Dopamine pathway and Parkinson's risk variants are associated with levodopa-induced dyskinesia

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Abstract

Background: Levodopa-induced dyskinesia (LID) is a common adverse effect of levodopa, one of the main therapeutics used to treat the motor symptoms of Parkinson's disease (PD). Previous evidence suggests a connection between LID and a disruption of the dopaminergic system as well as genes implicated in PD, including *GBA1* and *LRRK2*.

Objectives: To investigate the effects of genetic variants on risk and time to LID.

Methods: We performed a genome-wide association study (GWAS) and analyses focused on *GBA1* and *LRRK2* variants. We also calculated polygenic risk scores including risk variants for PD and variants in genes involved in the dopaminergic transmission pathway. To test the influence of genetics on LID risk we used logistic regression, and to examine its impact on time to LID we performed Cox regression including 1,612 PD patients with and 3,175 without LID.

Results: We found that *GBA1* variants were associated with LID risk (OR=1.65, 95% CI=1.21-2.26, p=0.0017) and *LRRK2* variants with reduced time to LID onset (HR=1.42, 95% CI=1.09-1.84, p=0.0098). The fourth quartile of the PD PRS was associated with increased LID risk ($OR_{fourth\_quartile}$=1.27, 95% CI=1.03-1.56, p=0.0210). The third and fourth dopamine pathway PRS quartiles were associated with a reduced time to development of LID ($HR_{third\_quartile}$=1.38, 95% CI=1.07-1.79, p=0.0128; $HR_{fourth\_quartile}$=1.38, 95% CI=1.06-1.78, p=0.0147).

Conclusions: This study suggests that variants implicated in PD and in the dopaminergic transmission pathway play a role in the risk/time to develop LID. Further studies will be necessary to examine how these findings can inform clinical care.

Introduction

Levodopa is one of the most commonly administered therapies for Parkinson's disease (PD), particularly to treat motor symptoms.[1] However, as the disease progresses and patients are exposed to long-term levodopa therapy, a significant proportion develops levodopa-induced dyskinesia (LID), a debilitating side effect characterized by involuntary, uncontrolled, and often choreiform movements.[2] LID is estimated to affect around 40-50% of PD patients within 4-6 years of initiating levodopa therapy,[3, 4] however, a subset of them manifests LID also within the first year of the therapy,[5] demonstrating the broad variability of LID risk and onset. The most widely accepted pathophysiologic hypothesis suggests that LID development is connected with a pulsatile stimulation of the dopamine receptors in the nucleus striatum.[6] This phenomenon occurs due to the progressive dopaminergic loss in PD, resulting in impaired presynaptic storage capacity of dopamine, and is exacerbated by elevated doses of levodopa.[6-8] Other pathways have also been implicated in LID development, including the glutamatergic, serotonergic and noradrenergic neural circuits.[7, 8]

Multiple environmental risk factors affecting LID have been identified, including levodopa dosage and duration of the therapy, use of dopamine agonists, PD age at onset (AAO), disease duration and severity, female sex and lower body mass index (BMI).[9-13] Most of the suggested genetic risk factors for LID are related to the dopamine pathway, including genes encoding the dopamine receptors, especially *DRD2* and *DRD3*,[14-16] the dopamine transporter *SLC6A3*,[17, 18] or enzymes that metabolize dopamine and are targeted by PD therapeutics,[19, 20] catechol-O-methyltransferase (*COMT*)[21-23] and monoamine oxidases A and B (*MAOA*, *MAOB*).[22-24] Interestingly, variants in *GBA1* and *LRRK2,* among the most frequent genetic risk factors for PD,[25, 26] have also been identified as potential risk factors for LID.[27-32] Carriers of *GBA1* and *LRRK2* variants show distinctive clinical presentations in PD, with *GBA1* variants being associated with a more rapidly progressive PD with earlier onset,[33] and *LRRK2* variants with an overall more benign disease course, but with also more frequent postural instability and gait difficulty as well as slightly earlier AAO

compared to sporadic PD.[34] Other variants reported in LID include those in *BDNF,* involved in neural plasticity,[35, 36] *GRIN2A,* encoding a glutamatergic receptor,[37] and *ADORA2A*, encoding the adenosine A2a receptor gene.[38] However, the association between LID and most of the above-mentioned putative genetic risk factors is still controversial, with most findings reported deriving from candidate genes studies that failed to be confirmed in replication studies. [39-44]

Here, we aimed to systematically evaluate how genetics affect the risk and rate of progression to LID including a total of 4,787 PD patients from multiple centers. For this purpose, we performed genome-wide association studies (GWAS) and downstream analyses focused on specific genes previously implicated in LID. In addition, we tested the effect produced by cumulative genetic risk on the occurrence and rate of progression to LID, including risk variants previously associated with PD and variants in genes involved in the dopaminergic transmission pathway.

Methods

Population

The study population included a total of 4,787 PD patients, of which 1,612 with and 3,175 without LID (Table 1). PD was diagnosed by movement disorder specialists according to the UK Brain Bank or International Parkinson Disease and Movement Disorders Society criteria.[45] LID diagnosis was made based on the Unified Parkinson's Disease Rating Scale (UPDRS) part IV and direct clinical evaluation. The participants were of European ancestry and their clinical and genetic data were collected from 15 different cohorts (Table 1), 12 of which were from the International Parkinson's Disease Genomics Consortium (IPDGC) and 3 from the Accelerating Medicines Partnership Parkinson's Disease (AMP-PD, https://amp-pd.org/). The latter includes the Parkinson's Disease Biomarkers Program (PDBP), Parkinson's Progression Markers Initiative (PPMI) and Harvard Biomarker Study (HBS) cohorts. The cohorts were included in the different analyses depending on data availability. The cohorts included in each analysis are specified in Supplementary Table 1.

Genetic analyses

Excluding the AMP-PD cohorts, with whole genome sequencing (WGS) data, the other centers (Table 1) were genotyped using the OmniExpress, NeuroX,[46] NeuroChip[47] or MegaChip GWAS array according to the manufacturer's instructions (Illumina Inc.). Quality control was performed following standard pipelines (detailed in https://github.com/neurogenetics/GWAS-pipeline) using Plink 1.9.[48] In brief, we filtered out heterozygosity outliers using an F-statistic cut-off of <-0.15 or >0.15. Individuals with a variant call rate <95% and sex mismatch were excluded. Variants missing in >5% of the participants, with disparate missingness between cases and controls (p<1E-04), or significantly deviating from Hardy-Weinberg equilibrium in controls (p<1E-04) were also removed. We used GCTA to check for relatedness closer than first cousins between participants (PIHAT>0.125). We performed imputation using the Michigan imputation server (https://imputationserver.sph.umich.edu/index.html#) with the Haplotype Reference Consortium reference panel r1.1 2016 under default settings. Ancestry outliers were detected using HapMap3 principal component analysis (PCA) data in R version 4.0.1.

After imputation, we selected variants with r2>0.8 and a minor allele frequency (MAF)>0.05, while retaining common risk variants in the *GBA1* (p.N370S, p.E326K and p.T369M) and *LRRK2* (p.G2019S, p.M1646T and p.R1441G/C) regions, to perform specific analyses on these variants (detailed below). These genes were specifically selected given their importance in PD etiology[25, 26] and recent clinical trials[49] as well as their previously suggested association with LID.[27-32] The carrier status of *GBA1/LRRK2* risk variants in individuals with and without LID is detailed in Supplementary Table 2 and Supplementary Table 3. Carriers of variants in the same gene were combined, so that the carrier status for *GBA1* and *LRRK2* refers to any aforementioned *GBA1* and *LRRK2* variants, respectively. To examine the association between the *GBA1* and *LRRK2* risk variant carrier status and LID occurrence we performed logistic regression, and to evaluate the association between the carrier

status and time to LID onset we performed Cox regression using the R package "survival" (https://cran.r-project.org/web/packages/survival/). The time to LID variable included in the Cox regression was defined as the period between the start of levodopa therapy and LID onset, as previously done.[50] When LID did not manifest, this parameter was right-censored at the last follow-up. We adjusted the analyses by multiple covariates including principal components (PCs), PD AAO, sex, levodopa dosage, levodopa equivalent daily dose (LEDD),[51, 52] dopamine agonist use, BMI, Hoehn and Yahr score (HY) and, exclusively for logistic regression, disease duration. For logistic regression analyses, we included the cumulative levodopa dosage and LEDD starting from the baseline (i.e., levodopa initiation) to the last time point (i.e., LID onset or last follow-up when LID was not present). In Cox regression, to avoid collinearity with the time to LID onset dependent variable, we replaced cumulative doses with doses at the last time point. All the covariates were selected using an Akaike Information Criterion (AIC)-based stepwise regression approach, which evaluated the model goodness of fit and selected the most appropriate covariates to include in the model. We performed the analyses separately in each cohort and then meta-analyzed the results using the R package "metafor" (https://cran.r-project.org/web/packages/metafor/index.html). Since variants in these genes have been previously associated with LID, we used a significance threshold of α=0.05.

Similar to the analyses on specific genes, to investigate the overall impact of genetics on LID risk and time to onset we also performed GWAS with, respectively, logistic and Cox regression adjusted for the above-specified covariates. Cox regression was performed using the SurvivalGWAS_SV software (https://www.liverpool.ac.uk/population-health/research/groups/statistical-genetics/survival-gwas-sv/).[53] We conducted the analyses in each cohort separately, and then meta-analyzed the results using the METAL software (https://genome.sph.umich.edu/wiki/METAL_Documentation) with a fixed effects model weighted by β coefficients and the inverse of the standard errors.

PD risk variant-based polygenic risk score

To assess the impact on LID of the cumulative genetic risk for PD we calculated polygenic risk score (PRS) for each PD patient including the 90 variants associated with PD in the most recent GWAS meta-analysis in Europeans.[54] PRS calculation was performed based on the weighted allele dose as implemented in PRSice2 using default clumping (https://choishingwan.github.io/PRSice/).[55] To investigate the association between the PRS and LID risk we performed logistic regression, while to evaluate the association between PRS and progression to LID we performed Cox regression. The analyses were adjusted for PCs, PD AAO, sex, HY and levodopa dosage, cumulative in logistic regression and at the last time point in Cox regression. These analyses were repeated using PRS as a continuous variable and then as a discrete variable by dividing the PRS into quartiles. For the analysis using PRS quartiles, we separately compared the association of individual membership to the second, third and fourth quartiles vs the first quartile with LID risk/progression.

Dopamine pathway polygenic risk score

To assess the impact of genes involved in the dopaminergic transmission pathway we also constructed a pathway polygenic risk score, or polygenic effect score (PES)[56] using the PRSet feature of PRSice2 (https://choishingwan.github.io/PRSice/prset_detail/). Genes involved in this pathway were obtained from Explore the Molecular Signatures Database (MSigDB, version 2023.1), a collection of annotated gene sets for use with Gene Set Enrichment Analysis (GSEA) software (https://www.gsea-msigdb.org/gsea/msigdb/). These genes included *CDK5, FLOT1, PARK7, CHRNB2, ADORA2A, CRH, CRHBP, DRD1, DRD2, DRD3, DRD4, DRD5, TOR1A, RASD2, PNKD, GDNF, ARRB2, PRKN, PTGS2, RAB3B, PINK1, SLC6A2, SLC, 6A3, SLC6A4, SNCA, TH, CNTNAP4* (detailed at http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/GOBP_SYNAPTIC_TRANSMISSION_DOPAMINERGIC). To select the variants in each of those genes to include in the analyses we used the LID GWAS meta-

analysis summary statistics, filtering variants with a p-value less than or equal to 0.05. In addition, we performed linkage disequilibrium (LD) clumping using the default r2=0.1 and selecting variants at 250 Kb of distance from the pathway-related genes. A total of 1000 permutations were implemented to generate the empirical p-value corresponding to the optimized PES prediction of the dependent variable in the target cohort. We then calculated individual PES for each target cohort. To avoid potential inflation due to the presence of the target cohort in the meta-analysis summary statistics, each time we calculated the PES for a target cohort we excluded such cohort from the meta-analysis using a leave-one-out approach. To investigate the association between the dopamine pathway PES and LID risk we performed logistic regression, while to evaluate the association between the PES and progression to LID we performed Cox regression, as specified above for the PRS analyses.

Results

GBA1 and LRRK2 variants show significant associations with LID risk and time to LID

Analyses focusing on *GBA1* showed that *GBA1* variants were significantly associated with LID risk (OR=1.65, 95% CI=1.21-2.26, p=0.0017, Fig. 1A). No association was found with time to LID (HR=1.25, 95% CI=0.99-1.58, p=0.0635, Fig. 1B). In contrast, *LRRK2* variants showed no association with LID risk (OR=1.18, 95% CI=0.84-1.67, p=0.3484, Fig. 2A) but were significantly associated with reduced time to development of LID (HR=1.42, 95% CI=1.09-1.84, p=0.0098, Fig. 2B)

In the GWAS genomic inflation was evaluated using quantile-quantile plots (Q-Q plots) and the lambda factor, showing no inflation and a slight deflation (lambda logistic regression=0.9709, lambda Cox regression=0.9555, Supplementary Fig. 1-2). GWAS using both logistic and Cox regression showed no significant association with LID risk or time to development of LID, respectively (Supplementary Fig. 3, Supplementary Fig. 4). We further examined whether variants previously associated with LID in the literature[14-18, 21-24] and from the LIDPD website (http://LiDpd.eurac.edu/) showed associations in the current GWAS, but we found no significant results (Supplementary Tables

4-5). A recent GWAS in LID (Martinez et al., 2023, MedRxiv) nominated significant signals in a progression GWAS meta-analysis. However, our study failed to confirm these findings and the reported variants did not reach the nominal significance of 0.05 in our GWAS (Supplementary Table 6).

PD risk variant-based polygenic risk score is associated with increased risk for LID

PRS analyses aggregating PD-associated variants showed that higher values of PRS were associated with a very mild increase in LID risk (OR=1.02, %95 CI=1.002-1.035, p=0.0298, Fig. 3B). When dividing the PRS in quartiles, logistic regression showed a significant association between the fourth quartile and LID, with a greater risk compared to the analyses using PRS as a continuous variable ($OR_{fourth\_quartile}$=1.27, 95% CI=1.03-1.56, p=0.0210, Fig. 3A, Supplementary Table 7). Cox regression did not show any significant associations between PRS and time to development of LID (Supplementary Fig. 5 A-B, Supplementary Table 8).

Dopaminergic transmission pathway polygenic effect score is associated with a reduced time to development of LID

Analyses on the dopaminergic transmission pathway PES showed that higher values of PES were associated with a reduced time to development of LID (HR=1.10, 95% CI=1.02-1.18, p=0.0088, Fig. 4B). In addition, the third and fourth PES quartile were also associated with a reduced time to development of LID with a more elevated effect size compared to the analyses on PES as a continuous variable ($HR_{third_quartile=}$1.38, 95% CI=1.07-1.79, p=0.0128; $HR_{fourth_quartile=}$1.38, 95% CI=1.06-1.78, p=0.0147, Fig. 4A, Supplementary Table 10). Logistic regression did not show any statistically significant associations between dopaminergic transmission PES and LID risk (Supplementary Fig. 6 A-B, Supplementary Table 9).

Discussion

In this study, we confirmed that *GBA1* variants were associated with increased risk for LID and demonstrated that *LRRK2* variants were associated with a reduced time to development of LID. Additionally, we found that PD PRS was associated with mildly increased risk for LID and that the dopaminergic transmission pathway PES is associated with a reduced time to development of LID.

Albeit some studies found contradictory results on the association between the *GBA1* and *LRRK2* variants and LID,[39-42] many others have shown that these variants play a role in LID development, [27-32] and in this study we also demonstrated that *LRRK2* variants might also affect the time to development of LID. The absence of significant signals in the risk and progression GWAS and, in general, the difficulty finding congruent results between different genetic studies investigating LID, as also reflected by the divergent results between the recent LID progression GWAS (Martinez et al., 2023, MedRxiv) and our study, may be due to the stronger contribution in LID development of environmental factors, especially pharmacologic- (dosage of dopaminergic drugs, use of amantadine) and disease-related factors.[9-13]

The significant association between the two PRS analyses suggests that aggregating multiple common variants that might have a scarce effect on LID individually could contribute to uncovering the overall genetic impact on LID. In particular, the association between the PRS including PD risk variants suggests that patients with a stronger genetic risk profile for PD are also more at risk for LID, a factor to consider for patient counselling and potential clinical trials, although the magnitude of the increased risk was small. We also demonstrated that the dopaminergic synaptic transmission pathway PES was associated with an increased rate of LID development, which is in line with previous pathophysiologic hypotheses[6-8] and studies suggesting an implication of dopamine pathway genes in the development of LID.[14-18, 21-24]

Unravelling the etiologic bases of LID is crucial to implement a tailored therapy for PD patients taking levodopa, adapting the therapeutic choices, dosage and management depending on the

individual risk factors of each patient. Over time, it could be beneficial to define a risk profile accounting for the single genetic and environmental factors associated with LID as well as the cumulative genetic risk provided by the PRS. This might be used to stratify patients for LID prevention clinical trials and lead to a more refined and personalized therapeutic approach for each individual. In addition to the benefits of the current symptomatic therapies, uncovering and confirming genetic factors affecting the risk and time to development of LID could also have important implications for targeted therapies. In particular, *GBA1* and *LRRK2* pathways are already candidate targets for newly developing drugs in clinical trials.[49] A LRRK2 inhibitor, BIIB122/DNL151, reached already experimental phase 3 (https://www.denalitherapeutics.com, 2021).[57] In addition, Ambroxol, a pharmacological chaperone for GCase capable of increasing its enzymatic levels, completed phase 2 and LTI-291, an activator of GCase, reached phase 1B.[58-60] As these drugs would likely be used in conjunction with symptomatic therapies, knowing that these pathways can be targeted to reduce the risk or delay the time of LID development could considerably improve the compliance and quality of life of PD patients taking dopaminergic treatments.

The current study has several limitations. First, the subjects were all of European ancestry and therefore the results in other populations might be different. Despite an overall large sample size, most of the individual cohorts included a limited number of participants, especially those having longitudinal data necessary for Cox regression, this impacted the power of the study and could have contributed to the lack of association in the GWAS. Some studies suggested that LID is affected more by the disease duration than by the therapy duration,[61] on this line PD AAO would represent a better baseline than levodopa initiation for the time to LID onset. However, this parameter was chosen in accordance with what was previously done with LID GWAS[50] and accounting for the recall bias that PD AAO suffers from, compared to levodopa initiation which represents a report made by the physicians. In addition, understanding the genetic basis of the time to LID from levodopa initiation can be of considerable relevance for patient counselling at the time of treatment administration.

Finally, we also accounted for the disease duration in each of our analyses with appropriate adjustments. Another limitation of this study was that not all the cohorts had the same amount of data available, which limited in part the design of the analytical model.

In conclusion, in the current study we demonstrated that PD risk variants and the dopaminergic transmission PRS are associated with increased risk of LID/time to development of LID. A better understanding of the role of genetics in LID development could reduce the impact of this adverse effect and enhance therapeutic management in PD.

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Author roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Cohort generation: A. Cohort recruitment, B. Sample processing, C. Data generation;
3. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
4. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

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Ethical Compliance Statement

IRB Study Number A11-M60-21A (21-11-023) was reviewed and approved by the Research Ethics Offices (REOs). Informed written patient consent was provided in each center before the inclusion of each in the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

Data availability

The LID GWAS summary statistics are publicly available on GWAS catalog (https://www.ebi.ac.uk/gwas/). All codes used for the analyses are available at https://github.com/gan-orlab.

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Fig. 1 A-B – Association between *GBA1* variants and LID

The meta-analysis forest plot shows the coefficient (black squares) and 95% confidence interval (bars) of the analyses in each single cohort. The size of the square is proportional to the weight the cohort had on the overall meta-analysis, based on their single standard error. The black diamond at the bottom represents the overall coefficient and confidence interval. **A**. Logistic regression between *GBA1* variants and LID risk; **B**. Cox regression between *GBA1* variants and time to development of LID.

FE: fixed effect model; AMP-PD: Accelerating Medicines Partnership Parkinson's disease, including the New Discovery of Biomarkers (BioFIND), the Harvard Biomarker Study (HBS) and the Parkinson's Disease Biomarkers Program (PDBP) cohorts; Barcelona: Hospital Universitari Mutua de Terrassa, Spain; CORIELL: NINDS Exploratory Trials in PD Long-Term Study 1 (NET-PD LS1), Coriell Institute for Medical Research, USA; DIGPD: Drug Interaction With Genes in Parkinson's Disease, France; LEAP: Levodopa in Early Parkinson's Disease, Netherlands; Luxemburg: Luxembourg Centre for Systems Biomedicine; Mayo: Mayo Clinic, USA; McGill: McGill University, Canada; Oviedo: Central University Hospital of Asturias, Spain; PreCEPT: Parkinson Research Examination of CEP-1347 Trial; SCOPA: SCales for Outcomes in PArkinson's disease; Sevilla: Universidad de Sevilla; Tartu: University of Tartu

Fig. 2 A-B - Association between *LRRK2* variants and LID

A. Logistic regression between *LRRK2* variants and LID risk; **B**. Cox regression between *LRRK2* variants and time to development of LID.

Fig- 3 A-B - Logistic regression between PRS aggregating PD risk variants and LID risk

A. The plot shows the association between each PRS quartile and LID risk compared with the first quartile, meta-analyzing the results across the cohorts. The Y axis represents the PRS quartile, the X axis the odds ratio (red dot) and 95% confidence interval (red bar). The presence of an asterisk indicates

a significant association (p<0.05). **B.** The forest plot shows the association between PRS as a continuous variable and LID risk.

CI: confidence interval.

Fig. 4 A-B - Cox regression between the dopaminergic transmission pathway PES and time to development of LID

A. The plot shows the association between each PES quartile and time to development of LID compared with the first quartile, meta-analyzing the results across the cohorts. The Y axis represents the PRS quartile, the X axis the hazard ratio (red dot) and 95% confidence interval (red bar). **B.** The forest plot shows the association between PES as a continuous variable and time to development of LID.

Supplementary Fig. 1 - Q-Q plot of LID risk GWAS using logistic regression

The Q-Q plot illustrates the negative log-adjusted p-values from the GWAS logistic regression for LID risk sorted into ascending order against the expected quantiles if the null hypothesis is true for all tests.

Supplementary Fig. 2 - Q-Q plot of time to development of LID GWAS using Cox regression

The Q-Q plot illustrates the negative log-adjusted p-values from the GWAS Cox regression for time to LID sorted into ascending order against the expected quantiles if the null hypothesis is true for all tests.

Supplementary Fig. 3 - Manhattan plot of LID risk GWAS

Manhattan plot showing the results of the GWAS meta-analysis, comparing PD patients with and without LID. The Y axis represents the negative logarithm of the p-value, the X axis represents the chromosomal position of the variants and each dot on the figure represents a variant. The red line represents the genome-wide Bonferroni-corrected statistical significance threshold ($5x10^{-8}$), while the blue line is the false-discovery rate-corrected significance threshold ($1x10^{-5}$).

Supplementary Fig. 4 - Manhattan plot of time to development of LID GWAS

Manhattan plot showing the results of the GWAS meta-analysis investigating the time to development of LID. The Y axis represents the negative logarithm of the p-value, the X axis represents the chromosomal position of the variants and each dot on the figure represents a variant. The red line represents the genome-wide Bonferroni-corrected statistical significance threshold ($5x10^{-8}$), whereas the blue line is the false-discovery rate-corrected significance threshold ($1x10^{-5}$).

Supplementary Fig. 5 A-B - Cox regression between PRS aggregating PD risk variants and time to development of to LID

A. The plot shows the association between each PRS quartile and time to development of LID compared with the first quartile, meta-analyzing the results across the cohorts. The Y axis represents the PRS quartile, the X axis the hazard ratio (red dot) and 95% confidence interval (red bar). The presence of an asterisk indicates a significant association (p<0.05). **B.** The forest plot shows the association between PRS as a continuous variable and time to development of LID.

CI: confidence interval.

Supplementary Fig. 6 A-B - Logistic regression between the dopaminergic transmission pathway PES and LID risk

A. The plot shows the association between each PES quartile and LID risk compared with the first quartile, meta-analyzing the results across the cohorts. The Y axis represents the PES quartile, the X axis the odds ratio (red dot) and 95% confidence interval (red bar). The presence of an asterisk indicates a significant association (p<0.05). **B.** The forest plot shows the association between PES as a continuous variable and LID risk.

CI: confidence interval.

Table 1 - Demographic characteristics of PD patients in the individual cohorts

AMP-PD: Accelerating Medicines Partnership Parkinson's disease, including the Parkinson's Disease Biomarkers Program (PDBP), Parkinson's Progression Markers Initiative (PPMI) and Harvard Biomarker Study (HBS) cohorts; Barcelona: Hospital Universitari Mutua de Terrassa, Spain; CORIELL: NINDS Exploratory Trials in PD Long-Term Study 1 (NET-PD LS1), Coriell Institute for Medical Research, USA; DIGPD: Drug Interaction With Genes in Parkinson's Disease, France; LEAP: Levodopa in Early Parkinson's Disease, Netherlands; Luxemburg: Luxembourg Centre for Systems Biomedicine; Mayo Clinic Florida: Mayo Clinic Florida, USA; McGill: McGill University, Canada; Oviedo: Central University Hospital of Asturias, Spain; PreCEPT: Parkinson Research Examination of CEP-1347 Trial; SCOPA: SCales for Outcomes in PArkinson's disease; Sevillla: Universidad de Sevilla; Tartu: University of Tartu; LID-, n: individuals without levodopa-induced dyskinesia; LID+, n: individuals with levodopa-induced dyskinesia; Age (SD): mean age (standard deviation); %Mal: percentage of males; Tot: total number of individuals per cohort.

Supplementary Table 1 - Cohorts included in the single analyses

Table showing the cohorts included in the single logistic and Cox regression analyses, including GWAS, analyses focused on *GBA1/LRRK2* variants and association analyses between PRS and LID. GWAS: genome-wide association study; *GBA1*: analyses focused on *GBA1* variants; *LRRK2*: analyses focused on *LRRK2* variants; PRS: polygenic risk score analyses; logistic: logistic regression; Cox: Cox regression.

Supplementary Table 2 - Carriers of *GBA1* variants across different cohorts

Carrier status for GBA1 variants p.N370S, p.E326K and p.T369M. GBA1 carriers LID-, N/tot: carriers of GBA1 variants without LID out of all patients without LID; GBA1 carriers LID+, N/tot: carriers of GBA1 variants with LID out of all the patients with LID; GBA1 carriers LID-, %: percentage of

carriers of GBA1 variants without LID; GBA1 carriers LID+ , %: percentage of carriers of GBA1 variants with LID

Supplementary Table 3 - Carriers of *LRRK2* variants across different cohorts

Carrier status for LRRK2 variants p.G2019S, p.M1646T and p.R1441G/C. LRRK2 carriers LID- , N/tot: carriers of LRRK2 variants without LID out of all patients without LID; LRRK2 carriers LID+ , N/tot: carriers of LRRK2 variants with LID out of all patients with LID; LRRK2 carriers LID- , %: percentage of carriers of LRRK2 variants without LID; LRRK2 carriers LID+ , %: percentage of carriers of LRRK2 variants with LID

Supplementary Table 4 - Logistic regression between variants previously associated with LID and LID risk

Summary statistics from the LID risk GWAS of variants previously associated with LID. Coordinates: chromosome:base pair; rs ID: variant rs number; gene: nearest gene; OR: odds ratio; StdErr: standard error.

Supplementary Table 5 - Cox regression between variants previously associated with LID and time to development of LID

Summary statistics from the time to development of LID GWAS of variants previously associated with LID. Coordinates: chromosome:base pair; rs ID: variant rs number; gene: nearest gene; HR: hazard ratio; StdErr: standard error.

Supplementary Table 6 - Logistic and Cox regression results for variants recently associated with time to development of LID

Summary statistics of the LID risk and time to development of LID GWAS for the variants previously nominated in the most recent LID survival GWAS (Martinez et al., 2023, MedRxiv).

OR: odds ratio; HR: hazard ratio; SE standard error.

Supplementary Table 7 – Logistic regression between PRS quartiles aggregating PD risk variants and LID risk

Logistic regression results for the association between PD risk variant-based PRS divided into quartiles and LID risk.

Quartile: quartile compared with the first quartile; OR: odds ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; p: p-value; sig: the asterisk indicates the results are significant.

Supplementary Table 8 – Cox regression between PRS quartiles aggregating PD risk variants and time to development of LID

Cox regression results for the association between PD risk variant-based PRS divided into quartiles and time to development of LID.

Quartile: quartile compared with the first quartile; HR: hazard ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; p: p-value; sig: the asterisk indicates the results are significant.

Supplementary Table 9 – Logistic regression between dopaminergic transmission pathway PES quartiles and LID risk

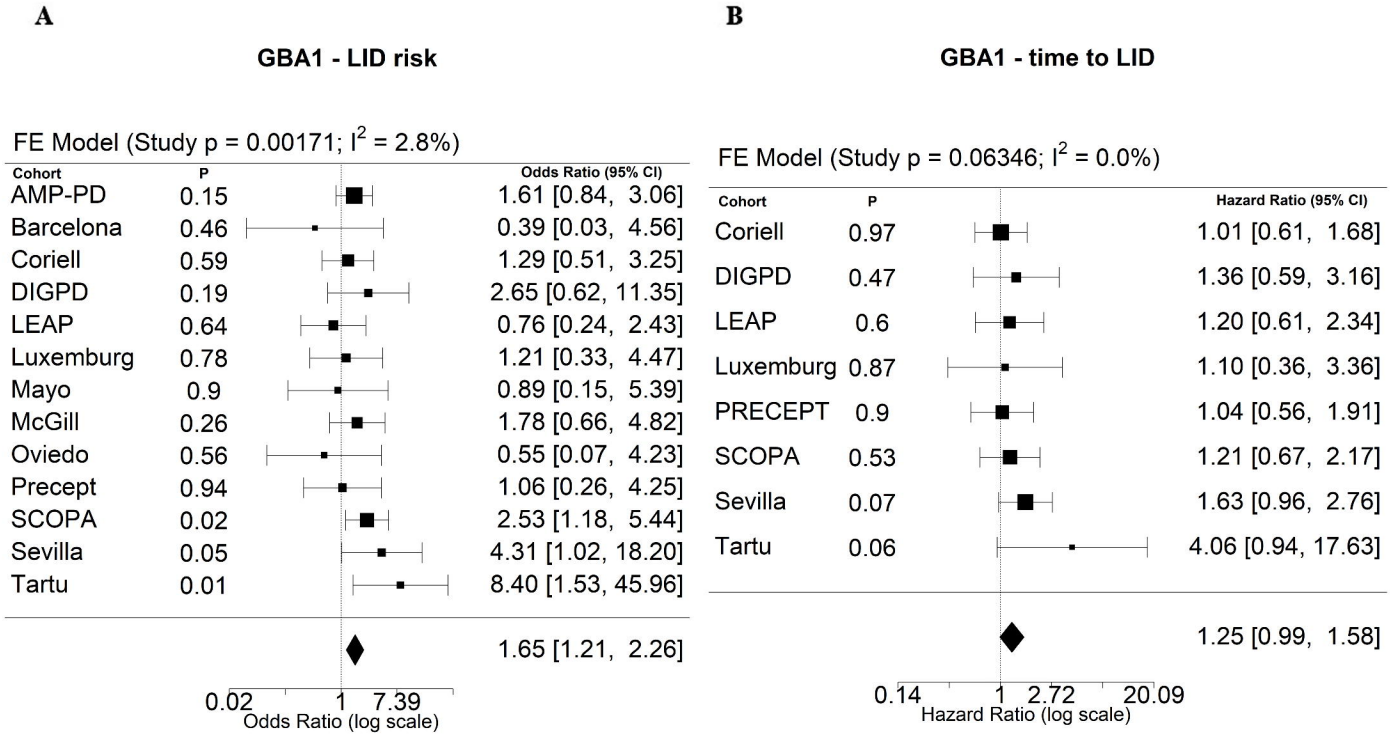
Logistic regression results for the association between dopaminergic transmission pathway PES divided into quartiles and LID risk.

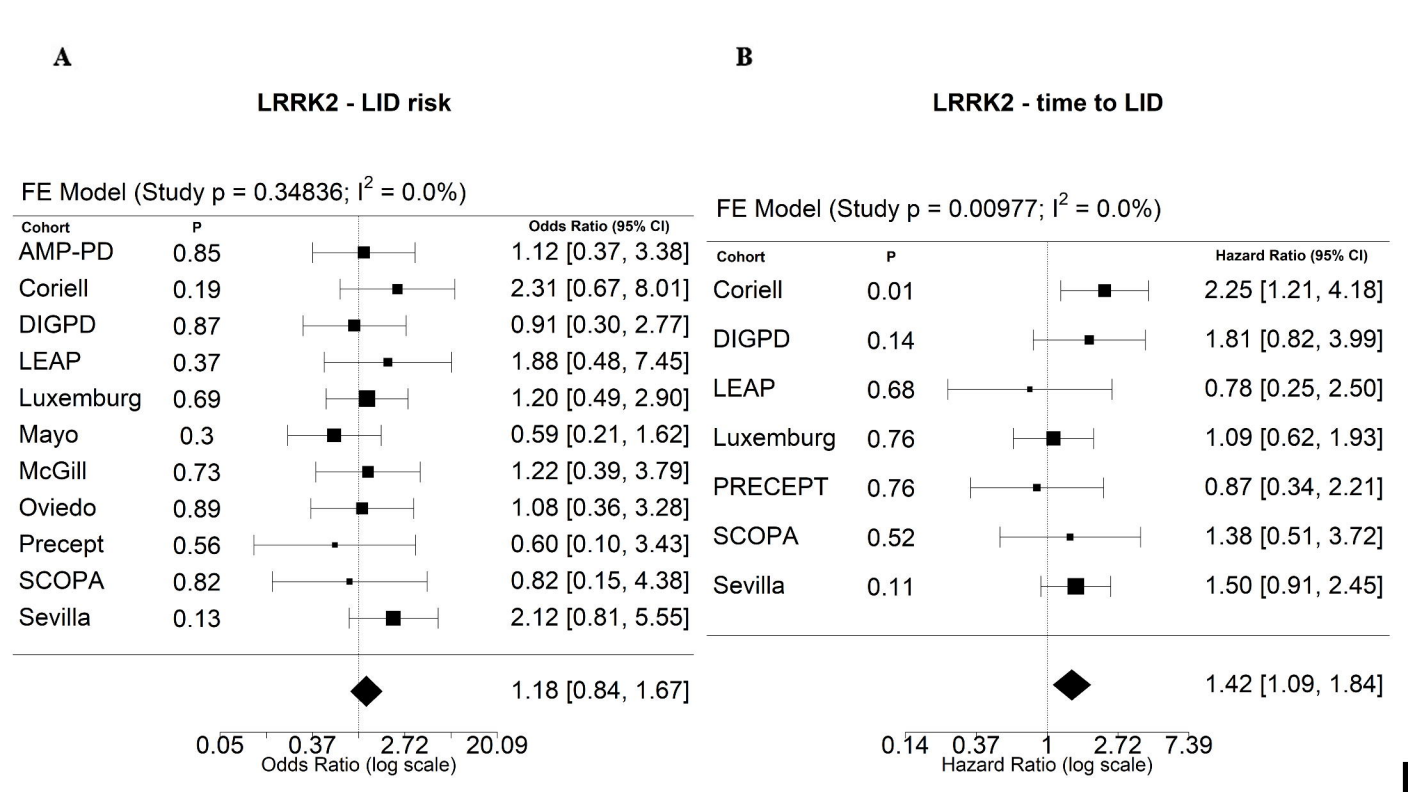
Quartile: quartile compared with the first quartile; OR: odds ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; p: p-value; sig: the asterisk indicates the results are significant.

Supplementary Table 10 – Cox regression between dopaminergic transmission pathway PES quartiles and time to development of LID

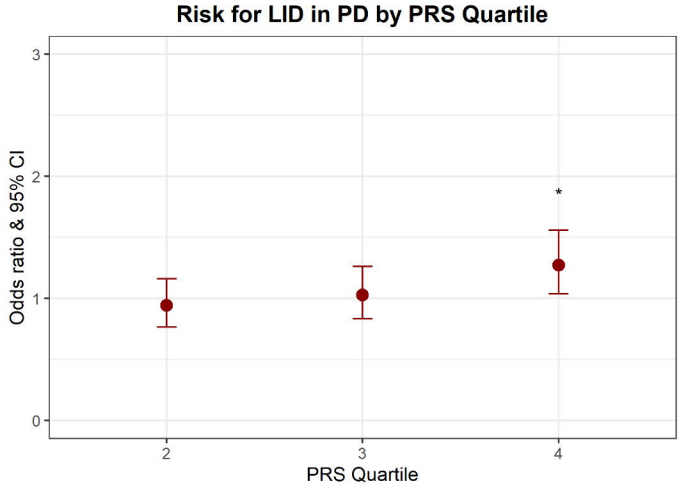
Cox regression results for the association between dopaminergic transmission pathway PES divided into quartiles and time to development of LID.

Quartile: quartile compared with the first quartile; HR: hazard ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; p: p-value; sig: the asterisk indicates the results are significant.

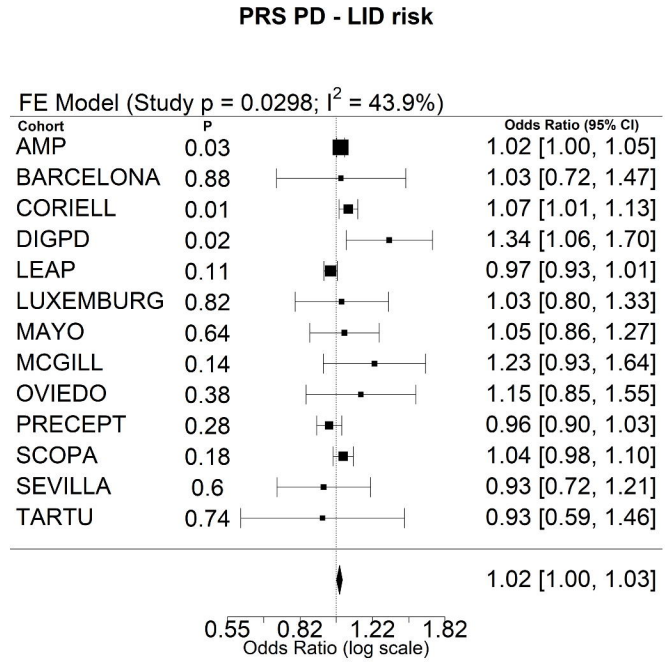

A
GBA1 - LID risk
FE Model (Study p = 0.00171; I² = 2.8%)
Cohort
P
Odds Ratio (95% CI)
AMP-PD 0.15 1.61 [0.84, 3.06]
Barcelona 0.46 0.39 [0.03, 4.56]
Coriell 0.59 1.29 [0.51, 3.25]
DIGPD 0.19 2.65 [0.62, 11.35]
LEAP 0.64 0.76 [0.24, 2.43]
Luxemburg 0.78 1.21 [0.33, 4.47]
Mayo 0.9 0.89 [0.15, 5.39]
McGill 0.26 1.78 [0.66, 4.82]
Oviedo 0.56 0.55 [0.07, 4.23]
Precept 0.94 1.06 [0.26, 4.25]
SCOPA 0.02 2.53 [1.18, 5.44]
Sevilla 0.05 4.31 [1.02, 18.20]
Tartu 0.01 8.40 [1.53, 45.96]
1.65 [1.21, 2.26]
0.02
1
7.39
Odds Ratio (log scale)
B
GBA1 - time to LID
FE Model (Study p = 0.06346; I² = 0.0%)
Cohort
P
Hazard Ratio (95% CI)
Coriell 0.97 1.01 [0.61, 1.68]
DIGPD 0.47 1.36 [0.59, 3.16]
LEAP 0.6 1.20 [0.61, 2.34]
Luxemburg 0.87 1.10 [0.36, 3.36]
PRECEPT 0.9 1.04 [0.56, 1.91]
SCOPA 0.53 1.21 [0.67, 2.17]
Sevilla 0.07 1.63 [0.96, 2.76]
Tartu 0.06 4.06 [0.94, 17.63]
1.25 [0.99, 1.58]
0.14
1
2.72
20.09
Hazard Ratio (log scale)


A
LRRK2 - LID risk
FE Model (Study p = 0.34836; I² = 0.0%)
Cohort
P
Odds Ratio (95% CI)
AMP-PD 0.85 1.12 [0.37, 3.38]
Coriell 0.19 2.31 [0.67, 8.01]
DIGPD 0.87 0.91 [0.30, 2.77]
LEAP 0.37 1.88 [0.48, 7.45]
Luxemburg 0.69 1.20 [0.49, 2.90]
Mayo 0.3 0.59 [0.21, 1.62]
McGill 0.73 1.22 [0.39, 3.79]
Oviedo 0.89 1.08 [0.36, 3.28]
Precept 0.56 0.60 [0.10, 3.43]
SCOPA 0.82 0.82 [0.15, 4.38]
Sevilla 0.13 2.12 [0.81, 5.55]
1.18 [0.84, 1.67]
0.05 0.37 2.72 20.09
Odds Ratio (log scale)
B
LRRK2 - time to LID
FE Model (Study p = 0.00977; I² = 0.0%)
Cohort
P
Hazard Ratio (95% CI)
Coriell 0.01 2.25 [1.21, 4.18]
DIGPD 0.14 1.81 [0.82, 3.99]
LEAP 0.68 0.78 [0.25, 2.50]
Luxemburg 0.76 1.09 [0.62, 1.93]
PRECEPT 0.76 0.87 [0.34, 2.21]
SCOPA 0.52 1.38 [0.51, 3.72]
Sevilla 0.11 1.50 [0.91, 2.45]
1.42 [1.09, 1.84]
0.14 0.37 1 2.72 7.39
Hazard Ratio (log scale)

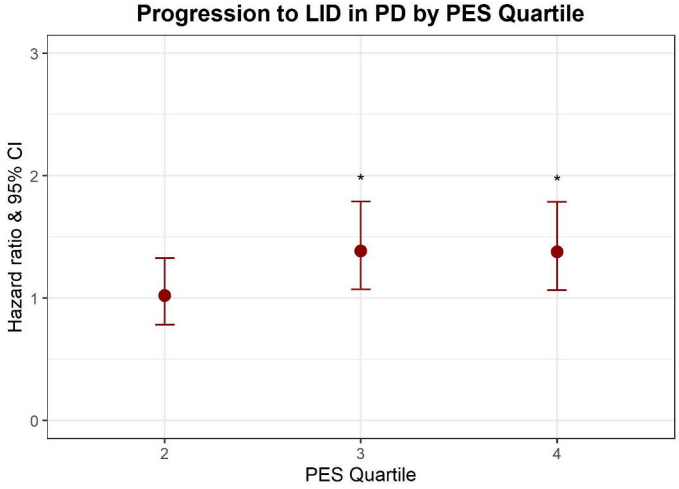
A


Risk for LID in PD by PRS Quartile
Odds ratio & 95% CI
3
2
1
0
*
2
3
4
PRS Quartile

B


PRS PD - LID risk
FE Model (Study p = 0.0298; I² = 43.9%)
Cohort
P
Odds Ratio (95% CI)
AMP 0.03 1.02 [1.00, 1.05]
BARCELONA 0.88 1.03 [0.72, 1.47]
CORIELL 0.01 1.07 [1.01, 1.13]
DIGPD 0.02 1.34 [1.06, 1.70]
LEAP 0.11 0.97 [0.93, 1.01]
LUXEMBURG 0.82 1.03 [0.80, 1.33]
MAYO 0.64 1.05 [0.86, 1.27]
MCGILL 0.14 1.23 [0.93, 1.64]
OVIEDO 0.38 1.15 [0.85, 1.55]
PRECEPT 0.28 0.96 [0.90, 1.03]
SCOPA 0.18 1.04 [0.98, 1.10]
SEVILLA 0.6 0.93 [0.72, 1.21]
TARTU 0.74 0.93 [0.59, 1.46]
1.02 [1.00, 1.03]
0.55
0.82
1.22
1.82
Odds Ratio (log scale)

A


Progression to LID in PD by PES Quartile
Hazard ratio & 95% CI
3
2
1
0
*
*
2
3
4
PES Quartile

B

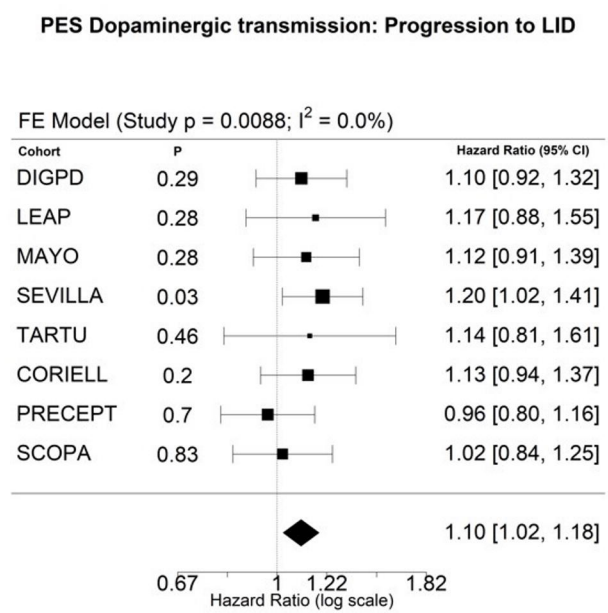

PES Dopaminergic transmission: Progression to LID
FE Model (Study p = 0.0088; I² = 0.0%)
Cohort
P
Hazard Ratio (95% CI)
DIGPD 0.29 1.10 [0.92, 1.32]
LEAP 0.28 1.17 [0.88, 1.55]
MAYO 0.28 1.12 [0.91, 1.39]
SEVILLA 0.03 1.20 [1.02, 1.41]
TARTU 0.46 1.14 [0.81, 1.61]
CORIELL 0.2 1.13 [0.94, 1.37]
PRECEPT 0.7 0.96 [0.80, 1.16]
SCOPA 0.83 1.02 [0.84, 1.25]
1.10 [1.02, 1.18]
0.67
1
1.22
1.82
Hazard Ratio (log scale)

Table 1 - Demographic characteristics of PD patients in the individual cohorts

Center	LID-, n	Age LID- (SD)	%Mal LID-	LID+, n	Age LID+ (SD)	%Mal LID+	Tot
Barcelona	103	73.3 (10.9)	50%	48	72.3 (7.7)	40%	151
CORIELL	221	62.7 (8.9)	67%	117	61.7 (9.6)	59%	338
DIGPD	220	67.5 (9.3)	62%	166	63.9 (10.4)	56%	386
LEAP	336	68.9 (8.8)	75%	75	67.7 (8.5)	50%	411
Luxembourg	330	67.8 (11.4)	66%	140	66.2 (10.0)	66%	470
Mayo Clinic Florida	404	75.8 (9.9)	69%	151	72.0 (10.1)	62%	555
McGill	258	63.2 (16.5)	34%	120	61.3 (15.7)	43%	378
Oviedo-HUCA	80	69.8 (8.9)	51%	110	70.4 (10.5)	55%	190
PDBP – PPMI – HBS (AMP-PD)	580	58.4 (12.4)	66%	87	56.1 (12.2)	53%	667
PreCEPT	181	61.6 (8.6)	68%	137	58.5 (9.7)	66%	318
SCOPA	109	59.1 (10.9)	66%	177	60.0 (10.6)	62%	286
Sevilla	180	69.7 (10.9)	61%	252	66.0 (11.1)	57%	432
Tartu	173	73.0 (8.2)	38%	32	72.0 (8.6)	50%	205
TOTAL	3175	67.0 (10.4)	52%	1612	65.2 (10.4)	54%	4787

AMP-PD: Accelerating Medicines Partnership Parkinson’s disease, including the Parkinson’s Disease Biomarkers Program (PDBP), Parkinson’s Progression Markers Initiative (PPMI) and Harvard Biomarker Study (HBS) cohorts; Barcelona: Hospital Universitari Mutua de Terrassa, Spain; CORIELL: NINDS Exploratory Trials in PD Long-Term Study 1 (NET-PD LS1), Coriell Institute for Medical Research, USA; DIGPD: Drug Interaction With Genes in Parkinson’s Disease, France; LEAP: Levodopa in Early Parkinson’s Disease, Netherlands; Luxemburg: Luxembourg Centre for Systems Biomedicine; Mayo Clinic Florida: Mayo Clinic Florida, USA; McGill: McGill University, Canada; Oviedo: Central University Hospital of Asturias, Spain; PreCEPT: Parkinson Research Examination of CEP-1347 Trial; SCOPA: SCales for Outcomes in PArkinson's disease; Sevillla: Universidad de Sevilla; Tartu: University of Tartu; LID-, n: individuals without levodopa-induced dyskinesia; LID+, n: individuals with levodopa-induced dyskinesia; Age (SD): mean age (standard deviation); %Mal: percentage of males; Tot: total number of individuals per cohort.