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RESEARCH ARTICLE

Annonaceae Consumption Worsens Disease Severity and Cognitive Deficits in Degenerative Parkinsonism

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ABSTRACT: Background: High consumption of *Annona muricata* fruit has been previously identified as a risk factor for atypical parkinsonism in the French Caribbean islands.

Objective: We tested whether consumption of Annonaceae products could worsen the clinical phenotype of patients with any form of degenerative parkinsonism.

Methods: We analyzed neurological data from 180 Caribbean parkinsonian patients and specifically looked for dose effects of lifelong, cumulative Annonaceae consumption on cognitive performance. Using unsupervised clustering, we identified one cluster with mild/moderate symptoms (N = 102) and one with severe symptoms including cognitive impairment (N = 78).

Results: We showed that even low cumulative consumption of fruits/juices (>0.2 fruit-years) or any consumption of herbal tea from Annonaceae worsen disease severity and cognitive deficits in degenerative parkinsonism including Parkinson's disease (OR fruits-juices: 3.76 [95% CI: 1.13–15.18]; OR herbal tea: 2.91 [95% CI: 1.34–6.56]).

Conclusion: We suggest that more restrictive public health preventive recommendations should be made regarding the consumption of Annonaceae products. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson; cognitive impairment; food toxin; Annonaceae; risk factor

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There is an unexpectedly high proportion of atypical parkinsonism (AP) in French Caribbean islands compared to Parkinson's disease (PD).^{1–3} Caribbean patients presenting with AP show low levodopa sensitivity, low education, lower cognitive performance than PD patients, and frequent symptoms among the following: hallucinations, rapid eye movement (REM) sleep behavior disorder,⁴ tremor, cortical myoclonus,⁵ dysautonomia,^{2,3} and falls and postural instability.^{2,3} However, a large majority of them do not fall into classic AP subtypes, as defined in European or Northern American populations. For example, patients with a

progressive supranuclear palsy (PSP)-like phenotype frequently suffer from hallucinations or dysautonomia² and develop widespread brain atrophy,⁶ (ie, clinical and histological features not seen in common forms of PSP).⁷ The reasons accounting for the higher proportion of atypical syndromes among degenerative parkinsonism cases and the presence of unusual phenotypes in the French Caribbean area are largely unknown. Genetic factors as well as chronic exposure to environmental agents could be involved.^{8,9}

Fruits, juices, and herbal teas from Annonaceae are widely consumed in the Caribbean for their taste as well as traditional medicine applications and cultural reasons^{1,2,8} but experimental and epidemiological evidence indicates that annonaceous acetogenins may possibly contribute to AP in the Caribbean. In particular, converging in vitro and in vivo studies have reported that acetogenins are potential neurotoxins through their capacity to induce mitochondrial dysfunction and tau-related abnormalities.^{8,10,11} These toxic effects result not only in damage to the nigrostriatal dopaminergic system but also to different populations of cortical and subcortical neurons.^{8,11} In addition, a seminal paper reported not only that regular consumption of Annonaceae was associated with an increased risk of developing AP but also that a stabilization or an improvement in patients' clinical condition occurs after stopping consumption.¹ Thereafter, a retrospective cohort study established that high cumulative consumption of at least 10 fruit-years (ie, one fruit/day every day for 10 years) of an Annonaceae fruit, *Annona muricata*, increased the risk of AP.²

Here, we investigated the link between Annonaceae consumption and clinical manifestations not only in atypical forms of parkinsonism but also in PD. Specifically, we examined whether Annonaceae consumption was potentially associated with the worsening of motor and cognitive symptoms in both clinical entities. We analyzed cross-sectional data from a group of French Caribbean patients with degenerative parkinsonism, in which lifelong cumulative consumption of Annonaceae products (fruit, juice, or herbal tea) was assessed. As cognitive decline is an early and frequent feature of AP, we focused on a possible dose–response relationship between lifelong cumulative consumption of Annonaceae products and cognitive performance in both AP and PD patients. This objective was further motivated by the field experience of neurologists who noticed that even patients fulfilling the diagnostic criteria for PD tended to frequently develop early cognitive alterations. We identified the minimal threshold of lifelong cumulative consumption of Annonaceae products associated with cognitive worsening using nonlinear relationship modeling. Applying unsupervised clustering to our clinical sample, we identified a group of participants with severe symptoms. We tested whether lifelong cumulative consumption of Annonaceae above a minimal

threshold increased both motor and nonmotor symptom severity in degenerative parkinsonism patients regardless of whether patients were classified as having PD or AP.

Methods

Study Design

We included patients from a cohort of 305 consecutive patients with degenerative parkinsonism prospectively included between 2012 and 2016 in a bicenter cross-sectional study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03368300) Id: NCT03368300, December 11, 2017) conducted in the French Caribbean islands of Guadeloupe and Martinique.³ This cohort described the clinical spectrum of parkinsonism in these two neighboring islands whose population was around 750,000 inhabitants at the time of the study. Parkinsonism was defined as bradykinesia, in combination with either resting tremor, rigidity, or both. Patients with a history, clinical manifestations, or neuroradiological findings suggestive of secondary parkinsonism were excluded. A detailed medical history and neurologic examination were conducted on all patients, including eye movement recording and detailed neuropsychological assessment when possible (not performed in patients with major dysarthria or very severe motor symptoms, very severe cognitive impairment, non-French speaking, or low educational level). Based on a post hoc analysis of the data, the patients were divided into two groups: (1) PD patients (PD group) who fulfilled the criteria for established or probable PD¹² and (2) patients with AP who did not meet the criteria for PD. The study was approved by the French Sud Ouest and Outre Mer III ethics committee (2011/86). Informed written consent was obtained from all patients.

Clinical Assessment

Clinical findings in the cohort of 305 patients have been previously described in detail.³ Demographic data, motor and nonmotor symptoms, disease onset, and comorbidities were recorded. The severity of the disease and related disability were evaluated using the Hoehn and Yahr staging and rating of Schwab and England activities of daily living. ON-state motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS)-3 rating scale. A positive response to levodopa was defined as a subjective perceived improvement, clearly documented by a reliable patient or caregiver, or a minimal 30% documented improvement in the UPDRS-3 score following a levodopa challenge. The Stiasny-Kolster REM sleep behavior disorder (RBD) screening questionnaire was used to detect RBD and a score ≥ 5 was considered positive.¹³

Cognitive Assessment

Global cognitive efficiency was assessed with the Mattis Dementia Rating Scale (MDRS)¹⁴ and Mini-

Mental State Examination (MMSE).¹⁵ Executive functions were assessed with the frontal assessment battery¹⁶ (FAB), frontal score,¹⁷ and the Trail Making Test A and B.¹⁸ Attention and working memory were assessed through forward and backward digit span tests. Verbal episodic memory was assessed with the Free and Cued Selective Recall Reminding Test (FCSRT).¹⁹ Language was assessed with the denomination test DO80.²⁰ Visuo-spatial abilities were assessed by the Visual Object and Space Perception (VOSP)²¹ test and Clock-Drawing Test (CDT).²² Limb apraxia was assessed using the Peigneux scale.²³ Behavioral symptoms were assessed with the Frontal Behavioral Inventory (FBI) scale.^{24,25}

Oculomotor Recordings

Vertical and horizontal mean saccade velocities, mean saccade latencies, and saccade gains were recorded using a video-based eyetracker (Mobile EBT[®], eyeBRAIN, www.eyebrian.com).²⁶

Consumption of Annonaceae

Participants were asked about food habits regarding the consumption of three fruits from the Annonaceae family available in the Caribbean islands: *A. muricata* (soursop, corossol, graviola, guanabana), *A. squamosa* (sweetsop, sugar apple, pomme-cannelle, saramuyo), and *A. reticulata* (custard apple, cachiman) (see Fig. S1). Consumption of Annonaceae fruits (or fruit juices) and herbal teas was evaluated separately for each fruit for successive periods of 10 years throughout the patient's life, and cumulative consumption was expressed in fruit-years, defined as the number of fruits and glasses of fruit juice for each fruit (one glass of juice = 1 fruit) per day multiplied by the frequency of consumption every year and the number of years of consumption (for example, a person who has eaten two fruits a day for 10 years, one fruit a day for 20 years or one fruit every 2 days for 40 years have all a cumulative consumption of 20 fruit-years).² Regarding herbal teas, the cumulative consumption was expressed in cup-years (one cup-year corresponds to one cup/day for 1 year). Finally, we combined both fruit/juice and herbal tea consumption by summing the above measures and expressing the result in an arbitrary unit corresponding to a fruit-or-cup-year unit. Dietary information was collected through a structured questionnaire built with dieticians and epidemiologists, and already used in previous studies.^{2,3} If needed, a family informant could help the patient to answer questions.

Statistical Analyses

Statistics were run using R software (R Core Team (2018), <https://www.R-project.org/>). We used restricted cubic splines^{27,28} to assess the nonlinear dose-response association between Annonaceae product

cumulative consumption and cognitive performance according to MDRS performance. This approach allowed the identification of the lowest cumulative consumption of Annonaceae products with a clinical impact.

Unsupervised clustering was used to identify subgroups of patients sharing similar clinical profiles. A similar approach previously identified a subgroup of subjects with probable dementia within an aging population.^{29,30} First, we identified a subset of 43 measures related to clinical assessment, cognitive performance, and oculomotor performance (see Table S2). For the clustering analysis, we discarded measures related to demography (age, sex, education, disease duration), comorbidities (hypertension, diabetes, dyslipidemia, alcohol use, body mass index), and Annonaceae consumption. We used data with fewer than 35% of the values missing (see Table S3 for the list of the discarded measures) and achieved an imputation using the *missMDA* package.³¹ Principal component analysis was run on imputed data, and hierarchical clustering was applied to the first two principal components using the *FactoMineR* package³² to identify clusters of patients with different symptom severities. We used the *nbClust* tool³³ to automatically determine the optimal number of subgroups within the sample, which was found to be 2.

Univariate between-group comparisons were achieved using Wilcoxon rank sum tests for continuous measures and χ^2 for categorical measures. Multivariate linear models for continuous measures or logistic models for binary categorical variables were used to confirm group differences while accounting for other potential confounding factors such as age, sex, education, and disease duration.

Multivariate logistic models were used to test the impact that consumption of Annonaceae products above a threshold value had on the risk of belonging to the severe group while accounting for potential confounding factors such as age, sex, education, disease duration, and comorbidities known to increase the risk of cognitive impairment and dementia (eg, hypertension, diabetes, obesity, dyslipidemia, and alcohol consumption).

Results

Participants

Among the 305 patients with parkinsonism in the French Caribbean islands from a community-based cohort from Guadeloupe and Martinique (2012–2016),³ 180 participants who had a detailed neuropsychological assessment (within the year of inclusion) provided data for this study (see Table S4 for comparison of patients included vs. excluded). Among them, 118 had oculomotor recordings. All 180 studied

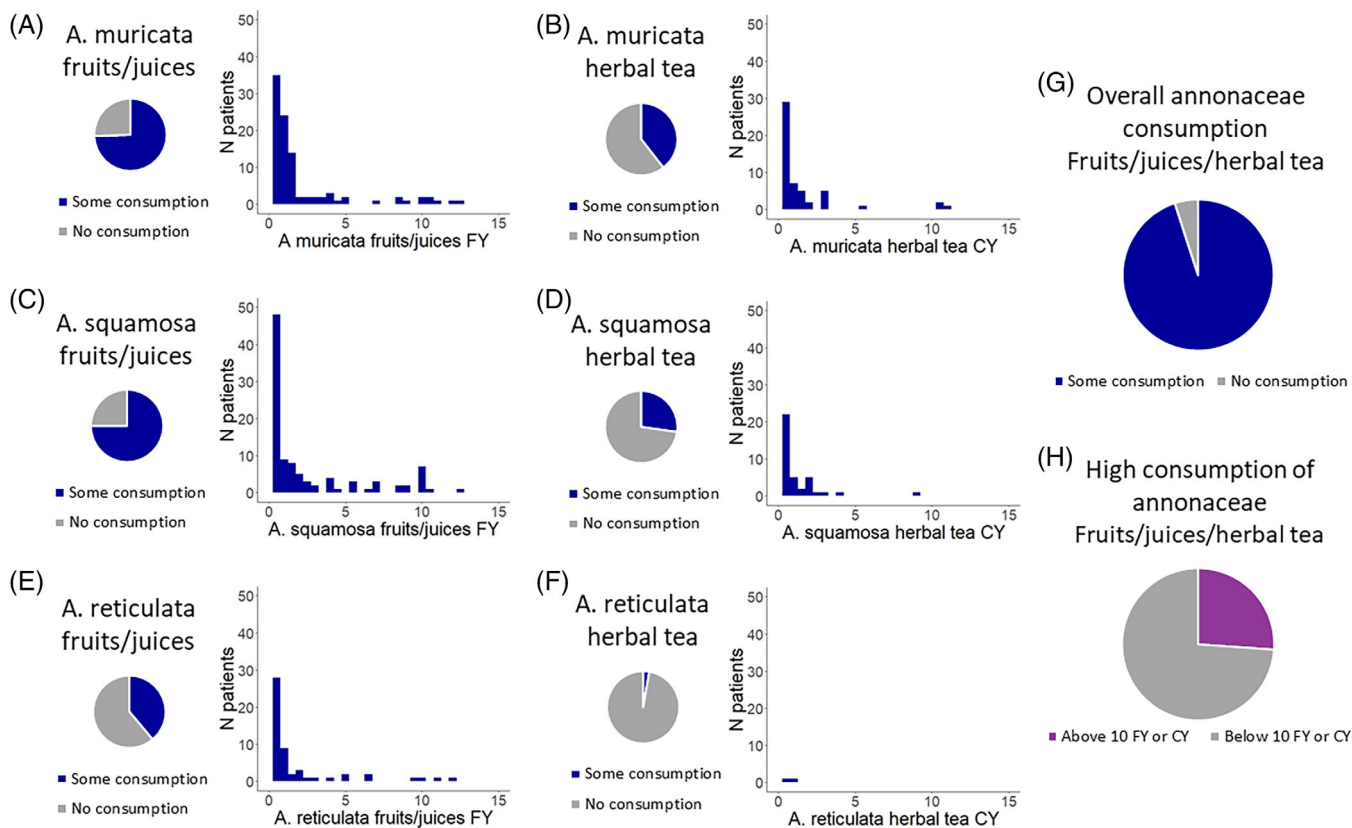


FIG. 1. Consumption of Annonaceae fruits/juices and herbal tea in the Caribbean parkinsonism cohort. Cumulative consumption of three Annonaceae (*Annona muricata* (A, B), *A. squamosa* (C, D), and *A. reticulata* (E, F)) in the Caribbean parkinsonism cohort. Fruit and juice consumption is provided in fruit-year (FY) units (A, C, E). Herbal tea consumption was provided in cup-year units (CY) (B, D, F). Histograms only report cumulative consumption under 15 FY or CY to improve graphical representation. The larger pie graphs describe the proportion of participants exposed to some Annonaceae (G) and the proportion of participants reporting high exposure to Annonaceae (above 10 FY or CY) (H).

patients answered a questionnaire about food consumption, including Annonaceae products. Among these 180 patients, 74 (41%) were classified as having probable PD and 106 (59%) as having AP (see flowchart in Fig. S5).

Annonaceae Consumption

Participants from the Caribbean parkinsonism cohort were often exposed to Annonaceae fruits and juices. Among the 180 participants, 137 participants (76.1%) acknowledged consumption of *A. muricata* fruits/juices, 135 (75%) consumed *A. squamosa* fruits/juices, and 70 (38.9%) consumed *A. reticulata* fruits/juices. Only 14 participants (7.8%) never or barely ever consumed one of these fruits. In addition, 71 participants (39.4%) acknowledged drinking infusions of *A. muricata*, 49 participants (27.2%) drank infusions of *A. squamosa*, and only 5 participants (2.8%) drank infusions of *A. reticulata* (Figs 1 and S1). Among Annonaceae consumers, a majority (72.8%) consumed these fruits throughout their whole life (Fig. S6). We

did not find any difference in Annonaceae consumption between PD and AP groups.

Impact of Annonaceae Consumption on Cognition

We used restricted cubic splines to model the nonlinear dose–effect relationship between cumulative consumption of Annonaceae products and global cognitive performance measured with the MDRS.^{34,35} We found that consumption of Annonaceae fruit, juice, and herbal tea above a low threshold limit value has a detrimental impact on cognition (Fig. 2). Cognitive performance assessed with the MDRS worsens above a cumulative consumption threshold of 0.2 fruit-years of Annonaceae fruit/juice (ie, one fruit every 5 days for 1 year) or with consumption of any quantity of Annonaceae herbal tea. The cognitive impact of Annonaceae cumulative consumption above a low threshold is observed in both PD and AP groups (Fig. S7). Similar thresholds are found if we study the

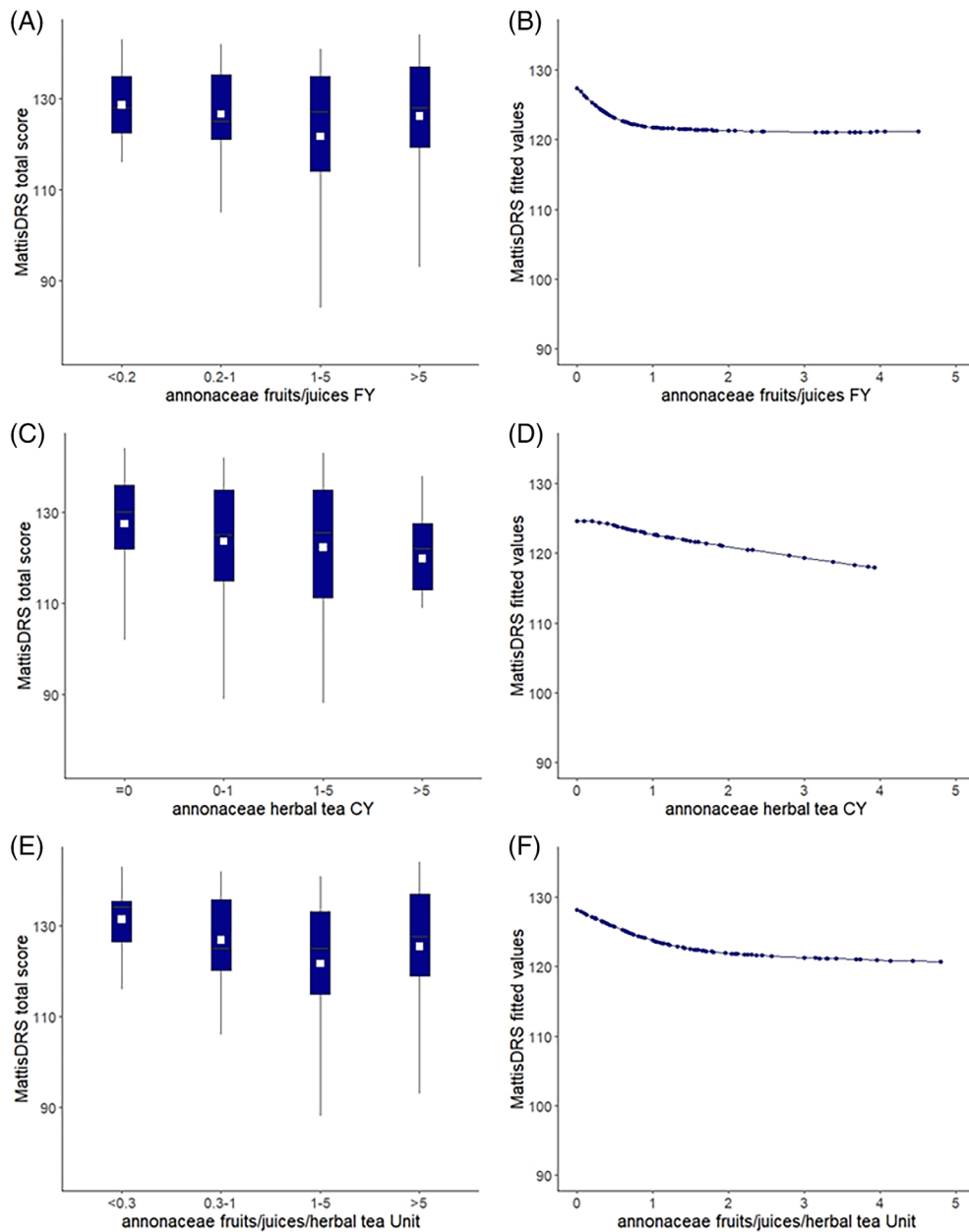


FIG. 2. Dose–effect nonlinear relationship between cumulative consumption of Annonaceae and cognitive performance. Dose–effect relationship between cumulative consumption of Annonaceae and cognitive performance based on the Mattis Dementia Rating Scale (MDRS). Box plots (white dot for mean) and restricted cubic splines are provided for Annonaceae fruits/juices in fruit-years (FY) (A, B), Annonaceae herbal tea in cup-years (CY) (C, D), and Annonaceae fruits/juices/herbal tea in composite units.

dose–effect relationship between cumulative consumption of Annonaceae products and motor symptoms according to the UPDRS-3 scale (Fig. S8).

Two Subgroups of Patients

Unsupervised clustering applied to the clinical data (neurological and behavioral symptoms, cognitive performance, and oculomotor recordings) identified two subgroups of patients: one with severe symptoms

including cognitive impairment ($N = 78$) and another one with mild-to-moderate symptoms ($N = 102$) (Table 1 [demographics and neurological features]; Table 2 [cognitive measures and oculomotor recordings]). The clinical features of the two patient subgroups remained different when the statistics were adjusted for age, sex, education, and disease duration.

The subdivision between patients with severe and mild/moderate symptoms does not fully match current clinical criteria for differentiating PD from atypical forms of

TABLE 1 Demographics and neurological features

Measure	N (range)	Subgroup 1 Mild-to-moderate profile	Subgroup 2 Severe degenerative Parkinsonism	P (Wilcoxon test or χ^2)	P adjusted for age, sex, education, and disease duration
Demographics					
Age	180 (30–90)	66.16 (9.09)	70.73 (9.09)	0.003	–
Sex ratio M/F	–	54/48	51/27	0.093	–
Low education (<primary school)	179 (0–1)	12.75%	28.57%	0.008	–
Age at onset	180 (30.81–90.22)	60.03 (10.73)	62.46 (10.89)	0.216	–
Duration of disease	180 (0–23)	5.26 (4.77)	7.56 (5.14)	<0.001	–
Parkinsonism severity					
UPDRS-3 motor	180 (3–73)	21.71 (12.76)	34.49 (14.28)	<0.001	<0.001
L-DOPA sensitivity (objective or subjective)	180 (0–1)	71.08%	45.45%	<0.001	<0.001
LEDD (mg/day)	180 (0–2250)	486.19 (385.04)	563.22 (411.99)	0.231	0.929
Hoehn & Yahr>3	178 (0–5)	7.92%	24.68%	0.004	0.022
Schwab & England $\leq 40\%$	178 (0–100%)	12.87%	32.47%	0.003	0.009
Neurological features					
Axial rigidity	178 (0–1)	45.10%	75.00%	<0.001	<0.001
Symmetry	180 (0–1)	22.77%	39.74%	0.014	0.058
Resting tremor	180 (0–1)	57.84%	43.59%	0.058	0.078
Postural instability	177 (0–1)	43.00%	83.12%	<0.001	<0.001
Falls	178 (0–1)	26.73%	70.13%	<0.001	<0.001
Vertical supranuclear palsy	178 (0–1)	8.91%	30.77%	<0.001	<0.001
Bladder incontinence	178 (0–1)	26.47%	57.89%	<0.001	<0.001
Orthostatic hypotension	177 (0–1)	35.64%	48.68%	0.081	0.101
SNK scale	180 (0–10)	4.76 (3.11)	5.74 (2.79)	0.038	0.224
Visual hallucinations	176 (0–1)	18.00%	46.75%	<0.001	<0.001
Auditory hallucinations	175 (0–1)	14.00%	25.00%	0.064	0.056

Abbreviations: M, male; F, female; UPDRS-3, Unified Parkinson’s Disease Rating Scale-Part 3; L-DOPA, levodopa; LEDD, L-dopa equivalent daily dose; SNK, Stiany and Kolster scale. Bold type denotes statistical significance.

parkinsonism: 58 of 106 (54.7%) participants with AP showed severe symptoms, whereas only 20 of 74 (27.0%) participants with PD were classified

as severe. Accordingly, a low Cohen’s kappa value ($\kappa = 0.26$; 95% CI: 0.13–0.4) indicated fair agreement between these two partitions.

TABLE 2 Cognitive measures and oculomotor recordings

Measure	N (range)	Subgroup 1 Mild-to-moderate Profile	Subgroup 2 Severe degenerative Parkinsonism	P (Wilcoxon test or χ^2)	P adjusted for age, sex, education, and disease duration
Cognitive measures					
MDRS	173 (0–144)	130.27 (9.99)	112.54 (20.92)	<0.001	<0.001
MMSE	159 (0–30)	25.64 (3.19)	21.41 (4.94)	<0.001	<0.001
FBI	102 (0–53)	8.33 (12.80)	14.84 (10.12)	<0.001	0.002
Frontal score	87 (21–60)	46.92 (8.25)	37.33 (10.16)	<0.001	<0.001
FAB	159 (2–18)	13.27 (3.03)	10.20 (3.56)	<0.001	<0.001
TMT-A (time, sec)	148 (25–331)	87.93 (48.10)	161.89 (80.50)	<0.001	<0.001
Forward span	165 (0–9)	5.06 (1.31)	4.89 (1.27)	0.001	0.013
Backward span	162 (0–8)	3.55 (1.10)	3.01 (1.20)	0.081	0.628
Denomination	164 (25–80)	73.34 (5.73)	65.34 (11.29)	<0.001	<0.001
FCSRT sum, free recall	109 (0–37)	23.75 (7.02)	19.15 (6.85)	0.002	0.004
FCSRT sum, total recall	107 (7–48)	41.81 (5.76)	37.33 (8.55)	0.003	0.002
FCSRT delayed free recall	110 (0–16)	8.20 (3.62)	6.53 (4.29)	0.068	0.051
FCSRT delayed total recall	106 (0–16)	14.70 (3.06)	12.73 (4.22)	0.002	0.015
FCSRT recognition	109 (4–16)	15.5 (1.4)	14.91 (2.18)	0.023	0.164
CDT	165 (0–7)	6.11 (1.30)	4.35 (2.27)	<0.001	<0.001
VOSP space	155 (0–10)	7.60 (2.23)	5.21 (3.00)	<0.001	<0.001
VOSP object	153 (0–20)	18.34 (2.14)	14.67 (5.00)	<0.001	<0.001
Praxis	156 (11–52)	44.27 (6.94)	34.97 (9.69)	<0.001	<0.001
Praxis–motor program	163 (0–15)	11.43 (4.06)	8.21 (5.20)	<0.001	<0.001
Praxis–dexterity	162 (0–10)	8.95 (2.06)	6.34 (3.03)	<0.001	<0.001
Praxis–ideomotor	162 (0–12)	10.76 (1.95)	9.35 (2.88)	0.002	<0.001
Praxis–buccofacial	162 (0–3)	2.82 (0.50)	2.52 (0.79)	0.002	0.012
Praxis–motor engram	159 (0–12)	10.38 (1.77)	8.65 (2.47)	<0.001	<0.001
Oculomotor recordings					
Vertical saccade velocity	119 (45–294)	177 (47)	138 (35)	<0.001	<0.001
Horizontal saccade velocity	126 (72–325)	219 (46)	175 (38)	<0.001	<0.001
	119 (136–573)	229 (48)	323 (88)	<0.001	<0.001

(Continues)

TABLE 2 *Continued*

Measure	N (range)	Subgroup 1 Mild-to-moderate Profile	Subgroup 2 Severe degenerative Parkinsonism	P (Wilcoxon test or χ^2)	P adjusted for age, sex, education, and disease duration
Vertical saccade latency					
Horizontal saccade latency	126 (126–409)	180 (35)	233 (58)	<0.001	<0.001
Vertical gain	118 (0.46–0.99)	0.80 (0.10)	0.74 (0.12)	0.003	0.008
Horizontal gain	126 (0.41–1)	0.85 (0.80)	0.77 (0.11)	<0.001	<0.001

Abbreviations: MDRS, Mattis Dementia Rating Scale; MMSE, Mini-Mental State Examination; FBI, Frontal Behavioral Inventory; FAB, Frontal Assessment Battery; TMT-A, Trail Making Test A; FCSRT, Free and Cued Selective Recall Reminding Test; CDT, Clock-Drawing Test; VOSP, Visual Object and Space Perception Test. Bold type denotes statistical significance.

TABLE 3 *Multivariate logistic models assessing the risk of severe degenerative parkinsonism (SDP)*

	Model 1	Model 2	Model 3	Model 4	Model 5
Age	1.066 (1.026–1.111)	1.056 (1.012–1.105)	1.056 (1.012–1.107)	1.060 (1.013–1.114)	1.051 (1.005–1.103)
Sex (male)	1.669 (0.865–3.260)	1.027 (0.487–2.167)	1.076 (0.505–2.296)	0.879 (0.402–1.910)	0.960 (0.445–2.063)
Low education	2.131 (0.947–4.919)	2.752 (1.108–7.148)	2.697 (1.066–7.137)	2.551 (1.000–6.784)	2.704 (1.058–7.214)
Disease duration	1.114 (1.044–1.195)	1.122 (1.042–1.216)	1.127 (1.045–1.225)	1.131 (1.049–1.231)	1.130 (1.047–1.229)
Annonaceae fruit/juice	–	–	3.758 (1.130–15.180)	–	–
Annonaceae herbal tea	–	–	–	2.907 (1.341–6.560)	–
Annonaceae fruit/juice/herbal tea	–	–	–	–	3.528 (1.102–13.826)

Model 1: Prob(SDP) ~ age + sex + low education + disease duration.

Model 2: Prob(SDP) ~ age + sex + low education + disease duration + adjusted for dementia risk factors (hypertension, diabetes, dyslipidemia, obesity, alcohol consumption).

Model 3: Prob(SDP) ~ age + sex + low education + disease duration + adjusted for dementia risk factors + Annonaceae fruit/juice consumption over 0.2 FY (fruit-years).

Model 4: Prob(SDP) ~ age + sex + low education + disease duration + adjusted for dementia risk factors + Annonaceae herbal tea consumption over 0 CY (cup-years).

Model 5: Prob(SDP) ~ age + sex + low education + disease duration + adjusted for dementia risk factors + Annonaceae fruit/juice/herbal tea consumption over 0.3 units.

Odds ratios and 95% confidence intervals from multiple logistic regression models.

Bold type denotes statistical significance.

Factors Associated with Severe Degenerative Parkinsonism

Several multivariate logistic regression models predicting the risk of severe degenerative parkinsonism were computed (Table 3). Older age and longer disease duration were associated with an increased risk of severe forms. After adjusting the analysis for risk factors suspected to increase the risk of cognitive impairment and dementia (ie, hypertension, diabetes, dyslipidemia, obesity, and alcohol consumption), we also demonstrated a detrimental effect of low education. Finally, the

cumulative consumption of more than 0.2 fruit-years of Annonaceae fruits/juices or of any quantity of Annonaceae herbal tea significantly increased the risk of severe degenerative parkinsonism (odds ratio [OR] Annonaceae fruits/juices: 3.76 [95% CI: 1.13–15.18]; OR Annonaceae herbal tea: 2.91 [95% CI: 1.34–6.56]). Accordingly, the combined cumulative consumption of any Annonaceae product above a threshold of 0.3 units (see Methods) increases the risk of severe forms of parkinsonism (OR Annonaceae fruits/juices/herbal teas: 3.53 [95% CI: 1.10–13.83]).

Discussion

In this cross-sectional study of 180 French Caribbean patients with degenerative parkinsonism we found that cumulative lifelong consumption of Annonaceae fruits, juices, or herbal teas was associated with a dose–response worsening of cognitive performance. Annonaceae consumption increased the risk of a severe form of parkinsonism with cognitive, behavioral, and motor disturbances, regardless of whether patients were classified as having PD or AP. We provide evidence that such consumption could be deleterious at a lower threshold limit value than previously reported. Taken together, our results provide evidence that Annonaceae products could contribute to the pathogenesis of degenerative parkinsonism in humans, including PD. As a precaution, we suggest that more restrictive public health preventive recommendations should be made regarding the consumption of Annonaceae products.

This study has several limitations. The recruitment of patients being limited to a relatively small geographical area, and the sample size appears relatively small compared to other studies attempting to demonstrate the influence of environmental factors in neurodegenerative disorders. Yet, this is the largest group of patients on which we could perform both a comprehensive clinical assessment and an accurate measurement of Annonaceae plant product consumption. A significant proportion of patients (111 of the 305 initial cohort) unable to undergo detailed neuropsychological assessment because they were too severe or had a low educational level were excluded. This could constitute a bias especially since low educational level was identified as a risk factor for developing AP in this population.³ However, patients with and without neuropsychological assessment did not differ regarding their Annonaceae consumption (Table S4). Because we do not have an exposure biomarker that could provide an objective estimation of lifelong cumulative consumption of Annonaceae products, we administered retrospective standardized questionnaires to patients, close to the ones that have been used in previous studies.^{1–3} Retrospective assessment of lifelong cumulative consumption remains a challenge, particularly for patients with cognitive impairment. Nevertheless, we found that participants had vivid memories regarding their consumption of Annonaceae and when appropriate we allowed them to benefit from the help of family informants. Only prospective longitudinal studies with careful quantification of Annonaceae product consumption could overcome this limitation inherent to the retrospective approach. In addition, because participants mostly consumed Annonaceae for their whole life in our sample, it was not possible to test the differential impact of early-life versus late-life exposure or to examine the lag time between exposure and clinical effect. Moreover, because

participants in this study consumed different Annonaceae fruits at the same time in different modes (fruits, juices, or herbal teas), the respective impact of each form of consumption was difficult to assess due to the limited number of consumers for certain fruits or modes of consumption. A different sample of participants exposed to Annonaceae fruits from another world region would therefore be of key interest for external validation of our results. The participants from the Caribbean degenerative parkinsonism cohort were also very often exposed to Annonaceae products, and all of them suffered from neurological symptoms (parkinsonism): as a consequence, the lack of a proper control group impeded the construction of a classic case–control study. Finally, several symptoms observed in Caribbean AP patients overlap with those developed by patients with anti-IgLON5 tauopathy, an entity first described during the inclusion period of our study.³⁶ Although we could not test the patients from the cohort studied in this article for anti-IgLON5 antibodies, three Caribbean patients with AP have been tested in 2020–2021 and they were all negative for anti-IgLON5.

A link between Annonaceae consumption and the risk of developing AP has previously been established. However, the critical threshold limit above which the risk increases remains to be clarified. In an initial study performed in the French West Indian island of Guadeloupe, participants were considered significant consumers of Annonaceae products if taking *A. muricata*, *A. squamosa*, and *A. reticulata* fruits/juices or herbal teas at least once a month for a minimum of 2 years. With this threshold, researchers found that AP patients consumed significantly more *A. muricata*, *A. squamosa*, and *A. reticulata* fruits than Caribbean PD patients. Consumption of Annonaceae herbal teas used in traditional medicine, essentially for sedation, was also more frequent in patients with AP.¹ In another case–control study, 75% of Guadeloupeans with atypical forms of parkinsonism compared to 20% in the group with PD reported a high cumulative lifelong consumption of *A. muricata* fruit/juice above 10 fruit-years (ie, one fruit or one glass of juice daily for 10 years).² In New Caledonia, a French South Pacific island where people eat Annonaceae fruits, atypical parkinsonism was also found to frequently occur (46%). Higher consumption of Annonaceae fruits was reported in patients with AP (73%) than in those with PD (34%).³⁷ The frequency of AP was also found to be higher in the Afro-Caribbean and Indian populations living in the UK and, interestingly, dietary intake of Annonaceae fruits was reported to be frequent in these migrant populations.³⁸ Taken together, these studies suggest that Annonaceae consumption increases the usual proportion of atypical forms of parkinsonism in a population of patients with degenerative parkinsonism.

Rather than comparing AP and PD groups, which show similar cognitive and motor worsening according to Annonaceae consumption, we choose to define groups based on symptom severity. Using nonlinear modeling we found that the minimal toxic threshold value of Annonaceae product consumption associated with cognitive impairment in the Caribbean degenerative parkinsonism cohort was 50 times lower than previously reported for fruits/juices² and that even occasional Annonaceae herbal tea consumption might have a cognitive impact. Unsupervised clustering identified a group of participants with severe symptoms: cognitive impairment, frequent hallucinations, severe motor symptoms, and functional impairment. Importantly, Annonaceae consumption variables and risk factors classically associated with cognitive impairment and dementia were not used for unsupervised clustering. The new Annonaceae consumption thresholds were then used in multivariate models to assess the risk of belonging to the group of patients with severe degenerative parkinsonism while accounting for potential confounding factors. We found that the cumulative consumption of Annonaceae fruits/juices/herbal teas increased the risk of severe forms (OR: 3.53 [95% CI: 1.10–13.83]).

The increased risk of developing severe parkinsonism in consumers of Annonaceae products could be related to a neurotoxic effect. In that respect, a number of experimental studies have demonstrated the neurotoxic potential of annonacin, the most abundant acetogenin in *A. muricata* that is also found in *A. squamosa* and *A. reticulata*. Acetogenins are neurotoxic long-chain fatty acids and potent lipophilic mitochondrial complex I inhibitors acting via inhibition of NADH ubiquinone oxidoreductase.^{39–42} In vitro, low nanomolar concentrations of annonacin lead to ATP depletion and neuronal death of both dopaminergic and nondopaminergic midbrain neurons.⁴³ When administered intravenously in rats through osmotic minipumps, annonacin has been shown to enter the brain, decrease ATP levels, and promote neurodegeneration in the basal ganglia.⁴⁴ In striatal neuronal cultures, annonacin induced retrograde movement of mitochondria from neurites to neuronal cell somas and redistribution of microtubule-associated protein tau (MAPT),⁴⁵ a protein crucially involved in memory function.⁴⁶ In line with this, oral consumption of *A. muricata* juice causes profound neuropathological changes and the development of tauopathy in both wild-type and MAPT-transgenic mice.^{10,11} Overall, both in vitro and in vivo studies indicate that annonacin is potent enough to cause neurodegeneration and related motor and cognitive deficits in Annonaceae consumers. Chronic mitochondrial complex I dysfunction, a prominent causal factor for parkinsonian neurodegeneration,⁴⁷ is likely to account for such effects.⁴⁴

The identification of two groups of patients (mild-to-moderate vs. severe) allowed us to detect a link between lifelong Annonaceae cumulative consumption and severity of degenerative parkinsonism, regardless of whether patients were classified as having PD or AP. This raises new perspectives to refine the clinical paradigm in relation to Caribbean parkinsonism. We previously described the Caribbean parkinsonism entity as a particular clinical form of AP selectively observed in the Caribbean area: initially as two subtypes (Guadeloupean PSP-like syndrome and Guadeloupean parkinsonism-dementia complex) with similar degrees of cognitive impairment² and then as a single disorder (Caribbean atypical parkinsonism).³ Here, the new findings suggest that exposure to Annonaceae can worsen the severity of disease manifestation in degenerative parkinsonism, regardless of the initial classification as PD or AP. The dose–response effect of Annonaceae consumption on cognitive performance further supports this hypothesis. We speculate that it may occur through the aggravation or extension of degenerative lesions within the brain. Knowing that patients with a PD phenotype suffer presumably from a synucleinopathy and AP patients most probably from a tauopathy, the question of the degenerative mechanisms activated through Annonaceae consumption merits discussion. Annonaceae neurotoxins could either trigger neuropathological changes such as a tauopathy as suggested by preclinical animal model studies and histological examination of rare brain autopsy cases,⁴⁸ or worsen any pre-existing α -synuclein- or tau-related changes involving the dopaminergic system. This could account for the higher proportion of AP in this geographical area and the presence of unusual AP phenotypes. Importantly, the present data also confirm our impression that in daily clinical practice, the course of PD tends to be more severe in the French Caribbean islands than in other geographical areas.

Conclusions

Annonaceae mostly grow in tropical areas (Central and South America, Sub-Saharan Africa, Indo-Malaysian region, and Northern Australia) whereas some Annonaceae species can also be found in temperate areas (*Asimina triloba* in Southeastern USA and *A. cherimola* in Spain). It implies that a large population is potentially exposed to Annonaceae products, taking into account the fact that 40% of the world's population live in tropical areas. There is an urgent need to raise public awareness about the neurotoxicity of Annonaceae, which are often praised for their taste and medicinal values. Health specialists should also investigate past exposure to Annonaceae products as a risk factor for a severe clinical profile with cognitive impairment and

hallucinations in patients with parkinsonism. Further studies are needed to investigate whether Annonaceae could be a risk factor for cognitive decline in other degenerative diseases or in healthy populations in tropical areas. ■

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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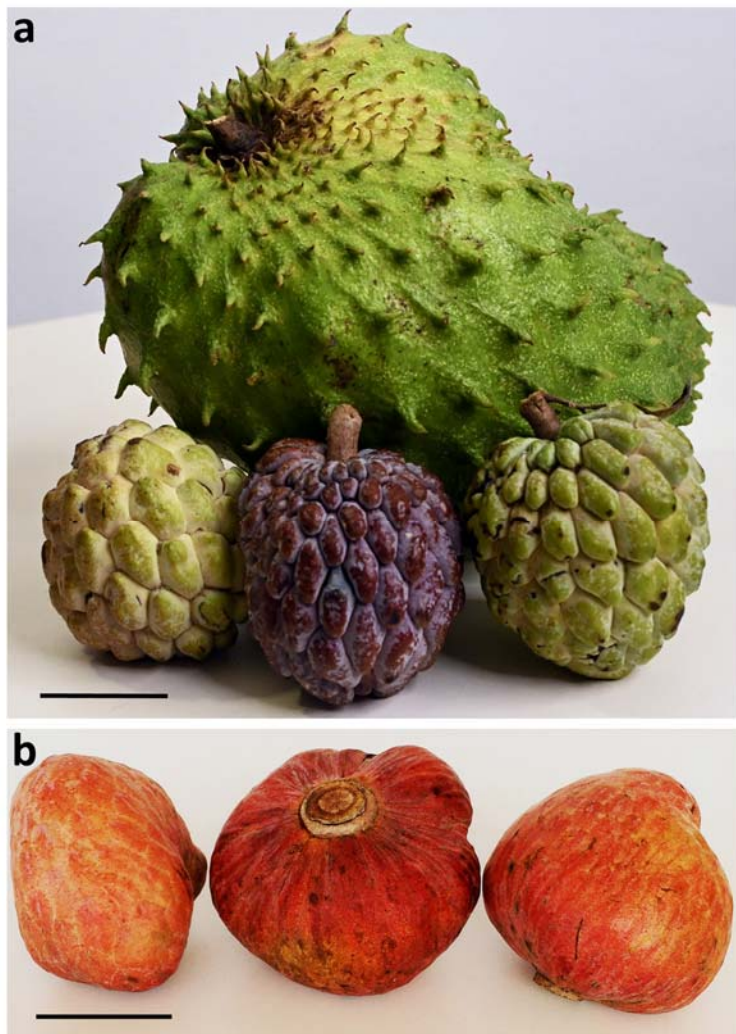
Author Roles

L.C.L., E.R., and A.L. contributed to the conception and design, acquisition, interpretation of data and drafting of the manuscript. R.E. and A.P. contributed to data collection. P.P.M. and H.C. contributed to drafting the manuscript. B.T. and A.G.M contributed to the statistical data analysis. A.C.B.L. and P.R. contributed to the interpretation of the data. A.L. provided general supervision of the research group, acquired funding, and was involved in critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

Financial Disclosures

All authors declare no conflict of interest concerning the research related to the manuscript.

Supplementary Figure S1: *Annonaceae* fruits most commonly consumed in the French Caribbean islands.



One *A. muricata* with three *A. squamosa* (a) and three *A. reticulata* (b). Scale bar is 5 cm.

Supplementary Table S2: Measures used for unsupervised clustering

Measures missing more than 35% of the values were discarded.

Cognitive measures	MMSE, MDRS, FAB, time for TMT-A, forward and backward span, DO80, clock drawing test, VOSP object, VOSP space, praxis
Oculomotor measures	Mean velocities and latencies for vertical and horizontal saccades, maximal velocities for vertical and horizontal saccades, and vertical and horizontal gains.
Neurological measures	UPDRS-3 motor score, levodopa sensitivity (either subjective or tested), Hoehn and Yahr, Schwab and England, Sniasky and Koslter scale, visual and auditory hallucinations, RBD disorder, axial and distal rigidity, postural instability, tremor, symmetry in motor symptoms, brisk reflexes, Babinski sign, grasping, dystonia, falls, orthostatic hypotension, walking disturbance, deglutition disorder, bladder dysfunction, supranuclear vertical palsy, and slow vertical saccades.

Supplementary Table S3: Discarded measures for unsupervised clustering

Demographics	Age, Sex ratio, Low education, Age at onset, disease duration
Cognitive measures	FBI, Frontal Score, FCSRT sum free recall, FCSRT sum total recall, FCSRT delayed free recall, FCSRT delayed total recall, FCSRT recognition
Comorbidities	Hypertension, diabetes dyslipidaemia, obesity, tobacco use, alcohol use
Annonaceae	Annonaceae cumulative consumption fruits/juices and herbal teas

FBI: frontal behavioural interview; FCSRT: Free and Cued Selective Recall Test.

Supplementary Table S4: Comparison of participants included in the study with participants excluded because of lack of neuropsychological assessment

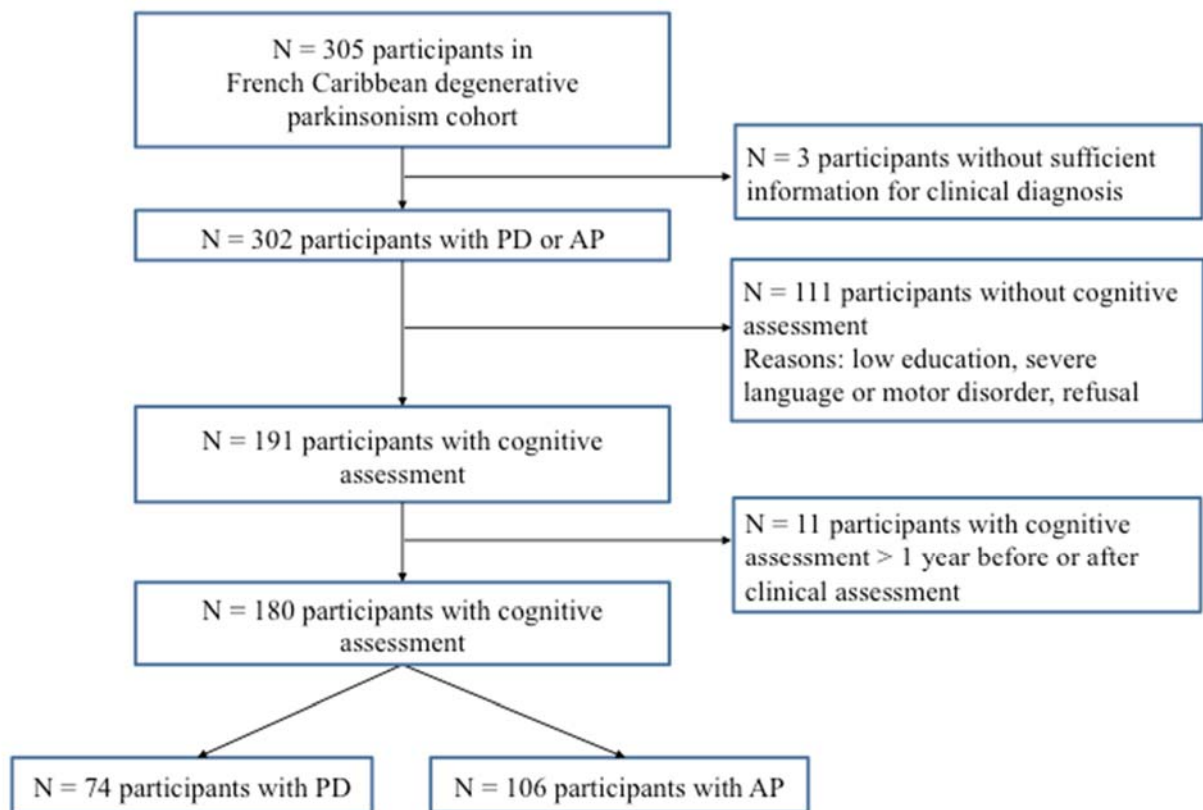
Compared to participants without cognitive assessment (N = 125, Figure 1), participants in the studied cohort (N = 180) were younger (69.83 ± 9.05 years vs. 67.12 ± 9.18 years, respectively; $p = 0.009$) and more educated (≥ 12 years of education, 36.8% vs. 48.1%, respectively; $p = 0.017$). No difference was observed between these two populations for sex distribution, disease duration and *Annonaceae* consumption (all $p > 0.1$).

	Without Cognitive Assessment	With Cognitive Assessment	p-value
Demographics			
Age*	69.83 (9.05)	67.12 (9.12)	0.009
Sex ratio M/F	62/57	103/75	0.327
Education (≥ 12 years)	36.8%	48.1%	0.017
Disease Duration	6.58 (6.02)	6.30 (5.07)	0.836
Parkinsonism severity			
UPDRS-3	35.73 (20.46)	27.15 (14.76)	<0.001
DOPA % sensitivity	30.70 (20.36)	37.21 (22.05)	0.041
Hoehn & Yahr > 3 (%)	36.00%	14.44%	<0.001
Schwab & England $\leq 40\%$ (%)	32.00%	20.56%	0.033
Atypical parkinsonism	71.43%	58.89%	0.027
Neurological features			
Axial Rigidity	72.03%	57.39%	0.011
Symmetry	45.38%	29.38%	0.005
Resting Tremor	52.94%	52.25%	0.907
Postural Instability	65.14%	60.57%	0.440
Falls	55.08%	45.45%	0.106
Vertical gaze palsy	27.03%	17.51%	0.054
Bladder dysfunction	48.74%	39.20%	0.105
Orthostatic Hypotension	37.84%	41.14%	0.578
Sleep Disorder	35.29%	51.98%	0.005
SNK scale	4.15 (2.92)	5.17 (3.01)	0.003

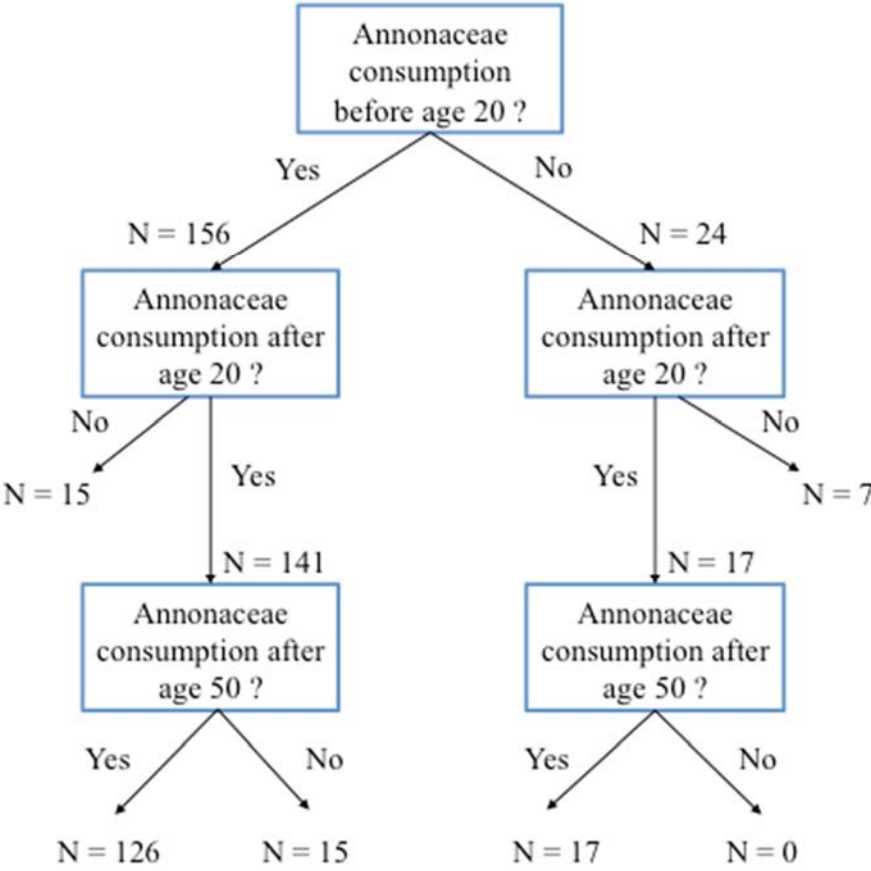
Visual Hallucinations	36.13%	30.86%	0.345
Auditive Hallucinations	24.58%	18.97%	0.250
Cognitive measures			
MMSE	19.36 (8.95)	23.81 (4.54)	<0.001
FAB	9.49 (5.31)	11.95 (3.60)	<0.001
Annonaceae consumption			
Annonaceae consumption ≥ 10 fruit or cup/year	32.00%	27.78%	0.376

* the reported age corresponds to age at the time of the neurological evaluation

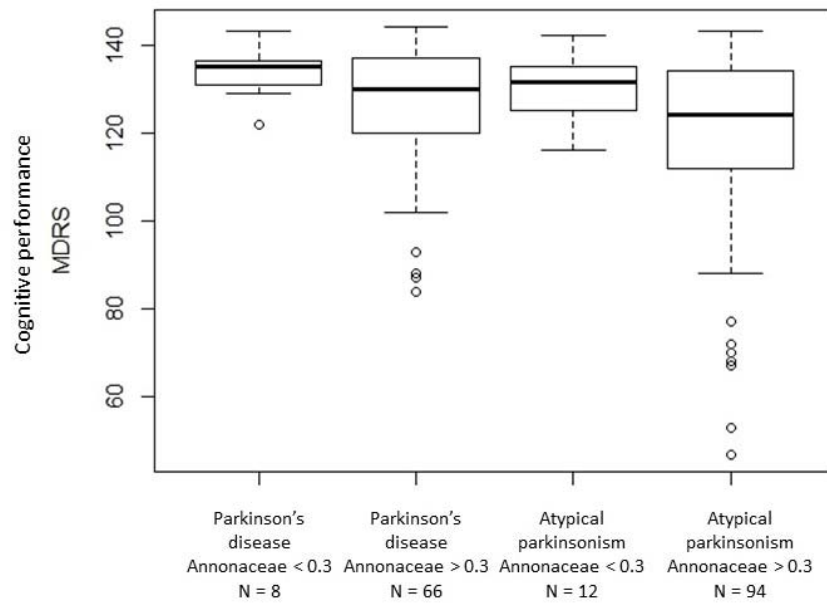
Supplementary Figure S5: Flowchart



Supplementary Figure S6: Annonaceae Consumption Flowchart



Supplementary Figure S7: *Cognitive performance (Mattis DRS) according to diagnosis and exposure to Annonaceae products*

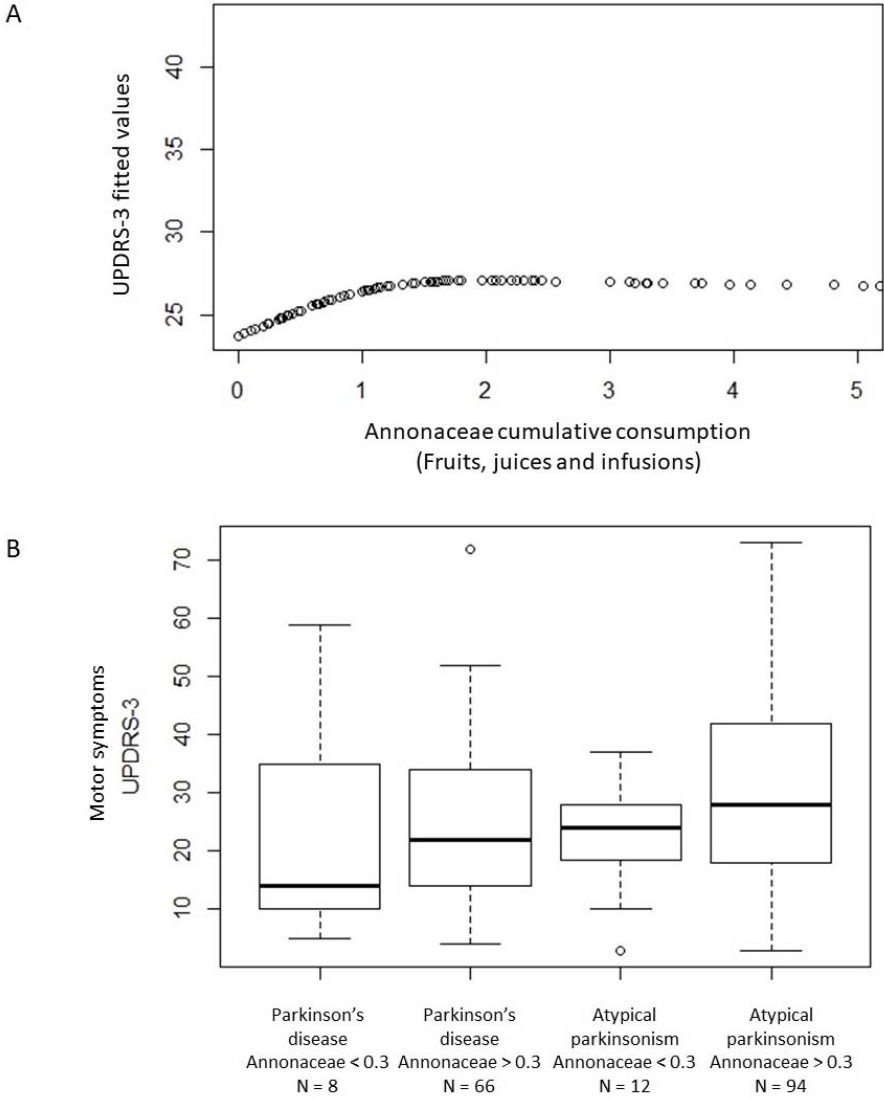


Annonaceae consumption (fruits, fruit juices and herbal tea above or below 0.3 fruit or cup-year unit). Normal cognitive performance at MDRS: above 136. Dementia probable below 123.

Supplementary Figure S8: Impact of Annonaceae consumption on motor symptoms.

A. Restricted cubic splines showing a dose-response worsening of motor symptoms (UPDRS-3) with cumulative consumption of Annonaceae.

B. Motor symptoms (UPDRS-3 scale) according to diagnosis and exposure to Annonaceae products.



Annonaceae consumption (fruits, fruit juices and herbal tea above or below 0.3 fruit or cup-year unit).