,15,17,25]
Asia-Pacific	
Middle East, North Africa, and South Asia: consensus from the MDS Task Force for the Middle East	50[58]
Australia	50[59]
China	40[60]
French Polynesia	51[61]
Guam	51[61]
India	40–50[62–64]
New Zealand	60[65]
South Korea	40–50[66]
Vietnam	50[67]
Japan	40–50[28]
Africa	
Morocco	45[68]
Nigeria	50[69]
South Africa	50[70]

There were no data published for countries not included in the table.
Abbreviation: EOPD, early-onset Parkinson's disease.

and prevalence of PD have been reported as higher in postmenopausal than in premenopausal women of similar age in multiple epidemiological studies.[88–90]

Many experimental and human observations suggest that estrogen may have a protective as well as a dopaminergic effect in PD,[91–104] whereas a smaller number suggests no benefit.[93,105–107] One cross-sectional study of 579 women with PD, 497 of whom developed menopause before PD onset, reported that later age of menopause was associated with older AAO and better *on* medication Unified Parkinson's Disease Rating Scale motor score.[108] In addition, a population-based study using the Mendelian randomization method reported that each year of delay in age at menopause was associated with a 7% decrease in PD risk.[109]

Regarding estrogen supplementation, a few studies[110–112] have shown that estrogen postmenopausal hormone replacement therapy (HRT) improves motor disability in women with PD, and a metanalysis of 14 observational studies reported that estrogen HRT did not increase the risk of PD.[107] On the other hand, progestin-only HRT seems to increase the risk of PD 3-fold in postmenopausal women.[113]

Taken together, these studies suggest that changes in the estrogen level can affect the predisposition to develop PD, making the average age at menopause of 50[114] another important factor to consider when defining the upper age cutoff for EOPD.

PD Clinical Features

Clinical features and their underlying biological mechanisms also need to be considered in the definition of the age cutoff for EOPD.

In a large retrospective study assessing the impact of AAO on clinical features and evolution of 593 patients, rigidity as the

predominant initial symptom was more frequent in patients with EOPD (AAO < 50), whereas gait instability as the predominant initial symptom was more frequent in patients with older onset PD.[14] There was no statistically significant difference in the frequency of tremor or bradykinesia as the predominant initial symptom among the groups, confirming results of previous studies[115] while contrasting with others whose results indicated both an increased or decreased rate of tremor in patients with earlier onset.[116–119] Another series of 422 patients reported as well that rigidity was a more frequent presenting symptom in the younger group (AAO < 50).[120] Dystonia has been suggested as a more frequent presenting symptom in EOPD (20% of patients with AAO < 45 vs. 3% of patients with AAO > 64) in a study of 358 patients. Within 2 years of onset, dystonia developed in an additional 11% of EOPD and 1% of late-onset PD (LOPD).[115] Most studies agree that patients with EOPD tend to have a slower progression of motor symptoms than those with LOPD.[121–127]

In addition, the prevalence of levodopa-induced dyskinesia (LID) was reported to decrease with advancing AAO, with a higher frequency before age 50. In 1 population-based study of 91 patients, the frequency of LID after 5 years of levodopa therapy was 40% in patients with PD onset before age 50, decreasing to 35.2% with an AAO between 50 and 69 years and 15.6% in patients with onset after 69 years.[128] Another study suggested that the risk of dyskinesia was reduced by 20% to 30% for each 10 years of older AAO.[129] In yet another series of 109 patients, the frequency of dyskinesia observed within 5 years of treatment was 80%, 26.7%, 22.7%, and 20% for onset between 40 and 49, 50 and 59, 60 and 69, and 70 and 79 years of age, respectively.[130] Finally, in a large retrospective study of 593 patients, dyskinesia developed in 70% of the patients with EOPD (AAO < 50), 34.1% of the patients with middle-onset PD (AAO 50–69), and 13% of the patients with LOPD (AAO > 69) ($P < 0.001$).[14] Similarly, treatment-related dystonia was 2 to 4 times more frequent in patients with PD with AAO < 50 compared with later AAO in that cohort,[14] whereas another cohort of 358 patients suggested that the risk for dystonia was highest with AAO < 48.[115]

Regarding nonmotor features, depression was reported twice as frequently in patients with EOPD (AAO < 50) than in patients with LOPD (AAO > 69).[14] Another controlled study similarly reported a higher rate of depression, worse emotional well-being, and poorer quality of life with AAO ≤ 45 years of age.[131] Finally, 1 Norwegian cohort reported that patients with EOPD (AAO < 50) had a longer survival but a reduced life expectancy compared with patients with later onset PD.[132] However, these data were not confirmed in a North American population study reporting a longer life expectancy in EOPD overall compared with LOPD.[15]

These clinical differences between EOPD and LOPD might have an anatomic substrate. Liu et al.[133] compared the striatal patterns of dopaminergic degeneration between 40 EOPD (AAO ≤ 50) and 47 LOPD (AAO > 50), as examined with ^{11}C-2β-carbomethoxy-3β-(4-fluorophenyl) tropane positron emission tomography (PET). Although dopamine transporter (DAT) scans from patients with LOPD showed relatively uniform involvement of both the caudate and putamen, the DAT scans of patients with EOPD showed more sparing of the caudate compared with the putamen. Given the involvement of the caudate in complex cognitive functions,[134–137] this might provide an explanation for the lower prevalence of these nonmotor symptoms in EOPD compared with LOPD.[17] On the other hand, a PET and 18F-fluorodopa scans study that included 27 patients aged 38 to 79 years reported a higher PD-induced increase in dopamine turnover compared with the decrease in dopamine synthesis and storage rate in patients of younger age compared with older patients. The authors suggested that this implied greater alteration of dopamine turnover in EOPD that could lead to larger swings in synaptic dopamine levels, which has been suggested as a possible contributor to a greater risk of motor fluctuations.[138]

Regarding a potential biochemical substrate separating EOPD from LOPD, a controlled study including 76 patients with PD and 75 sex- and age-matched controls reported that an AAO ≤ 50 was associated with lower levels of cerebrospinal fluid lactate and tau proteins,[139] providing biochemical support for using 50 years as an age cutoff.

Overall, the clinical data and their suggested underlying biological mechanisms support the use of AAO < 50 for the definition of EOPD as well.

Impact of PD on Employment and Social Perception

One last variable to consider in the determination of the upper age limit for EOPD is the impact on social perception and employment. Although the retirement age is usually approximately 65 years in most countries, using that age as the upper limit for EOPD would not be appropriate as the typical AAO of PD is in the early to mid-60s,[27] thus placing a cutoff of 65 years quite late in the natural history of the disease. In addition, the development of PD 3 years from retirement is unlikely to have the same impact on professional development than a diagnosis made 15 years earlier. Indeed, a study comparing 75 patients with EOPD (AAO < 50) and 66 patients with LOPD (AAO ≥ 50) reported that, among those who retired, 97% of the patients with EOPD retired early versus 73% of those with LOPD ($P = 0.003$).[19] Other studies have found that 54% of patients with EOPD retire early, and 94% are likely to give up work within 10 years of disease onset, with patients with AAO < 45 years likely to stop working on average 6 to 7 years after diagnosis.[140]

In a retrospective cohort review of 88 Irish patients with PD with AAO < 65 years, men aged 55 to 64 years were twice as likely to be unemployed than the general population, whereas unemployment among women was not significantly affected by PD. The authors also found that the median time

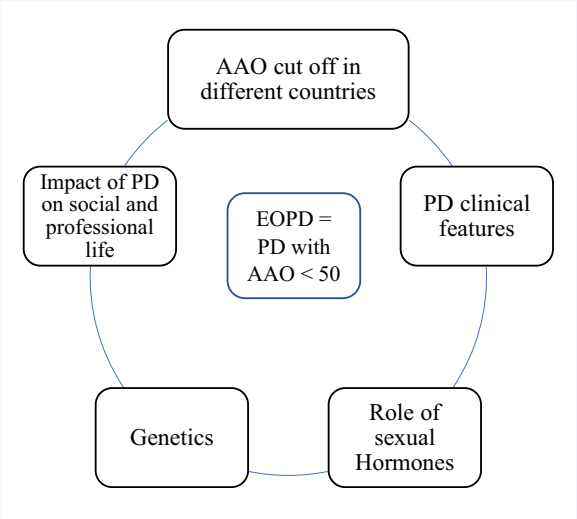

FIG. 2. Interplay of factors leading to defining EOPD as AAO < 50. EOPD, early-onset Parkinson's disease; AAO, age at onset; PD, Parkinson's disease.

to loss of employment was 7 years, with 40% still employed after 5 years from onset and 14% after 10 years. Among those who were still working at the time of the study, 77% had made adjustments at work. Of those who had stopped working as a result of PD, 82% were dissatisfied with their unemployment status.[141]

The burden of unemployment from EOPD goes beyond a financial cost, including social isolation, feelings of futility, lack of purpose and self-esteem, and lack of daily structure. Many patients with PD are most bothered by the perception that others might have of their impairment than by their impairment itself.[141,142] This higher level of stigma in patients with EOPD[17,143] seems to stem essentially from dysarthria, tremor, dyskinesia, and impact of the motor symptoms on activities of daily living such as eating and washing[144] and can manifest as a reluctance to seek help and ask for adjustments at work, which in turn decreases the chances of staying employed.

In a prospective 50-item survey aimed at clarifying patients' concerns in 222 individuals with PD, patients with EOPD (AAO < 50) reported significantly more concerns about difficulty with speaking ($P = 0.003$), washing and bathing ($P = 0.04$), or eating ($P = 0.003$) as well as with shaking ($P = 0.005$), dyskinesia ($P = 0.001$), low and/or depressed mood ($P = 0.01$), and anxiety and/or panic attacks ($P < 0.001$)—factors more likely to impact social or professional functioning—as greater concerns than typical-onset patients with PD.[144]

Finally, EOPD may present a challenge to relationships. Marriages or relationships of shorter duration can be more vulnerable to the strain a chronic illness can impose than those of longer duration,[145] with significantly worse marital discord scores in couples with EOPD than in those with LOPD in 1 study comparing 75 patients with EOPD (<50 years) and 66 patients with LOPD.[19] The impact of the generational difference on these results cannot be excluded because of the absence of a healthy control.[18] A retrospective study comparing 272 patients with EOPD (AAO < 50) and 690 patients with LOPD (AAO > 70) reported less caregiver strain in the EOPD group.[127] However, LOPD and their frequently similarly aged caregivers are each at greater risk of more medical comorbidities and financial strain, which are big contributors to caregiver strain and could be confounding factors.

In summary, considering the differential impact of the AAO of PD on professional and social life, using onset before age 50 years as the upper cutoff for the definition of EOPD seems reasonable (Fig. 2).

Conclusion

After careful review of the available literature and deliberation, the Early Onset Parkinson Disease Task Force created by the MDS recommends the use of early-onset Parkinson's disease instead of young-onset Parkinson's disease. Furthermore, after considering hormonal, clinical, and genetic factors as well as the differential impact of the AAO of PD on professional and social life, this task force recommends using an AAO before 50 years for the definition of EOPD. This task force hopes that these recommendations regarding nomenclature and definition will help uniformize future research on the specific challenges and unmet needs of this subset of patients with PD as well as guide and harmonize future research and other initiatives.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Disclosures

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