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Longitudinal association between dopamine agonists and weight in Parkinson's disease

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ABSTRACT

Objective. To examine the longitudinal relation of dopamine agonists (DA) use with body mass index (BMI) change and weight gain in Parkinson's disease (PD).

Methods. In a cohort of 356 patients with PD annually followed up to 6 years, BMI, antiparkinsonian drugs use, and impulse control disorders (ICDs) were assessed at each visit. DA dose trajectories were estimated using latent class mixed models. The association of DA use with BMI change and weight gain was examined using latent-process mixed models and time-dependent Cox models respectively, while adjusting for disease severity and levodopa (LD) use.

Results. In the mixed model, BMI (kg/m²) increased over the follow-up in DA users ($\beta_{DA \times time} = 0.13$, 95% CI=0.02, 0.24) compared to non-users, while it decreased in LD users ($\beta_{LD \times time} = -0.26$, 95% CI=-0.38, -0.13). We identified three trajectories of average daily DA dose over the follow-up. Patients in the high trajectory gained more weight than patients who never used DA (P=.001) and in the low (P=.02) or moderate (P=.04) trajectories. The incidence of weight gain of ≥ 6 kg was 2.10-fold (95% CI=1.03, 4.28) higher in DA users compared to non-users, while LD users were less likely to gain weight (HR=0.60, 95% CI=0.33, 1.11). Associations decreased in analyses adjusted for compulsive eating or ICDs.

Conclusion. Weight increased in DA users over 6 years, and DA use was associated with increased incidence of weight gain. These associations were partially explained by compulsive eating. Alternatively, weight decreased in LD users. These findings warrant careful monitoring of compulsive eating and weight in PD patients.

INTRODUCTION

While weight tends to increase up to 80 years in the general population [1], weight loss is common in Parkinson's disease (PD) [2, 3]. PD patients have lower weight than controls, and this difference increases with disease severity and duration [2]. Several factors are involved, including increased energy expenditure, appetite loss, nausea, vomiting, and gastrointestinal function impairment.

There is however considerable heterogeneity in weight trajectories. While in the past PD was considered as a disease of malnutrition, individual patients may be nowadays overweight/obese [2, 4, 5]. The global overweight epidemic may contribute to this observation. In addition, dopamine agonists (DA) are associated with impulse control disorders (ICDs) that may contribute to weight gain [6].

Few studies investigated the longitudinal association between DA and weight; they were usually small with a short follow-up [7-9]. Our objectives were twofold. First, we used data from a prospective study of PD patients to examine the longitudinal association of DA use with weight trajectories and weight gain, while adjusting for levodopa (LD) use and disease severity. Second, we examined whether the association between DA use and weight change was explained by ICDs.

METHODS

Patients

The Drug Interacting with Genes in PD (DIGPD) study is a longitudinal cohort study of PD patients consecutively recruited (5/2009-7/2013) in four French university hospitals and four general hospitals. Eligible patients were PD patients (UK-Parkinson's Disease Society Brain Bank criteria, UKPDSBB [10]) with ≤ 5 years disease duration at recruitment.

Following the baseline visit, 5 additional annual evaluations were performed over 6 years by movement disorders specialists who checked whether patients fulfilled UKPDSBB criteria. Patients diagnosed with atypical parkinsonism over the follow-up (n=11) were excluded. As patients had short disease duration at baseline, none had deep brain stimulation (DBS); 7 patients with DBS over the follow-up were censored at time of DBS.

The study (clinicaltrials.gov NCT01564992) was approved by French regulatory authorities and an ethical committee; all patients gave written informed consent.

Variables

Height/weight were measured at baseline in all centers. Weight was measured at each visit in the Paris center only; analyses are therefore restricted to patients from this centre. Body mass index (BMI) was computed as weight (kg)/baseline height squared (m²).

At baseline, the full history of antiparkinsonian drug use since disease onset was obtained using medical records and prescriptions (start/end dates of all drugs, doses). At subsequent visits, history of all prescriptions since previous visits was obtained. DA and LD doses are expressed in LD equivalents (LED) [11].

Baseline characteristics included age, sex, education, and disease duration.

At each visit, cognitive function was assessed with the mini-mental state examination (MMSE). Patients reported all their medications (Anatomical Therapeutic Chemical classification-ATC). We identified antidepressants (ATC-N06A). Disease severity was assessed through the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS parts I-IV) and Hoehn and Yahr scale; movement disorder specialists assessed whether patients were on/off state. Dyskinesias were assessed using MDS-UPDRS part-IV. Symptoms of dopaminergic dysregulation in the last 3 months before each visit were evaluated through semi-structured interviews (compulsive gambling [12], buying [13], eating [12], sexual behaviour [14]). ICDs were defined by at least one of these symptoms [6].

Statistical analysis

Patients without any BMI measure or with missing covariates were excluded (Supplementary Figure 1).

Longitudinal trajectories of daily DA and LD dose

We modelled mean trajectories of daily DA and LD dose over the follow-up (in persons with at least one DA or LD prescription) using latent class mixed models for non-Gaussian longitudinal markers [15]. Distributions of daily DA and LD dose were transformed using the Beta Cumulative Distribution Function link function that provided the best fit (Supplementary Figure 2). This approach assumes that the population is composed of G latent classes of patients (selected using the Bayesian information criterion). Models included $\text{time} + \text{time}^2$ and were adjusted for baseline age and disease duration. The intercept and slope ($\text{time} + \text{time}^2$) were treated as random effects.

Longitudinal association of DA use with BMI change

We examined the longitudinal association of time-dependent DA use with BMI change using latent-process mixed models with random intercept and slope. The Beta Cumulative Distribution Function link function provided the best fit (Supplementary Figure 2). Models were adjusted for baseline age and disease duration, sex, education, and time-dependent LD use, severity (MDS-UPDRS part-III), on-off state, and dyskinesias (MDS-UPDRS part-IV).

Analyses are based on three different definitions of time-dependent DA and LD use: (i) users vs. non-users in previous 12 months; (ii) mean daily dose over 12 months before each visit categorized at the median (based on all visits: DA=160mg, LD=300mg); (iii) trajectories of daily dose (defined above); for this model, the effect of DA and LD trajectories were not included at baseline, because they were not significantly associated with baseline BMI. P-values for trend were computed using mean daily doses and the trajectory number (0 to 3) as continuous variables. We examined whether associations were explained by compulsive eating or ICDs by adding them to the models as time-dependent covariates and computed the percentage reduction of regression coefficients.

We conducted several sensitivity analyses:

- Adjustment for time-dependent MMSE and use of other antiparkinsonian drugs (amantadine, anticholinergics, MAO-B inhibitors) or antidepressants.
- Because patients who dropped-out or died may be different compared to those who remained in the study, we took into account missing values due to drop-out or death through a joint model [16].
- The relation of DA and LD with BMI may be subject to time-dependent confounding by disease severity (Supplementary Figure 3). To address this issue, we used sequential conditional mean models [17].

Incidence of weight gain over the follow-up

We used time-dependent Cox proportional hazards regression to estimate the hazard ratio (HR) of gaining ≥ 6 kg (~ 1 -standard deviation [SD] of the weight difference between baseline and end of follow-up) according to time-dependent DA and LD use. Patients were followed since baseline until the first visit with a weight gain of ≥ 6 kg or last visit. Age was used as the time-scale; models were adjusted for baseline disease duration and height, and time-dependent disease severity (MDS-UPDRS part-III), on-off state, and LD use; sex, education, and dyskinesias were not retained (not significant). We examined whether associations were explained by compulsive eating or ICDs by adding them as time-dependent covariates and computed the percentage reduction of regression coefficients.

Analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC), and R 3.6 packages lcm-1.9.1 [18], JM-1.4–8 [16] (R-Foundation for Statistical Computing, Vienna); P-values are two-sided and those $\leq .05$ considered statistically significant.

Data availability

Anonymized data will be shared by request from any qualified investigator.

RESULTS

PD patients' characteristics

Of 374 patients included in the Paris center, we excluded 19 with missing BMI, treatments, or covariates, and retained 355 (Supplementary Figure 1); 66.5% of the patients attended ≥ 5 assessments, 25.9% attended 2-4 assessments, and 7.6% attended the baseline assessment only. 35 patients died over the follow-up, and of those who remained alive, 79 dropped-out before last visit (Supplementary Figure 1); there were no major baseline differences between patients who dropped-out and those who remained alive, while patients who died were older and used LD more frequently and at higher doses than patients who remained alive (Supplementary Table 1). Average follow-up was of 4.0 years (SD=1.7 years).

Supplementary Table 2 shows patient's baseline characteristics. Baseline mean BMI was 26.0 kg/m² (SD=3.9); male sex, lower education, disease severity, ICDs, compulsive eating, and antidepressant use were associated with higher BMI. Fifty four (15.2%) patients were obese (BMI \geq 30) and 156 (43.9%) overweight (25 \leq BMI<30); 145 (40.8%) had normal BMI (BMI<25). Compared to patients who had not used DA in the previous 12 months, DA users were younger and more often male, had longer disease duration, used less frequently LD and at lower doses, and had more frequently ICDs and compulsive eating.

Longitudinal trajectories of DA and LD dose

Figure 1 shows trajectories of daily DA dose. Three trajectories were identified: low (decreasing, 18.5%), moderate (increasing-decreasing, 29.9%), and high (increasing, 51.6%). Patients in the low dose trajectory were older, used more often LD, and had higher MDS-UPDRS part-I (Supplementary Table 3).

Three trajectories were identified for LD dose (Supplementary Figure 4): low-increasing (14.0%), increasing-decreasing (20.7%), high-increasing (65.4%).

Longitudinal association of DA use with BMI change

Overall, BMI decreased each year by -0.07 kg/m^2 (95% Confidence Interval [CI]= $-0.12, -0.02$). Female sex, higher education, and dyskinesias were associated with lower BMI throughout the follow-up (not shown). Age, baseline disease duration, and MDS-UPDRS Part III, and on-off state were not associated with BMI but forced in the analyses due to their association with treatments.

Analyses of the relation of DA and LD use with BMI are summarized in Table 1 (Model A) and Figure 2. Baseline BMI was similar in DA users and non-users ($P=.62$), while it was higher in LD users than non-users ($P=.005$) without a significant dose-effect relation ($P\text{-trend}=.09$); the difference in baseline BMI between DA and LD users was not statistically significant ($P=.12$). BMI increased over the follow-up in DA users compared to non-users ($\text{beta}=0.13, P=.02$), while it decreased in LD users compared to non-users ($\text{beta}=-0.26, P<.001$); the difference between DA and LD users was statistically significant ($P<.001$). There was no interaction between DA and LD ($P=.10$). The dose-effect relation was more pronounced for LD ($P<.001$) than DA ($P=.13$); in DA users, there was no significant difference between patients below and above the median ($P=.45$), while in LD users, BMI decreased faster in patients above the median compared to those below ($P<.001$).

Regarding DA trajectories, compared to non-users, BMI did not increase significantly for the low trajectory ($\text{beta}=0.12, P=.23$) while associations became stronger for the moderate ($\text{beta}=0.16, P=.08$) and significant for the high ($\text{beta}=0.29, P=.001; P\text{-trend}=.001$) trajectories; BMI increase was more pronounced in the high trajectory compared to the moderate ($P=.04$) and low ($P=.02$) trajectories. For LD, compared to non-users, BMI decrease was not

significant for the low-increasing trajectory (beta=-0.14, P=.28); it was more pronounced for the increasing-decreasing (beta=-0.28, P=.02) and high-increasing trajectories (beta=-0.22, P=.06; P-trend=0.09). There was no significant difference between high-increasing and low-increasing (P=.26) or increasing-decreasing (P=.37) trajectories.

After adjustment for compulsive eating, associations between DA and BMI change decreased but remained present (Table 1, Model B); adjustment for ICDs led to a smaller attenuation (Supplementary Table 4). Adjustment had a weaker effect for LD than DA.

Conclusions were similar after adjustment for MMSE, use of other antiparkinsonian drugs (not shown) or antidepressants (Supplementary Table 5), and after taking into account death and drop-out (Supplementary Table 6).

After taking into account time-dependent confounding through sequential conditional mean models, BMI was higher in DA users than non-users at each visit (beta=0.35, P=.03); the difference increased as DA dose increased (P-trend=.02; Supplementary Table 7). The difference between LD users and non-users was not statistically significant (beta=-0.10, P=.45), but higher doses tended to be associated with lower BMI (P-trend=.01).

DA use and incidence of weight gain over the follow-up

Over the follow-up, 75 patients (11 never DA users, 64 ever DA users) gained ≥ 6 kg. The cumulative incidence of weight gain of ≥ 6 kg was 30.9% (95% CI=23.6-38.3); it was 14.8% (95% CI=2.7-26.8) in never DA users and 33.0% (95% CI=24.9-41.1) in ever DA users.

Incidence of weight gain of ≥ 6 kg was 2.10-times higher in DA users compared to non-users (P=.04), with a dose-effect relation (P-trend=.03; Table 2). Although LD users were less

likely to gain weight, the association was not statistically significant (HR=0.60, P=.10; P-trend=.23).

Both ICDs and compulsive eating were associated with incidence of weight gain (Table 2). The HR for DA decreased by -15.9% after adjustment for compulsive eating but remained >1; the attenuation was weaker after adjustment for ICDs (-11.4%). For LD, compulsive eating and ICDs did not attenuate associations.

DISCUSSION

In this longitudinal study of PD patients, after adjustment for disease severity, dyskinesias, and age, DA users gained weight over the follow-up while LD users lost weight. Part of the association of DA use with weight gain was explained by compulsive eating.

According to a meta-analysis, PD patients had on average lower BMI than controls, although the difference was variable across studies; disease severity was associated with weight loss [3]. A variety of factors are involved in weight loss in PD [4]. Metabolic studies suggest that increased energy expenditure related to rigidity, tremor, and dyskinesias are involved. Other factors include appetite loss, nausea, vomiting, and gastrointestinal function impairment. In addition, DA may lead to changes in eating behavior (e.g., binge eating) by activating the reward system [4, 19].

Few studies investigated the longitudinal association between DA and weight change. One study of 58 patients with short follow-up (3 years) did not find any association between DA (\pm LD compared to LD only) and BMI change [8]. In another study, LD use and baseline LED were associated with more rapid annual weight loss in 1619 patients over 7 years compared to DA use [9]. In another study, the weight of 28 patients treated with pramipexole increased from 74.8 ± 13.2 kg to 77.4 ± 13.2 kg ($P < .001$) over 3 months [7]. Finally, a randomized trial showed a significant increase of ~ 1 kg in the pramipexole group relative to placebo over 12 weeks [20].

Analyses based on the average daily DA dose did not show a clear dose-effect relation. However, in analyses based on DA trajectories, patients in the high trajectory had the greatest weight gain over the follow-up, while it was less pronounced for the moderate trajectory and not significant for the low trajectory. These results highlight the interest of trajectory analyses; while, the mixed model uses the information on DA dose at each time point,

trajectory analyses use information on DA dose throughout the follow-up. In the survival analysis, patients above the median DA dose over all the follow-up had a 2.4-fold increased risk of gaining ≥ 6 kg. Even moderate weight gain in middle-age is associated with increased risk of incident cardiometabolic disease [21, 22] and cancer [23]. Larger studies are necessary to examine the relation between prolonged DA use and these outcomes in PD patients.

DA use is the main risk factor for ICDs, and compulsive eating is the most frequent ICD [6]. After adjustment for compulsive eating, the associations between DA and weight gain decreased but remained present. It is possible that we measured imperfectly changes in eating behavior, as questions on ICDs referred to the three months prior to each visit, or that some patients did not report them. Alternatively, it is possible that other mechanisms may be involved in this association. For instance, both ergot and non-ergot DA can induce oedema [24]. In the CALM-PD trial, pramipexole compared to LD was associated with a 3-fold increased risk of leg oedema; the 4-year incidence of leg oedema was 45% in pramipexole users [25]. The etiology of DA-induced oedema is not well understood, but it has been hypothesized that DA could interfere with sympathetic nervous system regulation [25], which also plays a key role in weight regulation [26].

Regarding LD, while cross-sectional studies suggested that LD can be associated with ICDs [27], a previous longitudinal analysis of our data showed no association between LD and ICDs [6]. In addition, in the present study, adjustment for compulsive eating or ICDs had a weaker effect on BMI change for LD than DA.

Disease severity represents a time-dependent confounder of the relation between DA or LD use and BMI (Supplementary Figure 3). Analyses were adjusted for time-dependent disease severity, as well as LD use and dyskinesias which also correlate with severity. In addition, we used a statistical method designed to handle time-dependant confounding that

confirmed that BMI was higher by $\sim 0.5\text{kg/m}^2$ in DA users compared to non-users, with a dose-effect relationship [17].

In agreement with other studies [9, 28, 29], LD use was associated with decreasing BMI in the linear mixed model, although this pattern was less significant for LD trajectories, using survival analysis, and after adjusting for time-dependent confounding.

Our study has limitations. First, patients were included in referral centers and relatively young. Because DA are more frequently used in younger patients, this may contribute to overestimate weight gain frequency. Second, the proportion of patients who died or dropped-out before the end of follow-up was not negligible. However, there were no major differences between patients who dropped-out and remained alive, and a statistical method that takes into account missing values due to drop-out or death led to similar conclusions. Third, previous studies showed that DBS leads to weight gain [4]. Few patients underwent DBS over the follow-up, and they were censored at the time of surgery; we were therefore unable to examine the relation between DBS and weight change. Fourth, MDS-UPDRS part-III was measured on- or off-state, and analyses were adjusted for this variable. At each visit, $>80\%$ of patients were on-state which leads to underestimate disease severity, but in a similar way for all patients and visits and independently of BMI. We repeated our analyses after adjusting for time-dependent Hoehn and Yahr and results were unchanged (not shown). Fifth, one study of 7 patients on DA showed that in 5 patients who lowered the dose or discontinued treatment, no further weight gain occurred [30]. The small number of patients who discontinued DA in our study did not allow us to examine whether BMI declined after discontinuation. Finally, BMI at each visit was computed based on baseline height, leading to underestimate BMI if height decreased significantly over the follow-up. In a French study ($n=1,520$, 65-85 years), the 10-year change in height was -2.0 cm (95% CI: -2.2 , -1.9); therefore, a strong impact on our findings is unlikely [31].

The main strength of our study is the longitudinal annual assessment of a relatively large cohort of PD patients that allowed us to take into account the full history of DA use and BMI change over 6 years. We used a flexible statistical approach that captures nonlinear trajectories [18], and carried out a number of sensitivity analyses that confirmed the robustness of our findings.

Our study emphasizes the need to carefully monitor changes in eating behavior and weight as PD progresses, particularly weight gain in DA users and weight loss in LD users.

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DISCLOSURES

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CONTRIBUTIONS

Fanny Artaud: Study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript for intellectual content.

Pei-Chen Lee: Interpretation of data, critical revision of manuscript for intellectual content.

Graziella Mangone: Acquisition and interpretation of data, critical revision of manuscript for intellectual content.

Marie Vidailhet: Interpretation of data, critical revision of manuscript for intellectual content.

Jean-Christophe Corvol: Acquisition and interpretation of data, study supervision, critical revision of manuscript for intellectual content.

Alexis Elbaz: Study concept and design, analysis and interpretation of data, drafting of the manuscript, study supervision, critical revision of manuscript for intellectual content.

All authors have approved the final article.

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FIGURE LEGEND

Figure 1. Trajectories of the daily dose of dopamine agonists (DAs) with 95% pointwise confidence intervals

Daily DA dose was assessed annually; at each time point, it is defined as the daily dose over the previous 12 months. 95% pointwise confidence intervals were obtained by a Monte Carlo method.

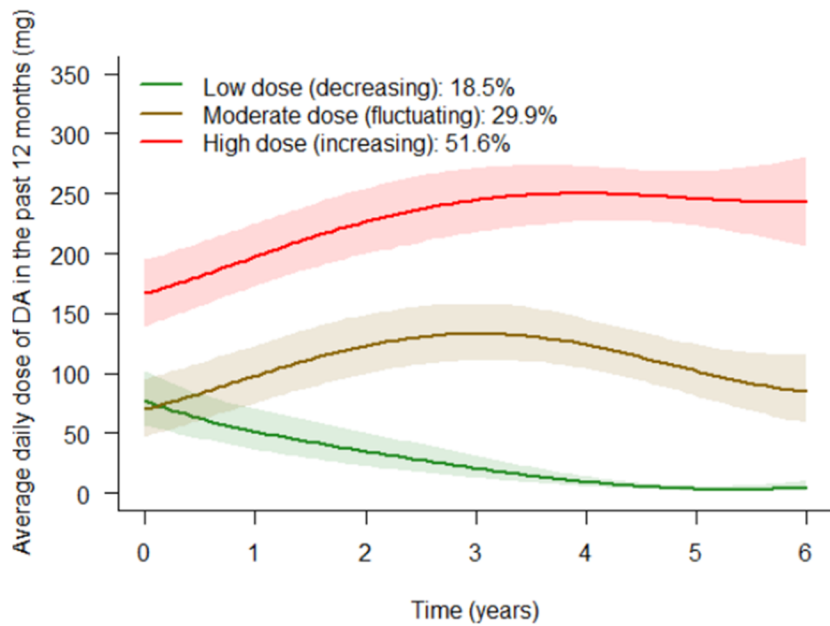
Figure 2. Predicted trajectories of body mass index (BMI) with 95% pointwise confidence intervals according to use of dopamine agonists (DAs)

Regression coefficients of the corresponding models are shown in Table 1 (Model A).

1– Predicted trajectories of BMI according to DA use (time-dependent). The curves correspond to the average trajectory of BMI in patients who never took DA during the follow-up (blue) and in patients who remained on DA throughout the follow-up (red).

2– Predicted trajectories of BMI according to daily DA dose categorized at the median (time-dependent). The curves correspond to the average trajectory of BMI in patients who never took DA over the follow-up (blue) and in patients with DA doses below (green) or above (red) the median throughout the follow-up.

3– Predicted trajectories of BMI according to trajectories of daily DA dose over the follow-up. The curves correspond to the average trajectory of BMI in patients according to their trajectory of daily DA dose (defined in Figure 1).



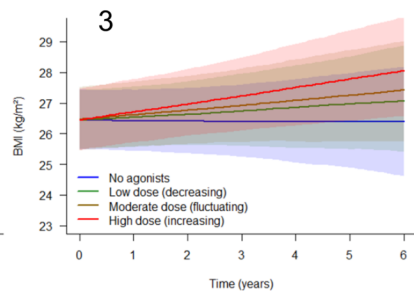
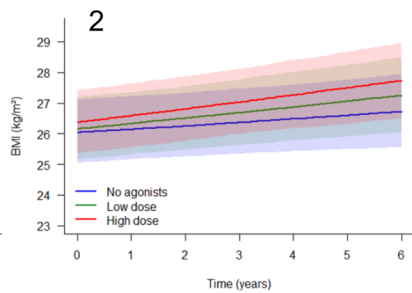
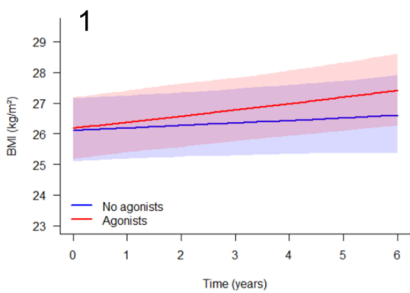


Table 1. Longitudinal associations of use of dopamine agonists (DA) and levodopa (LD) with the latent process of change of body mass index (BMI, kg/m²) over the follow-up before (model A) and after adjustment for compulsive eating (model B).

Characteristics	Model A ^a			Model B ^b			$\Delta\%$ ^c
	Estimate (95% CI)	P	P-trend	Estimate (95% CI)	P	P-trend	
1 – DA and LD use (time-dependent)							
DA use (yes vs no)	0.09 (-0.26, 0.44)	.62		0.07 (-0.28, 0.42)	.68		-18.4
LD use (yes vs no)	0.45 (0.14, 0.76)	.005		0.42 (0.11, 0.73)	.009		-6.0
Time (per 1 year)	0.09 (-0.06, 0.24)	.26		0.08 (-0.07, 0.24)	.28		
DA use × Time	0.13 (0.02, 0.24)	.02		0.11 (0.01, 0.22)	.04		-11.4
LD use × Time	-0.26 (-0.38, -0.13)	<.001		-0.25 (-0.38, -0.13)	<.001		-2.1
2 – Median of daily DA and LD dose (time-dependent)							
Daily DA dose	No use	Ref.		Ref.			
	< median	0.14 (-0.22, 0.51)	.45	0.12 (-0.24, 0.49)	.51		-12.3
	≥ median	0.35 (-0.06, 0.76)	.10	0.31 (-0.10, 0.72)	.14	.09	-10.9
Daily LD dose	No use	Ref.		Ref.			
	< median	0.19 (-0.14, 0.52)	.26	0.15 (-0.18, 0.48)	.38		-20.7
	≥ median	0.60 (0.21, 0.99)	.003	0.58 (0.19, 0.97)	.004	.11	-3.3
Time (per 1 year)		0.12 (-0.04, 0.27)	.14	0.12 (-0.04, 0.28)	.13		
Daily DA dose × Time	No use	Ref.		Ref.			
	< median	0.08 (-0.04, 0.20)	.20	0.07 (-0.05, 0.19)	.27		-14.1
	≥ median	0.12 (-0.01, 0.24)	.06	0.10 (-0.03, 0.22)	.13	.24	-19.0
Daily LD dose × Time	No use	Ref.		Ref.			
	< median	-0.15 (-0.28, -0.02)	.03	-0.14 (-0.28, -0.01)	.04		-4.4
	≥ median	-0.35 (-0.50, -0.21)	<.001	-0.36 (-0.50, -0.22)	<.001	<.001	1.4
3 – Trajectories of daily DA and LD dose							
Time (per 1 year)		-0.01 (-0.28, 0.26)	.95	-0.01 (-0.29, 0.27)	.95		
DA trajectories × Time	No use × Time	Ref.		Ref.			
	Low dose × Time	0.12 (-0.07, 0.31)	.23	0.11 (-0.08, 0.31)	.25		-4.7
	Moderate dose × Time	0.16 (-0.02, 0.34)	.08	0.15 (-0.04, 0.33)	.12		-9.6
	High dose × Time	0.29 (0.11, 0.46)	.001	0.27 (0.09, 0.45)	.003	.002	-6.7
LD trajectories × Time	No use × Time	Ref.		Ref.			
	Low-increasing × Time	-0.14 (-0.39, 0.11)	.28	-0.15 (-0.40, 0.10)	.23		11.2
	Increasing-decreasing × Time	-0.28 (-0.53, -0.04)	.02	-0.28 (-0.53, -0.04)	.02		0.1
	High-increasing × Time	-0.22 (-0.45, 0.01)	.06	-0.22 (-0.45, 0.02)	.07	.15	-3.1

DA, dopamine agonist; LD, levodopa.

^a The longitudinal trajectory of BMI was modeled using a latent-process mixed model adjusted for age at baseline (centered at 62 years), disease duration at baseline (centered at 2 years), sex (reference, women), education (reference, low education), time-dependent MDS-UPDRS III (centered at 26), time-dependent on-off state (reference, on state), and time-dependent dyskinesias (reference, no). Main effects of DA and LD represent their association with BMI at baseline while the interactions of time with DA, LD, and trajectories represent their association with BMI change.

^b Model B = Model A + time-dependent compulsive eating (reference, no).

^c Percentage reduction in the association between DA or LD and BMI after adjustment for compulsive eating ($\Delta = 100 \times (\beta_{\text{Model B}} - \beta_{\text{Model A}}) / \beta_{\text{Model A}}$), where A is the model without adjustment for compulsive eating and B is the model adjusted for compulsive eating.

Table 2. Relation between use of dopamine agonists (DA) and weight gain of ≥ 6 kg over the follow-up, before (model A) and after adjustment for compulsive eating (model B) or ICDs (model C).

Characteristics		N cases	Inc %	Model A ^a		Model B ^b			Model C ^c		
				HR (95% CI)	P	HR (95% CI)	P	$\Delta\%$ ^d	HR (95% CI)	P	$\Delta\%$ ^d
1 – DA use (time-dependent)											
DA use	No	11	3.2	1.00 (Ref.)	--	1.00 (Ref.)	--	--	1.00 (Ref.)	--	--
	Yes	64	6.9	2.10 (1.03, 4.28)	.04	1.87 (0.91, 3.83)	.09	-15.9	1.93 (0.94, 3.96)	.07	-11.4
LD use	No	19	10.7	1.00 (Ref.)	--	1.00 (Ref.)	--	--	1.00 (Ref.)	--	--
	Yes	56	5.1	0.60 (0.33, 1.11)	.10	0.59 (0.32, 1.11)	.10	3.0	0.58 (0.31, 1.08)	.08	7.3
Compulsive eating	No			--	--	1.00 (Ref.)	--	--	--	--	--
	Yes			--	--	1.94 (1.14, 3.30)	.02	--	--	--	--
ICDs	No			--	--	--	--	--	1.00 (Ref.)	--	--
	Yes			--	--	--	--	--	1.67 (1.02, 2.72)	.04	--
2 – Median of daily DA dose (time-dependent)											
DA use	No	11	3.2	1.00 (Ref.)	--	1.00 (Ref.)	--	--	1.00 (Ref.)	--	--
	< median	23	5.5	1.69 (0.77, 3.70)	.19	1.56 (0.71, 3.43)	.27	-15.6	1.60 (0.73, 3.51)	.24	-10.9
	\geq median	41	8.1	2.40 (1.13, 5.12)	.02	2.04 (0.94, 4.44)	.07	-18.5	2.15 (0.99, 4.63)	.05	-12.8
				--	.03 ^e	--	.11 ^e	--	--	.07 ^e	--
LD use	No	19	10.7	1.00 (Ref.)	--	1.00 (Ref.)	--	--	1.00 (Ref.)	--	--
	< median	28	6.2	0.65 (0.34, 1.24)	.19	0.65 (0.34, 1.26)	.20	-1.3	0.64 (0.33, 1.22)	.17	5.3
	\geq median	28	4.4	0.57 (0.28, 1.14)	.11	0.53 (0.26, 1.09)	.08	11.0	0.54 (0.26, 1.08)	.08	10.6
				--	.23 ^e	--	.20 ^e	--	--	.18 ^e	--
Compulsive eating	No			--	--	1.00 (Ref.)	--	--	--	--	--
	Yes			--	--	1.84 (1.07, 3.18)	.03	--	--	--	--
ICDs	No			--	--	--	--	--	1.00 (Ref.)	--	--
	Yes			--	--	--	--	--	1.64 (1.00, 2.68)	.05	--

DA, dopamine agonist; LD, levodopa. Inc, incidence.

Hazard ratios (HR) and 95% confidence intervals (CI) were computed using time-dependent Cox proportional hazards models. Age is used as the time-scale.

^a Model A is adjusted for disease duration at baseline, height at baseline, time-dependent MDS-UPDRS III, and time-dependent on-off state; sex, education, and dyskinesias were not retained in the survival model because they were not associated significantly with the outcome.

^b Model B = Model A + time-dependent compulsive eating.

^c Model C = Model A + time-dependent ICDs.

^d Percentage reduction in the association between DA and weight gain after adjustment for compulsive eating ($\Delta=100 \times (\beta_{\text{Model B}} - \beta_{\text{Model A}}) / \beta_{\text{Model A}}$) or ICDs ($\Delta=100 \times (\beta_{\text{Model C}} - \beta_{\text{Model A}}) / \beta_{\text{Model A}}$).

^e P-trend.