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Cognitive and functional changes in prediagnostic phase of Parkinson Disease: A population-based study.

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ABSTRACT

Introduction: Prodromal non-motor symptoms precede, often by decades, motor signs and diagnosis of Parkinson's disease. It is however still uncertain if cognitive changes belong to the spectrum of non-motor prodromal Parkinson's disease. Thanks to the very long-term follow-up of the PAQUID population-based cohort, we assessed trajectories of cognitive complaints and functioning over a 13-year period before the diagnosis of late onset Parkinson's disease.

Methods: This study relies on a matched nested case-control sample selected from the cohort. Of the 3,777 initial subjects of the cohort, 43 developed incident Parkinson's disease over the follow-up. The mean age at diagnosis was 78.0 (standard deviation= 5.8) years and 46.5% were men. These cases were matched to 86 elderly control subjects. Scores of different cognitive domains, daily function, and depressive symptoms were described throughout the follow-up using mixed-effects models.

Results: No significant global cognitive decline preceded the diagnosis of late onset Parkinson's disease. However, psychomotor speed appeared significantly slower 2 years before the diagnosis and depressive symptoms 12 years before. Global score of instrumental activities of daily living became altered 2-3 years preceding the diagnosis of late onset Parkinson's disease, including the use of public transportation that was altered ten years before the diagnosis.

Conclusion: In late onset Parkinson's disease, while global cognitive functions seem preserved, psychomotor speed starts to decline 2 years before the diagnosis and activities of daily living are also impacted. Depressive symptoms appear very early in the prediagnostic phase.

1. Introduction

Cognitive impairment represents the main non-motor burden of late-stage Parkinson's disease (PD), particularly in late-onset disease. It is associated with health-related quality of life deterioration, poor functional prognosis, institutionalization and increased mortality [1, 2]. Some studies also reported the existence and the prognosis value of early cognitive changes in PD. It can be observed in 15-42 % of patients at the time of diagnosis, even before any treatment has begun [3, 4]. Moreover, some authors hypothesized that cognitive changes may even be observed before the diagnosis and thus may belong to the clinical spectrum of the premotor prodromal phase of PD [5].

Prodromal PD can start decades before diagnosis and typically includes non-motor symptoms such as rapid-eye-movement (REM) sleep behaviour disorder, hyposmia or depression [6, 7]. However, in contrast to other non motor symptoms, cognitive symptoms are less understood as prodromal signs of PD. Out of several studies that investigated cognition in early stage PD [8, 9], only two population-based studies investigated cognitive changes in the prediagnostic phase of PD [10, 11]. They observed that motor features appeared two to four years before the diagnosis of PD, while no cognitive changes in the prediagnostic phase of PD manifested clearly.

A better knowledge of non-motor symptoms such as cognitive impairment in the pre-diagnostic phase of PD in addition to other markers such as (REM) sleep behaviour disorder or hyposmia may help at identifying at-risk individuals. The result may be a better timing for neuroprotective trials i.e. before substantial neuronal loss has occurred [12, 13]. It may also improve our understanding of the pathophysiological mechanisms of prodromal PD. In this context, it is important to determine whether or not cognitive changes appear at the prodromal phase of PD. In the present study, we assessed trajectories of cognitive and functional changes

over a 13-year period before the diagnosis of PD, thanks to the very long-term follow-up of the PAQUID population-based cohort [2, 14].

2. Methods

2.1. Study population and Protocol

The PAQUID cohort consists of a population-based sample of 3,777 French community-dwelling individuals aged 65 and older [15]. The Paquid study protocol was approved by the ethic committee of the Bordeaux University Hospital, and all participants gave their informed consent. Subjects were evaluated at home at the initial visit (V0) and at 1 (V1), 3 (V3), 5 (V5), 8 (V8), 10 (V10), 13 (V13) and 15 (V15) years by trained investigators. At each visit, items related to basic demographic data, personal medical history, current symptoms and diseases, and medications were collected. In addition, tests and scales of cognitive performances, cognitive complaints, functional abilities, and depressive symptomatology were assessed.

2.1.1. Assessment of cognitive function

The cognitive function was evaluated by the following tests and scales. The Mini-Mental State Examination (MMSE) was used as an index of global cognitive performance [16]. The recognition form of the Benton Visual Retention Test measured short-term visual memory. The Isaacs Set Test (IST), which consists in generating words belonging to semantic categories in 15 seconds, measured semantic verbal fluency. The Wechsler Similarities test (WST) (first five pairs), which consists in saying in what way two things are alike, measured conceptual knowledge. The Zazzo's cancellation test (ZCT) [17] consisting in cancelling target signs randomly distributed among distractors measured selective attention test and psychomotor speed (2 scores were used: the number of accurately identified target signs and the time to perform the task). The Digit Symbol Substitution Test (DSST) exploring attention

and psychomotor speed consists in digit-symbol pairs followed by a list of digits. Under each digit the participant is asked to write down the corresponding symbol as fast as possible. The number of correct symbols within 90 sec was collected. All the cognitive tests were assessed at each follow-up except for ZCT and DSST which were not available at V3.

2.1.2. Assessment of cognitive complaints

Cognitive complaints were assessed by a questionnaire requiring participants to rate their own perception of their current cognitive difficulties from 3 items of the questionnaire, each ranging from 0 (no perceived difficulty) to 2 (perceived difficulty with a complaint to the doctor): (i) forgetfulness in daily living, (ii) perceived difficulties in learning new information, and (iii) perceived difficulties in word finding. The score ranges from 0 to 6 points.

2.1.3. Assessment of depressive symptoms

Depressive symptomatology was assessed using the Centre for Epidemiologic Studies-Depression Scale (CESD); the score ranges from 0 to 60.

2.1.4. Assessment of functioning level

The functioning level was assessed with the French version of the Lawton's scale of Instrumental Activities of Daily Living (IADL): we used four IADL, including telephone use, transportation, medication, and domestic finances, which have been shown to correlate with cognitive performance [18]. A score was calculated by summing the grades of dependency for each activity; the score ranges from 4 (no disability) to 15 (high disability). We evaluated also each IADL separately.

2.1.5. *Diagnosis of Parkinson's disease*

All incident cases of parkinsonism were identified by a standardized procedure and subsequently validated by a committee of experts as previously described in details [14]. Briefly, the diagnosis of probable PD was made according to the UKPDSBB criteria [19] which require at least akinesia/bradykinesia plus one of three other cardinal signs, no other cause of parkinsonism and supportive features such as tremor at rest, initial asymmetry of symptoms, initial good/excellent (>50%) response to L-Dopa or to other dopaminergic drugs, and a coherent evolution of symptoms during follow-up (long-term drug response, L-Dopa-induced dyskinesia, slow progression of disability). The response to L-Dopa was based on the data collected as part of the study and from medical records and was confirmed by a contact with the general practitioner taking care of the subject. Other differential diagnoses considered were secondary parkinsonism, mainly vascular parkinsonism and drug-induced parkinsonism, but also atypical parkinsonian syndrome such as Lewy body disease (LBD), multiple system atrophy or supra nuclear palsy, as no other secondary cause was found [14]. The overall age- and sex-adjusted incidence rate of PD in the PAQUID Study is 2.6 per 1000 person-years [14], within the range found in two other longitudinal cohort studies enrolling people over 65 years [20, 21].

2.1.6. Study protocol

This study relies on a matched nested case-control sample selected from the cohort. Data from baseline screening (V0) were not included because of the “first-passing effect” on neuropsychological tests [22]. The first follow-up visit (V1) was considered as the baseline visit. To be included in the incident PD sample, participants had to have the following characteristics: (1) To be diagnosed without any parkinsonian syndrome at the baseline visit (V1); (2) to be diagnosed with PD at any follow-up visits in the subsequent 15 years (i.e., at

V3, V5, V8, V10, V13, or V15); and (3) to be diagnosed without any parkinsonian syndrome at the visit just prior to PD diagnosis. Two healthy controls (HC) were selected for each PD case at the diagnosis visit of the case (matching visit); to be included in the HC sample, participants had to have the following characteristics: (1) To match with an incident PD case according to age (± 5 years), sex, and education (three classes: no diploma, primary educational level, higher); (2) to be free of PD or other parkinsonian syndromes and dementia diagnosis at the matching visit; and (3) to be diagnosed free of PD and dementia at the follow-up visit just after the matching visit.

2.2. Statistical analysis

The evolution of cognitive, functional, and depression scores is described throughout 13 years. The time of follow-up ranges from T-13 years to T0, where 0 is the time at diagnosis for the incident cases of PD and the matching visit for the HC. Longitudinal analyses of the different measures were done using a latent process mixed model, an extension of the mixed-effects linear model for longitudinal outcomes that accounts for the intra-subject correlation of repeated measures and handles non Gaussian outcomes [23]. Each observed score is assumed to be a non-linear transformation of a latent Gaussian variable. The change over time of the latent variable (the normalized score) is described by a linear mixed model with a subject-specific quadratic function of time. To account for possible different evolution of PD and HC over time, each model includes an interaction between the PD status and the quadratic function of time (without further adjustment for covariates). The non-linear transformation is either a flexible continuous link function defined by a combination of I-splines for quantitative scores or a probit link function for ordinal scores. The parameters from the transformation function and from the linear mixed models are estimated simultaneously. We were able to test (i) whether the evolution over time of each score differed in PD compared to HC using a Wald test on time and time squared, and (ii) whether the predicted levels of each

score at different times differed in PD compared to HC at different times. For each trajectory, only the 12 years prior to the diagnosis of PD were shown in the figures because there were too few cases 13 years prior to diagnosis. Analyses were done in R with essentially `lcm` function of `lcm` R package for fitting the latent process mixed models. Parameter estimates were tested at the 5% significance level using univariate or multivariate Wald tests [24].

3. Results

3.1. Sample Description

Of the 3,777 initial participants of the cohort, 43 have developed incident PD during the 14 years of follow-up. The mean age at diagnosis was 78.0 (standard deviation (SD) = 5.8) years, 46.5% were men, 37.2% had no diploma. The PD cases were matched to 86 HC (Figure 1 and Table e-1).

3.2. Evolution of cognitive functioning scores

Figure 2 displays respectively the evolution of the MMSE and BVRT scores, representing global cognitive scores, among the 43 incident PD cases and their 86 matched HC. There were no differences in cognitive evolution before the diagnosis of PD between cases and HC, regardless of these cognitive tests (Table e-1).

Figure 3 displays the WST score, the IST score, the DSST score, the ZCT score and the ZCT time score in our population study. Among all these cognitive tests, only the ZCT time score significantly differed in incident PD compared to the HC about 2 years before the diagnosis even if group-by-time interaction was not significant (P-value= 0.09 for group-by-time interaction). Mean time to perform the ZCT increased with ageing of the cohort; whereas the increase was very modest in the HC, it grew regularly and linearly in future PD subjects and became significantly higher than that of HC two years before the diagnosis. However, the ZCT score did not differ between the two groups with a similar evolution over time: an

increase score followed by a slight decrease. The WST score remained stable over time in both groups whereas the IST score and the DSST score decreased over time.

3.3. Evolution of depressive symptoms

As shown on figure 4, as 12 years before the diagnosis, the mean score of depressive symptoms of the future PD subjects was significantly higher all along the 12-year pre-diagnosis period compared to HC without difference between the both trajectories (p-value= 0.52 for group-by-time interaction).

3.4. Evolution of the memory complaints

The evolution of the memory complaints score in incident PD subjects and HC is shown in Figure 4 (right panel). Even if globally, the evolution of memory complaints was not significantly different between the both groups (p-value = 0.09 for group-by-time interaction), compared to HC, future PD subjects presented a significant higher memory complaint score between 12 to 4 years before the diagnosis. From then this difference disappeared, memory complaints of PD subjects decreasing over the time before the diagnosis.

3.5. Evolution of the IADL Score

The trajectories of the total IADL score (including telephone use, medication, family budget and transportation) between the future PD subjects and the HC were not significantly different over time (p-value = 0.71 for group-by-time interaction for the total score of IADL. But, about 2 to 3 years before the diagnosis, the total score of IADL increased in favour of appearance of functional dependence for future PD subjects compared to HC (Figure 5). Taken individually, we did not find any difference for the IADL sub-score of telephone use, medication or domestic finances between the two groups. Only the score evaluating

transportation became significantly different (higher disability) 10 years before the diagnosis for future PD subjects compared to HC.

4. Discussion

Thanks to the long-term follow-up of the PAQUID cohort, we reported trajectories of cognition, cognitive complaints, depressive symptoms and daily functioning in the prediagnostic phase of PD. Over the 12-year period preceding the diagnosis, future PD presented more depressive symptoms than HC and 8 years before the diagnosis (between 12 years to 4 years) they declared more memory complaints. Ten years before the diagnosis, prodromal PD showed a higher functional impairment in transportation and ability to travel outside home and 3 years before the diagnosis, an extension of the difficulties to IADLs. Concerning cognition, the impairment concerns exclusively the time performance in the ZCT, significantly slower compared to HC, 2 years before the diagnosis of PD; whereas we did not find significant change on the visuo-spatial memory, verbal fluency or abstract thinking.

At the time of diagnosis, it is well known that numerous cognitive domains are impaired in particular attention, executive functions, psychomotor speed and retrieval processes of memory [25, 26]. Regarding the prediagnostic phase however, very little is known as underlined by several reviews [12, 27]. Several prodromal PD studies reported either impairment in global cognition [28], or in executive function [29], in the group at risk (defined by risk factors and early non motor features in PREDIC-PD study or hyposmia and reduced dopamine transporter binding in PARS study) compared to healthy controls.

However, these studies did not provide information on the phenoconversion of these individuals considered at high risk, in particular the proportion of future PD and future LBD cases. This point seems crucial when taking into account the results of the large cohort study of idiopathic REM sleep behaviour disorder (RBD) studied by Postuma et al. [30]. While the authors found slight differences between future PD and LBD concerning motor variables,

hyposmia or dysautonomia, they found striking differences regarding cognition, which was preserved in future PD but altered in future LBD [30]. Limited knowledge on prodromal cognition in PD may be due to the lack of longitudinal studies having properly followed-up the patients several years before the full diagnosis of PD in an unselected population. We have identified only two such population-based prospective cohort studies: the Honolulu-Asia-Aging study and the Rotterdam Study [10, 11]. In the Honolulu-Asia-Aging they found no detectable global cognitive impairment in future PD compared to the control elderly population (evaluated by Cognitive Abilities Screening Instrument, CASI), only a lower executive function performance (composite score) was associated with the risk of development of PD. In the Rotterdam study, the future PD subjects tended to show a decline in the MMSE and the Stroop test task, 1 to 3 years before the diagnosis of PD, and to have more depressive symptoms at the time of diagnosis, but results were not statistically significant. They observed that bradykinesia and rigidity appeared 2 to 4 years before the diagnosis of PD. IADL (notably travelling) were affected 4 to 6 years before the diagnosis [11]. Other psychometric tests (the Letter Digit Substitution Test, word fluency test) or memory complaints were unchanged. Nonetheless, as mentioned by the authors themselves, the tests evaluating the attention-executive function were under-represented in their study. In our study, thanks to a more complete battery, we observed that while no major changes could be found in nearly all the tests considered, a decrease in time performance to the ZCT could be observed about 2 years before diagnosis of PD, reflecting a psychomotor alteration. The ZCT relying on both psychomotor speed and selective attention processes, it is difficult to disentangle what aspect is involved in such a performance decrease. Noteworthy, this slowing in performance was however not accompanied by a decrease in accuracy since no increase of errors was found. In both groups, we found rather an increase in the ZCT score over time before a secondary decrease. A similar slope shape for ZCT score and similar slowing in the

ZCT were found in the same cohort in pre-demented subjects, 3 years before the diagnosis of any causes of dementia. These results were in favour of a learning effect in an automatic task but with an isolated psychomotor slowing [31]. Concerning the neural substrates, the presence of a psychomotor slowing or an impairment in daily functioning in the prediagnostic phase of PD may be partially mediated by early extrastriatal disease pathology or nondopaminergic systems as supported by animal studies [32]. Furthermore, abnormalities in noradrenergic or cholinergic pathways have been implicated in cognitive dysfunction in early stage of PD and in Braak's pathologic staging, the involvement of these neurotransmitter systems occurs in stage 2 or 3 in premotor PD phase [33]. Nevertheless, cognitive slowing speed has been associated with an increased risk of developing various brain outcomes: dementia, AD, PD, disability, depressive symptoms potentially mediated by a variety of pathophysiological abnormalities including inflammatory biomarkers, white matter lesions, lobar microbleeds, regional leukoaraiosis, reduced myelin integrity, beta-amyloid deposition and reduced interhemispheric connectivity [34]. Taken together, neural substrates of psychomotor slowing in prodromal phase of PD may be due to extrastriatal pathology involving noradrenergic or cholinergic pathways or may not be specific of one particular pathophysiologic process but may be a marker of brain vulnerability.

From a functional point of view, this psychomotor slowing may contribute to impair the IADL transportation item in the prediagnosis phase of PD, while more cognitively demanding IADL seemed preserved until 3 years before the diagnosis. However this speculation needs further confirmation in a dedicated study.

Depressive symptoms in prodromal phase of PD diagnosis should also be discussed. Several [7, 13, 35] but not all [36] studies reported results supporting the hypothesis that depression may be a risk factor as well as a prodromal symptom of PD. The fact that we observe a significant difference in future PD compared to controls as early as 12 years before the

diagnosis, is more in favour of the risk factor. However, the presence of depressive symptoms over the prodromal phase of PD could impact cognition or memory complaints. When the trajectories of memory complaints of future PD and HC were adjusted on CESD score overtime (results in supplementary material, Figure e-1), the difference between both groups disappeared, which seems in favour of a consequence of depressive symptoms on memory. Nevertheless, the depressive symptoms did not explain the psychomotor speed slowing because the difference on ZCT time score between the future PD and the HC remained present even after adjustment on CESD score over time (Figure e-2). At the time of onset of psychomotor slowing in future PD, we also observed an increase in the intensity of depressive symptoms (Figure 4). The presence of depressive symptoms long before the diagnosis of PD could be considered as a risk factor; however, the recrudescence of depressive symptoms 2-3 years before the diagnosis could rather be a consequence. This could explain the U-shaped trajectory of depressive symptoms in the prodromal phase of PD.

Strengths of our study include (1) a long term follow-up before the diagnosis of PD in such a population-based cohort; (2) a comprehensive and prospective procedure to diagnose PD and to exclude alternative diagnoses; and (3) repeated neuropsychological assessments with exploration of several cognitive domains. Our study has however several limitations: (1) the low number of incident PD cases observed [14] and (2) a non-exhaustive battery of cognitive tests, which was originally designed to explore instrumental rather than executive functions alterations. Indeed, global cognition was explored by the MMSE, while a test more sensitive to dysexecutive changes such as the MOCA would have been more suitable [37]; moreover exploration of verbal memory was lacking. These limits are explained by the population-based epidemiological setting of the study, the knowledge and literature at the time of study design (25 years ago) and the fact that the cohort was originally designed for the study of dementia of the Alzheimer's type. Also, our results are only transposable to an elderly PD

population aged over 65; it is unknown if these results are applicable to a younger PD population.

In conclusion, this population-based study with a long-term follow-up is one of the few studies that explores cognition, cognitive complaints, depressive symptoms and functioning more than ten years before the diagnosis of late onset PD. While global cognition is preserved in the prodromal phase of PD, psychomotor slowing starts about two years before diagnosis and depressive symptoms appear very early in the process. Psychomotor speed tests might be therefore more useful than global cognitive function tests as predictive tools for PD diagnosis in an elderly population at high risk and/or with prodromal symptoms. This needs however to be further explored in specifically designed cohorts.

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Documentation of author roles

Alexandra Foubert-Samier was involved in data collection, analysis, data interpretation and writing of the initial draft. Catherine Helmer was involved in data collection, analysis and data interpretation. Mélanie Le Goff was involved in data collection and analysis and data interpretation. Florian Guillet was involved in analysis and data presentation. Cécile Proust-Lima was involved in analysis and data presentation. Hélène Jacqmin-Gadda was involved in analysis and data interpretation. Hélène Amieva was involved in design and data collection, and data interpretation. Jean-François Dartigues was involved in design, data collection and analysis; data interpretation and writing of the initial draft. François Tison was involved in data collection, data interpretation and writing the initial draft. All authors read and approved the final version of the manuscript.

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REFERENCES

- [1] A.W. Willis, M. Schootman, N. Kung, B.A. Evanoff, J.S. Perlmutter, B.A. Racette, Predictors of survival in patients with Parkinson disease, *Arch. Neurol.* 69 (2012) 601-607.
- [2] F. Perez, C. Helmer, A. Foubert-Samier, S. Auriacombe, J.F. Dartigues, F. Tison, Risk of dementia in an elderly population of Parkinson's disease patients: a 15-year population-based study, *Alzheimers Dement.* 8 (2012) 463-469.
- [3] A.J. Yarnall, D.P. Breen, G.W. Duncan, T.K. Khoo, S.Y. Coleman, M.J. Firbank, C. Nombela, S. Winder-Rhodes, J.R. Evans, J.B. Rowe, B. Mollenhauer, N. Kruse, G. Hudson, P.F. Chinnery, J.T. O'Brien, T.W. Robbins, K. Wesnes, D.J. Brooks, R.A. Barker, D.J. Burn, I.-P.S. Group, Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study, *Neurology* 82 (2014) 308-316.
- [4] M. Poletti, D. Frosini, C. Pagni, F. Baldacci, V. Nicoletti, G. Tognoni, C. Lucetti, P. Del Dotto, R. Ceravolo, U. Bonuccelli, Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naïve patients with Parkinson's disease, *J. Neurol. Neurosurg. Psychiatry* 83 (2012) 601-606.
- [5] B. Hanna-Pladdy, K. Jones, R. Cabanban, R. Pahwa, K.E. Lyons, Predictors of mild cognitive impairment in early-stage Parkinson's disease, *Dement. Geriatr. Cogn. Dis. Extra.* 3 (2013) 168-178.
- [6] A. Iranzo, J.L. Molinuevo, J. Santamaria, M. Serradell, M.J. Marti, F. Valldeoriola, E. Tolosa, Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study, *Lancet Neurol.* 5 (2006) 572-577.
- [7] H. Gustafsson, A. Nordstrom, P. Nordstrom, Depression and subsequent risk of Parkinson disease: A nationwide cohort study, *Neurology* 84 (2015) 2422-2429.
- [8] K.F. Pedersen, J.P. Larsen, O.B. Tysnes, G. Alves, Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study, *JAMA Neurol.* 70 (2013) 580-586.
- [9] A. Hanganu, C. Bedetti, C. Degroot, B. Mejia-Constain, A.L. Lafontaine, V. Soland, S. Chouinard, M.A. Bruneau, S. Mellah, S. Belleville, O. Monchi, Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally, *Brain* 137 (2014) 1120-1129.
- [10] G.W. Ross, R.D. Abbott, H. Petrovitch, C.M. Tanner, L.R. White, Pre-motor features of Parkinson's disease: the Honolulu-Asia Aging Study experience, *Parkinsonism. Relat. Disord.* 18 (2012) S199-202.

- [11] S.K. Darweesh, V.J. Verlinden, B.H. Stricker, A. Hofman, P.J. Koudstaal, M.A. Ikram, Trajectories of prediagnostic functioning in Parkinson's disease, *Brain* 140 (2017) 429-441.
- [12] S. Fengler, I. Liepelt-Scarfone, K. Brockmann, E. Schaffer, D. Berg, E. Kalbe, Cognitive changes in prodromal Parkinson's disease: A review, *Mov. Disord.* 32 (2017) 1655-1666.
- [13] A.Schrag, L. Horsfall, K. Walters, A. Noyce, I. Petersen, Prediagnostic presentations of Parkinson's disease in primary care: a case-control study, *Lancet Neurol.* 14 (2015) 57-64.
- [14] F. Perez, C. Helmer, J.F. Dartigues, S. Auriacombe, F. Tison, A 15-year population-based cohort study of the incidence of Parkinson's disease and dementia with Lewy bodies in an elderly French cohort, *J. Neurol. Neurosurg. Psychiatry.* 81 (2010) 742-746.
- [15] J.F. Dartigues, M. Gagnon, P. Barberger-Gateau, L. Letenneur, D. Commenges, C. Sauvel, P. Michel, R. Salamon, The Paquid epidemiological program on brain ageing, *Neuroepidemiology* 11 (1992) 14-18.
- [16] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, *J. Psychiatr. Res.* 12 (1975) 189-198.
- [17] Zazzo, Test des deux barrages. Actualités pédagogiques et psychologiques, Delachaux et Nestlé, Neuchâtel, 1974.
- [18] P. Barberger-Gateau, D. Commenges, M. Gagnon, L. Letenneur, C. Sauvel, J.F. Dartigues, Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers, *J. Am. Geriatr. Soc.* 40 (1992) 1129-1134.
- [19] W.R. Gibb, A.J. Lees, The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease, *J. Neurol. Neurosurg. Psychiatry.* 51 (1988) 745-752.
- [20] J. Benito-Leon, F. Bermejo-Pareja, J.M. Morales-Gonzalez, J. Porta-Etessam, R. Trincado, S. Vega, E.D. Louis, G. Neurological Disorders in Central Spain Study, Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain, *Neurology* 62 (2004) 734-741.
- [21] L.M. de Lau, P.C. Giesbergen, M.C. de Rijk, A. Hofman, P.J. Koudstaal, M.M. Breteler, Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study, *Neurology* 63 (2004) 1240-1244.
- [22] H. Jacqmin-Gadda, C. Fabrigoule, D. Commenges D, J.F. Dartigues, A 5-year longitudinal study of the Mini-Mental State Examination in normal aging, *Am. J. Epidemiol.* 145 (1997) 498-506.
- [23] C. Proust-Lima, V. Philipps, B. Liqueur, Estimation of extended mixed models using latent classes and latent processes., the R Package lamm. *Journal of Statistical Software* 78 (2017) 1-56.
- [24] C. Proust-Lima, V. Philipps, J.F. Dartigues, D.A. Bennett, M.M. Glymour, H. Jacqmin-Gadda, C. Samieri, Are latent variable models preferable to composite score approaches when assessing risk factors of change? Evaluation of type-I error and statistical power in longitudinal cognitive studies, *Stat. Methods Med. Res.* (2017) 962280217739658.
- [25] I. Litvan, D. Aarsland, C.H. Adler, J.G. Goldman, J. Kulisevsky, B. Mollenhauer, M.C. Rodriguez-Oroz, A.I. Troster, D. Weintraub, MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI, *Mov. Disord.* 26 (2011) 1814-1824.
- [26] D. Muslimovic, B. Post, J.D. Speelman, B. Schmand, Cognitive profile of patients with newly diagnosed Parkinson disease, *Neurology* 65 (2005) 1239-1245.
- [27] D. Weintraub, A.I. Troster, C. Marras, G. Stebbins, Initial cognitive changes in Parkinson's disease, *Mov. Disord.* 33 (2018) 511-519.
- [28] A.J. Noyce, A. Schrag, J.M. Masters, J.P. Bestwick, G. Giovannoni, A.J. Lees, Subtle motor disturbances in PREDICT-PD participants, *J. Neurol. Neurosurg. Psychiatry* 88 (2017) 212-217.
- [29] L.M. Chahine, D. Weintraub, K.A. Hawkins, A. Siderowf, S. Eberly, D. Oakes, J. Seibyl,

M.B. Stern, K. Marek, D. Jennings, PARS Investigators, Cognition in individuals at risk for Parkinson's: Parkinson associated risk syndrome (PARS) study findings, *Mov. Disord.* 31 (2016) 86-94.

[30] R.B. Postuma, A. Iranzo, M. Hu, B. Högl, B.F. Boeve, R. Manni, W.H. Oertel, I. Arnulf, L. Ferini-Strambi, M. Puligheddu, E. Antelmi, V. Cochen De Cock, D. Arnaldi, B. Mollenhauer, A. Videnovic, K. Sonka, K.Y. Jung, D. Kunz, Y. Dauvilliers, F. Provini, S.J. Lewis, J. Buskova, M. Pavlova, A. Heidbreder, J.Y. Montplaisir, J. Santamaria, T.R. Barber, A. Stefani, E.K. St Louis, M. Terzaghi, A. Janzen, S. Leu-Semenescu, G. Plazzi, F. Nobili, F. Sixel-Doering, P. Dusek, F. Bes, P. Cortelli, K. Ehgoetz Martens, J.F. Gagnon, C. Gaig, M. Zucconi, C. Trenkwalder, Z. Gan-Or, C. Lo, M. Rolinski, P. Mahlknecht, E. Holzkecht, A.R. Boeve, L.N. Teigen, G. Toscano, G. Mayer, S. Morbelli, B. Dawson, A. Pelletier, Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study, *Brain* 142 (2019) 744-759.

[31] H. Amieva, H. Mokri, M. Le Goff, C. Meillon, H. Jacqmin-Gadda, A. Foubert-Samier, J.M. Orgogozo, Y. Stern, J.F. Dartigues, Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline, *Brain* 137 (2014) 1167-1175.

[32] X. Li, L. Redus, C. Chen, P.A. Martinez, R. Strong, S. Li, J.C. O'Connor, Cognitive dysfunction precedes the onset of motor symptoms in the MitoPark mouse model of Parkinson's disease, *PLoS One* 15 (2013) e71341.

[33] H. Braak, E. Ghebremedhin, U. Rüb, H. Bratzke, K. Del Tredici, Stages in the development of Parkinson's disease-related pathology, *Cell. Tissue Res.* 18 (2004) 121-134.

[34] H. Amieva, C. Meillon, C. Proust-Lima, J.F. Dartigues, Is Low Psychomotor Speed a Marker of Brain Vulnerability in Late Life? Digit Symbol Substitution Test in the Prediction of Alzheimer, Parkinson, Stroke, Disability, and Depression, *Dement. Geriatr. Cogn. Disord.* 47 (2019) 297-305.

[35] F. Fang, Q. Xu, Y. Park, X. Huang, A. Hollenbeck, A. Blair, A. Schatzkin, F. Kamel, H. Chen, Depression and the subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study, *Mov. Disord.* 25 (2010) 1157-1162.

[36] J.H. Bower, B.R. Grossardt, D.M. Maraganore, J.E. Ahlskog, R.C. Colligan, Y.E. Geda, T.M. Therneau, W.A. Rocca, Anxious personality predicts an increased risk of Parkinson's disease, *Mov. Disord.* 25 (2010) 2105-2113.

[37] S. Hoops, S. Nazem, A.D. Siderowf, J.E. Duda, S.X. Xie, M.B. Stern, D. Weintraub, Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease, *Neurology* 73 (2009) 1738-1745.

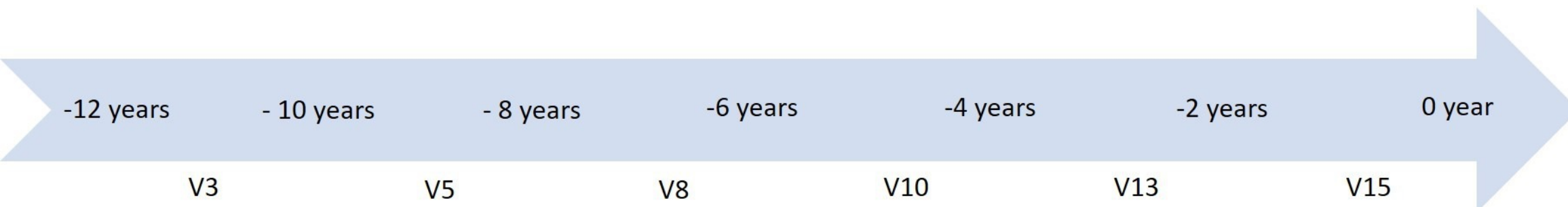
Figure 1: Number of incident Parkinson's disease cases and healthy controls (HC) participating across visits (Follow-up in years before the diagnosis of Parkinson's disease)

Figure 2 For each cognitive test, MMSE and BVRT, the results are presented as estimated evolution of mean score and 95% confidence interval (CI) over the 13 years preceding the diagnosis of Parkinson's disease (PD; green curve for future PD subjects; grey curve for healthy control subjects).

Figure 3 Performances on WST score, on IST score, on DSST score, ZCT score and on ZCT time score are presented as estimated evolution of mean score and 95% confidence interval (CI) over the 13 years preceding the diagnosis of Parkinson's disease (PD; green curve for future PD subjects; grey curve for healthy control subjects).

Figure 4 CESD score and score of memory complaint are presented as estimated evolution of mean score and 95% confidence interval (CI) over the 13 years preceding the diagnosis of Parkinson's disease (PD; green curve for future PD subjects; grey curve for healthy control subjects).

Figure 5 Total score of IADL and IADL-Transportation score are presented as estimated evolution of mean score and 95% confidence interval (CI) over the 13 years preceding the diagnosis of Parkinson's disease (PD; green curve for future PD subjects; grey curve for healthy control subjects).



-12 years

- 10 years

- 8 years

-6 years

-4 years

-2 years

0 year

V3

- 0 case
- 1 HC

V5

- 1 case
- 4 HC

V8

- 6 cases
- 11 HC

V10

- 8 cases
- 17 HC

V13

- 14 cases
- 21 HC

V15

- 21 cases
- 62 HC

