

# Idiopathic Hyposmia As a Preclinical Sign of Parkinson's Disease

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**Olfactory dysfunction is an early and common symptom in Parkinson's disease (PD). In an effort to determine whether otherwise unexplained (idiopathic) olfactory dysfunction is associated with an increased risk of developing PD, we designed a prospective study in a cohort of 361 asymptomatic relatives (parents, siblings, or children) of PD patients. A combination of olfactory detection, identification, and discrimination tasks was used to select groups of hyposmic (n = 40) and normosmic (n = 38) individuals for a 2-year clinical follow-up evaluation and sequential single-photon emission computed tomography (SPECT), using [<sup>123</sup>I]β-CIT as a dopamine transporter ligand, to assess nigrostriatal dopaminergic function at baseline and 2 years from baseline. A validated questionnaire, sensitive to the presence of parkinsonism, was used in the follow-up of the remaining 283 relatives. Two years from baseline, 10% of the individuals with idiopathic hyposmia, who also had strongly reduced [<sup>123</sup>I]β-CIT binding at baseline, had developed clinical PD as opposed to none of the other relatives in the cohort. In the remaining nonparkinsonian hyposmic relatives, the average rate of decline in dopamine transporter binding was significantly higher than in the normosmic relatives. These results indicate that idiopathic olfactory dysfunction is associated with an increased risk of developing PD of at least 10%.**

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Olfactory deficits in Parkinson's disease (PD) were first empirically documented in 1975.<sup>1</sup> Over the ensuing years, it has become clear that most patients with PD have olfactory disturbances that are not restricted to a single functional modality but include impairments of odor detection, differentiation, and identification.<sup>2–6</sup> At the earliest clinical stage of the disease, profound deficits in each of these modalities have been demonstrated.<sup>4,6</sup> Olfactory deficits also have been found in asymptomatic relatives of patients with either familial or sporadic forms of PD.<sup>7,8</sup> Recently, we reported a subclinical degeneration of the nigrostriatal dopaminergic system in some hyposmic relatives of PD patients.<sup>9</sup> These findings suggest that olfactory dysfunction might be a prodromal or preclinical sign of PD.

An important pathological characteristic of PD is the degeneration of dopaminergic neurons located in the substantia nigra, pars compacta, and their projections to striatal regions. The extent of the degeneration of the nigrostriatal dopaminergic system in PD can be visualized *in vivo* by means of positron emission tomography (PET) or single-photon emission computed tomography (SPECT), using radioligands for the dopamine transporter.<sup>10</sup> Based on *in vivo* PET and

SPECT imaging of the dopaminergic system and post-mortem cell counts of pigmented neurons in the substantia nigra, the onset of dopaminergic neuronal loss seems to antedate the clinical diagnosis of PD by approximately 4 to 6 years.<sup>11–13</sup> Over the period between the presumed onset of dopaminergic neuronal loss and the clinical diagnosis of PD, that is, the preclinical phase of PD, as many as 58 to 64% of the dopaminergic neurons projecting to the putamen already have been lost.<sup>14,15</sup>

PD-related pathological changes in the substantia nigra are always accompanied by extensive extranigral pathology.<sup>16</sup> According to a novel and provocative pathological staging system for PD by Braak and colleagues, the neuropathological process actually may start in extranigral structures, including the olfactory bulb and related portions of the anterior olfactory nucleus.<sup>17</sup> Assuming that PD-related pathology indeed first occurs outside the nigra, the preclinical phase of PD may be substantially longer than imaging data of the nigrostriatal system suggest. Moreover, the early pathological involvement of the anterior olfactory system further emphasizes the potential value of hyposmia as a preclinical sign of PD.

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Identifying subjects with an increased risk of developing PD may contribute to the development of neuroprotective treatment strategies, because a preclinical diagnosis would not only allow neuroprotective agents to be administered earlier in the disease process, but also enable us to study proposed mechanisms of neurodegeneration (such as oxidative stress) closer to the onset of neuronal loss.<sup>18</sup>

The aim of this study was to determine whether otherwise unexplained olfactory dysfunction is associated with an increased risk of developing PD. To this end, we set up a prospective study in a cohort of 361 asymptomatic relatives of PD patients. A combination of olfactory tests was used to select groups of hyposmic ( $n = 40$ ) and normosmic ( $n = 38$ ) individuals for a 2-year clinical follow-up evaluation and sequential [<sup>123</sup>I]β-CIT SPECT to assess nigrostriatal dopaminergic function at baseline and 2 years from baseline. A validated questionnaire, sensitive to the presence of parkinsonism, was used in the follow-up of the remaining 283 relatives.

## Subjects and Methods

### *Study Population/Subjects*

This study involved 361 first-degree relatives (285 children, 73 siblings, and 3 parents) of patients with sporadic PD. Subjects were recruited partly from the general population and partly from family members of patients at the outpatient clinic for movement disorders of the VU University Medical Center. As described previously,<sup>9</sup> relatives were included when they fulfilled the following criteria: (1) clinical diagnosis of PD in the affected relative obtained by a neurologist or established retrospectively using information obtained from the unaffected relatives; (2) absence of a history of other (neuropsychiatric) disorders or conditions known to influence olfactory function; (3) no medication that might influence dopamine transporter binding and/or olfactory function; (4) absence of parkinsonism as defined by the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) criteria<sup>19</sup>; (5) Unified Parkinson's Disease Rating Scale (UPDRS) motor score less than 5; (6) Cambridge examination for mental disorders (CAMCOG) orientation and memory section score greater than 26. All participants gave written informed consent; the protocol of the study was approved by the Health Council of The Netherlands and the local medical ethical committees of both the VU University Medical Center and the Academic Medical Center. In a previous report, we have presented baseline data of the first 250 first-degree relatives who were included in this study.<sup>9</sup>

### *Study Design*

At baseline, all 361 subjects were submitted to a combination of olfactory processing tasks (Fig 1). Considering the superior sensitivity and specificity of a combination of olfactory processing tasks over any individual test,<sup>6</sup> the average  $Z$ -score over the three olfactory tests was chosen as a measure of olfactory function. Participants were selected for SPECT scanning from five consecutive groups of 70 to 80 partici-

pants to limit the interval between olfactory testing and baseline SPECT scanning. To reduce the effect of age- and sex-related differences in olfactory performance,<sup>20</sup> we created a rank order based on average  $Z$ -scores for men and women separately in the three groups of subjects aged 50 to 59 years and in the two groups of individuals aged 60 to 75 years. In each group, those individuals with the 10% lowest average  $Z$ -scores (with the additional requirement that the performance on each of the olfactory tasks had to be below group average) were considered hyposmic. In this way, 40 hyposmic relatives (29 children, 11 siblings) were identified. Similarly, 38 relatives (31 children, 2 siblings) with the highest average  $Z$ -scores (and all olfactory scores above group mean) were selected. The groups selected for SPECT scanning did not differ in demographics (Table 1).

Two years from baseline, 72 of the 78 individuals that were scanned at baseline were available for a follow-up screening with repeated SPECT scanning, neuropsychological testing, and neurological evaluation (see Fig 1). Of the 283 relatives not selected for baseline SPECT scanning, 275 completed a questionnaire sensitive to the presence of parkinsonism as part of the 2-year follow-up evaluation (see Fig 1). Relatives with possible parkinsonism according to the questionnaire were invited to the outpatient clinic for movement disorders of the VU University Medical Center for clinical evaluation.

### *Olfactory Processing Tasks*

Olfactory function was assessed, as described previously, by means of a combination of an odor detection, an odor discrimination task, and an odor identification task.<sup>9</sup>

### *Clinical and Neuropsychological Evaluation*

Two years from baseline, clinical evaluation of all individuals selected for [<sup>123</sup>I]β-CIT SPECT scanning was conducted by a movement disorders specialist and included a screening neurological examination and a specific assessment to detect the presence of parkinsonism as defined by the UK-PDSBB criteria.<sup>1</sup> Motor function was rated by means of the motor section of the UPDRS. A UPDRS motor score of five or more was considered as a sign of motor dysfunction, not necessarily as part of a parkinsonian syndrome. Individuals who had developed clinical PD before the 2-year follow-up evaluation and were already using medication were tested off-medication, at least 12 hours after their evening dose.

In addition to the neurological evaluation, the CAMCOG also was repeated 2 years from baseline. A CAMCOG score under 27 was considered indicative of cognitive dysfunction possibly as part of a developing dementing illness.

Individuals with possible parkinsonism according to the questionnaire were submitted to a structured clinical workup, comprising a standard history taking and a neurological examination including the UPDRS motor score. A blinded movement disorders specialist, not involved in the baseline screening, performed the structured clinical workup.

### *Single-Photon Emission Computed Tomography Scanning*

SPECT scanning and analysis of bilateral striatal, bilateral putamen, and bilateral caudate [<sup>123</sup>I]β-CIT binding for each

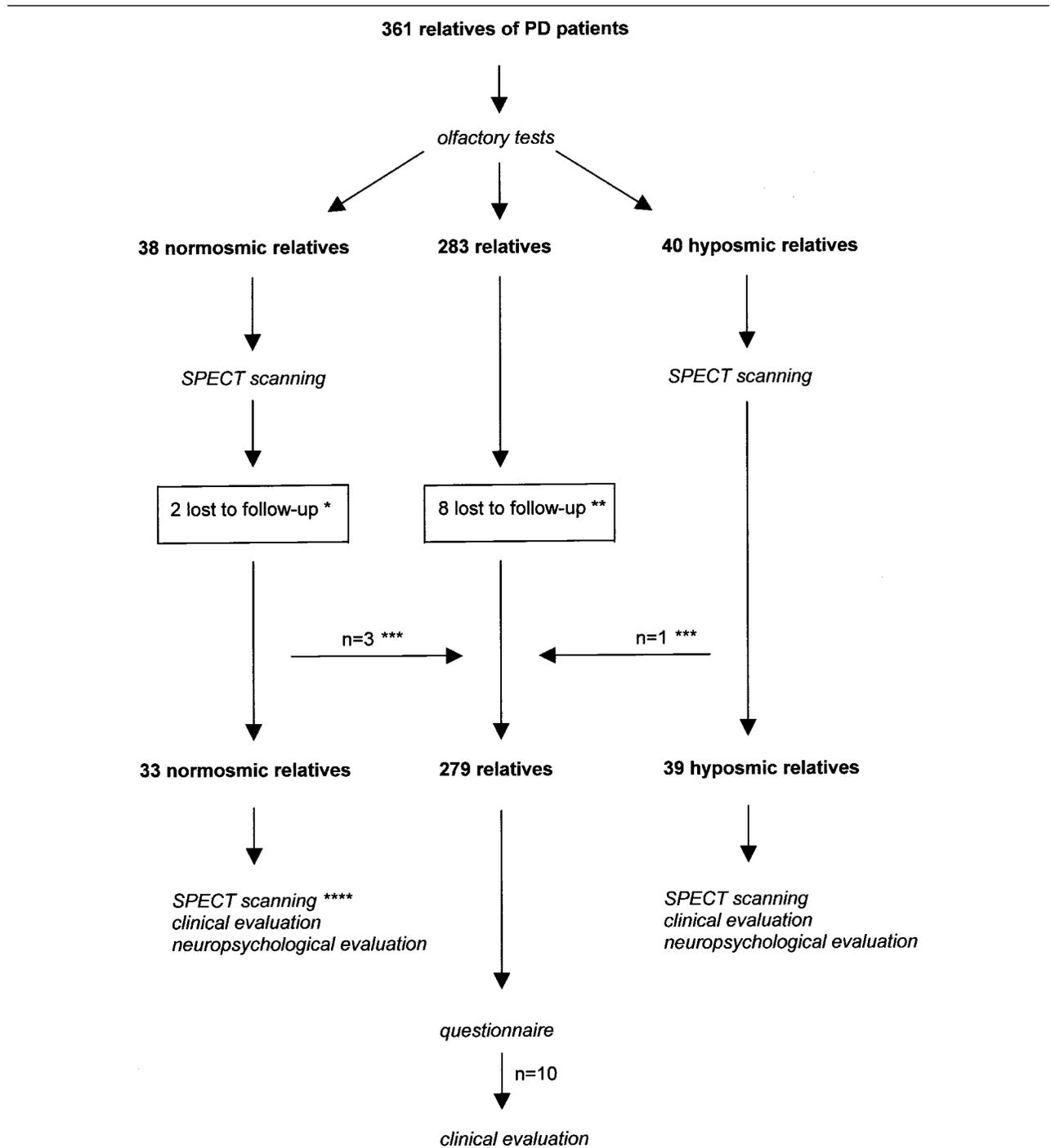


Fig 1. Flowchart illustrating the overall design of the study. \*Two lost to follow-up, one of whom died. \*\*Eight lost to follow-up, five of whom died. \*\*\*Three normosmic relatives and one hyposmic relative switched to the questionnaire group. \*\*\*\*One relative did not have SPECT because of selective serotonin reuptake inhibitor use. PD = Parkinson's disease; SPECT = single-photon emission computed tomography.

baseline and follow-up scan was performed using a previously described method.<sup>9</sup> Four baseline SPECT scans, in one hyposmic relative and three normosmic relatives, could not be analyzed quantitatively because of technical problems. All SPECT scans were analyzed by the same investigator, blinded to olfactory performance.

#### Questionnaire

A Dutch translation of a screening questionnaire for PD, designed by Tanner and colleagues<sup>21</sup> and validated by Duarte and colleagues<sup>22</sup> was administered 2 years from baseline. This mail questionnaire comprises nine symptom questions.

Table 1. Demographic Data for Participants

Demographic	All Subjects (n = 361)	Normosmic Relatives (n = 38)	Hyposmic Relatives (n = 40)
Sex (male/female)	157/204	17/21	19/21
Age (mean ± SD)	58.7 ± 6.6	58.5 ± 6.6	59.2 ± 5.8

With a cutoff score of three or more positive responses, sensitivity and specificity to detect parkinsonism are 95% and 89%, respectively. An extra question was added to establish whether a physician had made a diagnosis of PD over the course of the follow-up period. Three or more positive responses to the screening questionnaire, as well as a positive response to the additional question, were considered indicative of possible parkinsonism.

#### Data Analysis

For both baseline and follow-up SPECT scans, group means of each binding parameter were calculated and compared by means of Student's unpaired *t* test. In addition, age-adjusted means of each SPECT parameter, including its 95% confidence interval, were determined in the group of normosmic relatives. Individual values of hyposmic relatives were considered abnormal if they fell outside the 95% confidence interval of the age-adjusted means of the group of normosmic individuals.

Changes in [<sup>123</sup>I]β-CIT binding ratios over the 2-year follow-up period were analyzed by calculating the rate of change in [<sup>123</sup>I]β-CIT binding expressed as a percentage of baseline [<sup>123</sup>I]β-CIT binding for each participant and each SPECT parameter using the following formula:

$$\frac{(\text{follow-up SPECT} - \text{baseline SPECT})}{\text{baseline SPECT}} \times 100\%$$

Because the baseline scans of three normosmic and a single hyposmic relative could not be analyzed quantitatively, changes in [<sup>123</sup>I]β-CIT binding over time could be determined for 30 normosmic relatives and 38 hyposmic relatives. Linear regression analysis was used to compare changes in [<sup>123</sup>I]β-CIT binding ratios over time between the groups. The 2-year follow-up data were used as the dependent variable and group as an independent variable. By adding the baseline value as an independent variable, changes in [<sup>123</sup>I]β-CIT binding ratios are corrected for the baseline value. Because age and sex did not differ between the groups (using univariate analysis of variance and a  $\chi^2$  test, respectively), these factors were not used as independent variables.

## Results

#### Olfactory Processing Tasks

The average scores on the different olfactory processing tasks are listed in Table 2. Olfactory task performance in the group of selected hyposmic relatives was comparable to that of patients in the early clinical stages of PD.

#### Neuropsychological Testing

A single hyposmic relative had a CAMCOG score of 24, 2 years from baseline. An additional neurological and neuropsychological evaluation combined with a magnetic resonance imaging scan of the brain led to a diagnosis of mild cognitive impairment most likely with a vascular cause.

#### Clinical Evaluation

Two years from baseline, four relatives of the original group of 40 hyposmic relatives had developed clinical PD as defined by the UK-PDSBB criteria. First clinical symptoms appeared 9 to 19 months after baseline testing. Two years from baseline, off-medication UPDRS motor scores were, respectively, 10, 15, 15, and 18. Two relatives were taking a dopamine-agonist and a combination of a dopamine-agonist with L-dopa, respectively, and had a good clinical response. The other two relatives were not taking antiparkinsonian medication. None of the other hyposmic relatives, nor any of the normosmic relatives available for clinical follow-up, fulfilled the criteria for a parkinsonian syndrome according to the UK-PDSBB criteria. Three normosmic relatives and one hyposmic relative had UPDRS motor scores ranging from 6 to 8. However, because none of these relatives had signs of a progressive disorder, they did not fulfill UK-PDSBB criteria for PD.

In the questionnaire group, 10 subjects had three or four (of nine) positive responses to the screening questionnaire. Clinical evaluation did not show a parkinsonian syndrome in these subjects; all UPDRS motor scores were under 5. No subject had a positive response to the additional question.

#### [<sup>123</sup>I]β-CIT Single-Photon Emission Computed Tomography Imaging

Mean SPECT binding ratios at baseline and 2 years from baseline for the hyposmic and normosmic groups are listed in Table 3. At baseline, a slight, but not statistically significant difference was found between the groups. Two years from baseline, mean bilateral striatal and putamen binding ratios were significantly lower in the group of hyposmic relatives compared with the group of normosmic relatives.

Despite the absence of significant group differences in [<sup>123</sup>I]β-CIT binding at baseline, 7 of the 39 hyposmic relatives showed one or more reduced [<sup>123</sup>I]β-CIT binding ratios outside the 95% confidence interval of the age-adjusted means of the normosmic relatives (left and right striatal [<sup>123</sup>I]β-CIT binding ratios are illustrated in Fig 2). In three hyposmic relatives, all of six binding ratios calculated were strongly reduced. Two hyposmic relatives had two abnormal values, that is, right striatal combined with either right putamen or right caudate [<sup>123</sup>I]β-CIT binding. Last, two hyposmic relatives each had a single binding ratio deviating mar-

Table 2. Scores on Olfactory Processing tasks (mean ± SD), Measured at Baseline

	All Subjects (n = 361)	Normosmic Relatives (n = 38)	Hyposmic Relatives (n = 40)	Early PD (group size)
Odor detection	13.3 ± 2.1	14.8 ± 1.3	10.8 ± 1.9	11.0 ± 2.6 (n = 24)
Odor discrimination	20.9 ± 4.5	25.7 ± 2.0	15.5 ± 3.6	17.4 ± 4.9 (n = 24)
Odor identification	9.7 ± 1.7	10.9 ± 0.9	7.3 ± 2.1	7.5 ± 3.1 (n = 14)

The results of olfactory testing using the same tasks in groups of early stage PD patients are listed for comparison.

SD = standard deviation; SPECT = single-photon emission computed tomography; PD = Parkinson's disease.

ginally from normosmic control values, that is, reduced right putamen and right striatum [<sup>123</sup>I]β-CIT binding ratio, respectively. A single normosmic relative had a marginally reduced right striatal [<sup>123</sup>I]β-CIT binding ratio. Interestingly, the four hyposmic relatives with the most strongly reduced baseline [<sup>123</sup>I]β-CIT binding (the three relatives with all binding ratios reduced and the relative with reduced right striatal and right putamen [<sup>123</sup>I]β-CIT binding ratios) developed clinical PD 9 to 19 months from baseline scanning (see above).

Two years from baseline, five hyposmic relatives had three or more reduced [<sup>123</sup>I]β-CIT binding ratios (left and right striatal [<sup>123</sup>I]β-CIT binding ratios are illustrated in Fig 3). These included the four relatives who developed clinical PD. The fifth relative, who had an isolated reduced right putamen binding ratio at baseline, now had reduced left striatal and bilateral putamen [<sup>123</sup>I]β-CIT binding ratios. All other relatives with initially reduced [<sup>123</sup>I]β-CIT binding ratio(s) had normal scans 2 years from baseline. In a single normosmic relative (who had normal [<sup>123</sup>I]β-CIT binding ratios at baseline) right striatal and right putamen binding ratios were just outside the 95% confidence interval of normosmic values.

The mean rates of change in [<sup>123</sup>I]β-CIT binding ratios over the 2-year follow-up period are listed in Table 4. With the exception of left caudate [<sup>123</sup>I]β-CIT binding, the average rate of decline in all other [<sup>123</sup>I]β-CIT binding ratios was significantly higher in the

group of hyposmic relatives than in the group of normosmic relatives, even when the four hyposmic relatives who developed clinical PD were excluded from the analysis. In the group of hyposmic relatives, the rate of decline in caudate [<sup>123</sup>I]β-CIT uptake was lower than the rate of decline in putamen uptake.

Figure 4 illustrates the individual values for the rates of change in left and right striatal [<sup>123</sup>I]β-CIT binding, expressed as percentage change from baseline in [<sup>123</sup>I]β-CIT binding ratios. A particularly rapid loss of binding occurred in five, as of yet nonparkinsonian hyposmic relatives, three of whom had high (deviating from the normosmic control values) baseline striatal binding values. Among these relatives with rapid loss of binding was the only nonparkinsonian hyposmic relative with reduced [<sup>123</sup>I]β-CIT binding ratios 2 years from baseline. In contrast, the single normosmic relative with two slightly decreased absolute binding ratios 2 years from baseline did not have an increased rate of decline in striatal binding over the 2-year period.

### Discussion

In this prospective study in a cohort of first-degree relatives of PD patients, only those individuals with an otherwise unexplained hyposmia as well as strongly reduced [<sup>123</sup>I]β-CIT binding ratios at baseline, indicative of a subclinical degeneration of the dopaminergic system, went on to develop clinical PD within a follow-up period of 2 years. Two-year follow-up SPECT scanning showed an additional hyposmic rela-

Table 3. Specific to Nonspecific [<sup>123</sup>I]β-CIT Binding Ratios (mean ± SD) at Baseline and at 2 Years

Location	Baseline		Two-Year Follow-up	
	Normosmic Relatives (N = 35)	Hyposmic Relatives (N = 39)	Normosmic Relatives (N = 32)	Hyposmic Relatives (N = 39)
Left striatum	5.38 ± 0.7	5.26 ± 1.5	5.44 ± 0.9	4.86 ± 1.1 <sup>a</sup>
Right striatum	5.25 ± 0.7	5.13 ± 1.4	5.28 ± 0.9	4.74 ± 1.1 <sup>a</sup>
Left putamen	4.33 ± 0.6	4.16 ± 1.2	4.31 ± 0.8	3.69 ± 0.9 <sup>a</sup>
Right putamen	4.05 ± 0.6	3.85 ± 1.1	4.04 ± 0.8	3.55 ± 1.0 <sup>a</sup>
Left caudatus	6.35 ± 0.8	6.33 ± 1.9	6.39 ± 1.1	5.92 ± 1.3
Right caudatus	6.41 ± 0.8	6.41 ± 1.7	6.46 ± 1.2	5.91 ± 1.3

<sup>a</sup>Significantly different from normosmic group (*p* < 0.05).

SD = standard deviation; PD = Parkinson's disease.

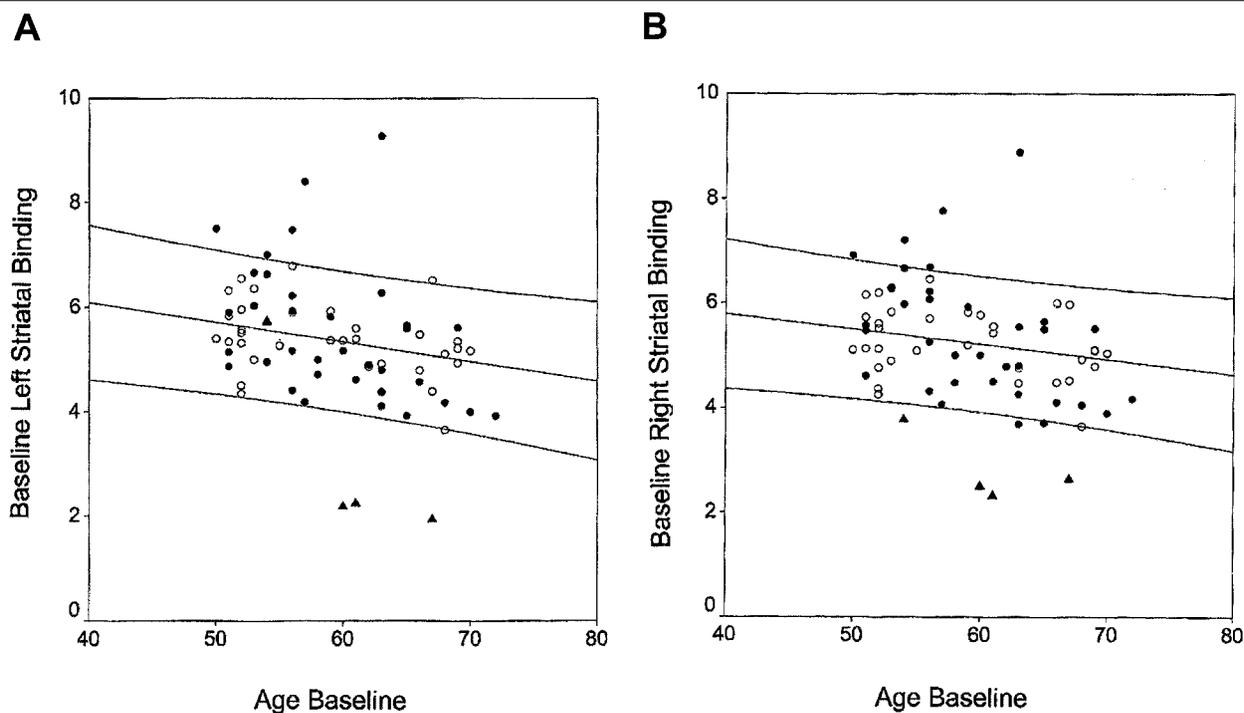


Fig 2. Scatterplots of left (A) and right (B) striatal [ $^{123}\text{I}$ ] $\beta$ -CIT binding ratios at baseline. Normosmic relatives (open circles;  $n = 35$ ) Hyposmic relatives (filled circles;  $n = 35$ ); hyposmic relatives who developed clinical parkinsonism (fill triangles;  $n = 4$ ); the age-adjusted means and the 95% confidence interval of [ $^{123}\text{I}$ ] $\beta$ -CIT binding values in the group of normosmic relatives (solid lines).

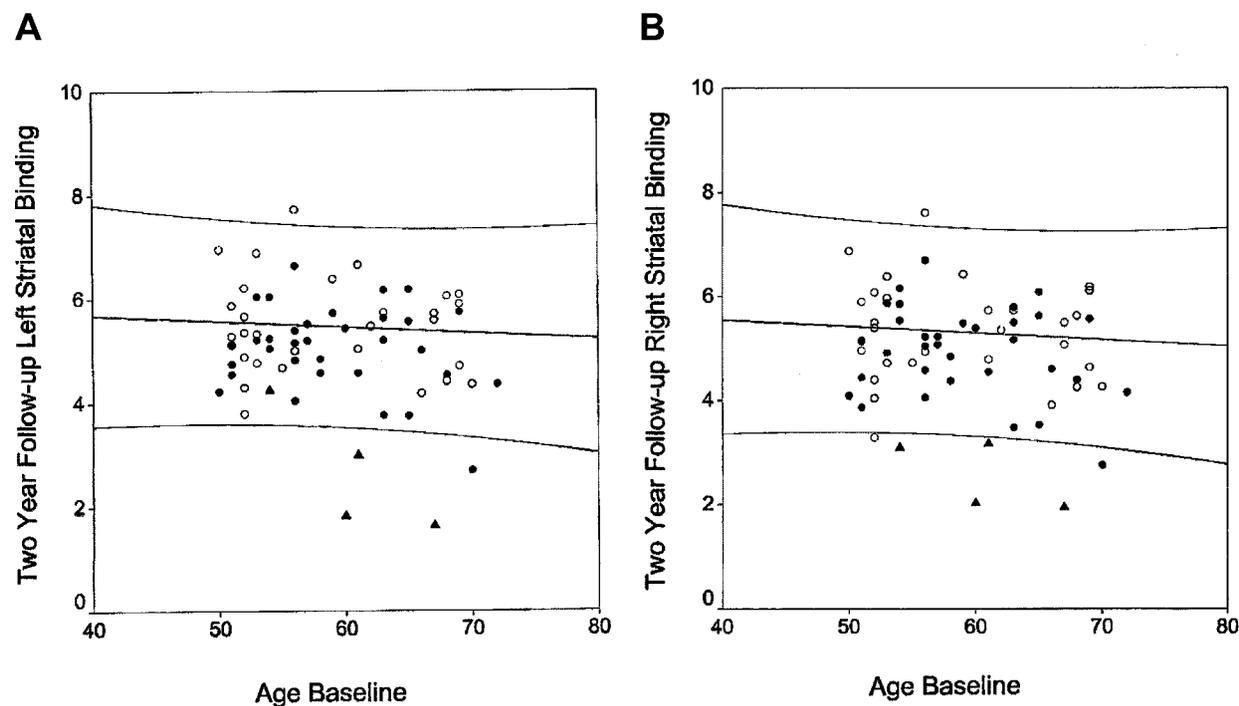


Fig 3. Scatterplots of left (A) and right (B) striatal [ $^{123}\text{I}$ ] $\beta$ -CIT binding ratios 2 years from baseline. Normosmic relatives (open circles;  $n = 32$ ); hyposmic relatives (filled circles;  $n = 35$ ); hyposmic relatives who developed clinical parkinsonism (filled triangles;  $n = 4$ ); the age-adjusted means and the 95% confidence interval of [ $^{123}\text{I}$ ] $\beta$ -CIT binding values in the group of normosmic relatives (solid lines).

Table 4. Percentage Change from Baseline (mean  $\pm$  SD) of [ $^{123}$ I] $\beta$ -CIT Binding Ratios over the 2 Year Follow-up Period

Location	Normosmic Relatives, Total (N = 30)	Hyposmic Relatives		
		Total (N = 38)	No Parkinsonism (N = 34)	Parkinsonism (N = 4)
Left striatum	2.46 $\pm$ 17.3	-5.61 $\pm$ 18.5 <sup>a</sup>	-5.59 $\pm$ 17.8 <sup>a</sup>	-5.75 $\pm$ 26.9
Right striatum	2.61 $\pm$ 17.0	-6.27 $\pm$ 17.7 <sup>a</sup>	-6.19 $\pm$ 16.5 <sup>a</sup>	-6.94 $\pm$ 29.0
Left putamen	0.60 $\pm$ 19.0	-10.04 $\pm$ 15.2 <sup>a</sup>	-9.85 $\pm$ 15.3 <sup>a</sup>	-11.64 $\pm$ 16.4
Right putamen	1.99 $\pm$ 18.0	-7.03 $\pm$ 19.5 <sup>a</sup>	-6.46 $\pm$ 18.1 <sup>a</sup>	-11.91 $\pm$ 32.4
Left caudate	2.14 $\pm$ 17.5	-3.81 $\pm$ 20.3	-3.76 $\pm$ 19.7	-4.24 $\pm$ 29.2
Right caudate	2.84 $\pm$ 18.8	-5.94 $\pm$ 19.4 <sup>a</sup>	-6.57 $\pm$ 18.8 <sup>a</sup>	-0.59 $\pm$ 26.5

Linear regression analysis using absolute [ $^{123}$ I] $\beta$ -CIT binding ratios (Table 3) was used to analyze group differences.

<sup>a</sup>Significantly different from normosmic group ( $p < 0.05$ )

tive with strongly reduced [ $^{123}$ I] $\beta$ -CIT binding ratios. Moreover, in the group of hyposmic relatives, the average rate of decline in dopamine transporter binding was significantly higher than in the group of normosmic relatives.

In the age group studied (50–75 years), the prevalence of clinical PD is approximately 1%, whereas the prevalence of incidental Lewy Body disease (ILBD), which is supposed to represent the preclinical stage of PD, is at least 4%.<sup>19</sup> In our population of 361 relatives of PD patients, there should be at least 14 to 15 individuals with ILBD. This number actually could be even higher, because relatives of PD patients have a three to four times higher prevalence of clinical PD.<sup>23,24</sup> So far, four relatives in our cohort developed clinical PD over a period of 2 years. Another five asymptomatic hyposmic relatives, one of whom also had abnormally reduced [ $^{123}$ I] $\beta$ -CIT binding 2 years from baseline, had a particularly rapid decrease in [ $^{123}$ I] $\beta$ -CIT binding over the 2-year follow-up period (far exceeding the expected age related decline<sup>25</sup>), possibly indicating subclinical disease.

Motor signs (bradykinesia, gait disorders, rigidity, and tremor) without underlying neurological disease are commonly found during clinical examinations of elderly subjects and their prevalence increases strongly with age.<sup>26,27</sup> The presence of a slight motor dysfunction in three normosmic and one hyposmic relatives (as evidenced by a UPDRS motor score between 6 and 8) therefore is not necessarily indicative of a developing parkinsonian syndrome. More extensive follow-up will be conducted to resolve this issue.

The average annual rate of decline in striatal [ $^{123}$ I] $\beta$ -CIT binding was increased in both the small group of hyposmic relatives who later developed clinical PD as well as in the group of hyposmic relatives that remained asymptomatic. The average change in striatal [ $^{123}$ I] $\beta$ -CIT binding in the four hyposmic relatives who developed PD during the follow-up period of 2 years was 6.3%, which is less than the 6 to 13% annual reduction found in previous studies.<sup>11,12,28,29</sup>

However, this difference may be related to a single outlier (Fig 4A, B) in this small group. Among the hyposmic relatives that remained asymptomatic, the average annual decline in [ $^{123}$ I] $\beta$ -CIT binding was 3%. Five asymptomatic but hyposmic relatives had a particularly high annual loss of striatal binding of 15 to 23% (30–45% over 2 years), possibly indicative of an early accelerated degeneration of the nigrostriatal dopaminergic system in the preclinical phase of PD. It could, of course, be argued that this high annual rate of decline in [ $^{123}$ I] $\beta$ -CIT binding might be explained by inter-individual variability. Given an age-related annual reduction in striatal [ $^{123}$ I] $\beta$ -CIT uptake in healthy subjects of only 0.8%,<sup>25</sup> this is not very likely. Furthermore, none of the normosmic relatives in our study had a comparably high rate of decline in striatal binding (see Fig 4).

In designing this study, it appeared to be difficult to define hyposmia in an absolute way, given the substantial interindividual differences in olfactory function as well as important age- and sex-related effects. Nevertheless, using arbitrary cutoff values based on average Z-scores, we were able to demonstrate that (otherwise unexplained) diminished olfactory performance is associated with an increased risk of developing PD. Along the course of our longitudinal study, with more individuals developing clinical PD, we may be able to derive more exact cutoff values for the olfactory tasks used.

Based on the number of hyposmic relatives of PD patients (4 of 40) who developed clinical PD so far, idiopathic olfactory dysfunction seems to confer a risk of 10% of developing PD. The increased rate of decline in [ $^{123}$ I] $\beta$ -CIT binding, suggestive of a subclinical degeneration of the nigrostriatal system, in another 12% of hyposmic relatives, indicates that the risk of developing PD in the presence of idiopathic hyposmia may be as high as 22%. A more extensive follow-up of the cohort of relatives of PD patients is required to determine whether these subjects with an increased rate of loss of [ $^{123}$ I] $\beta$ -CIT binding indeed will go on to

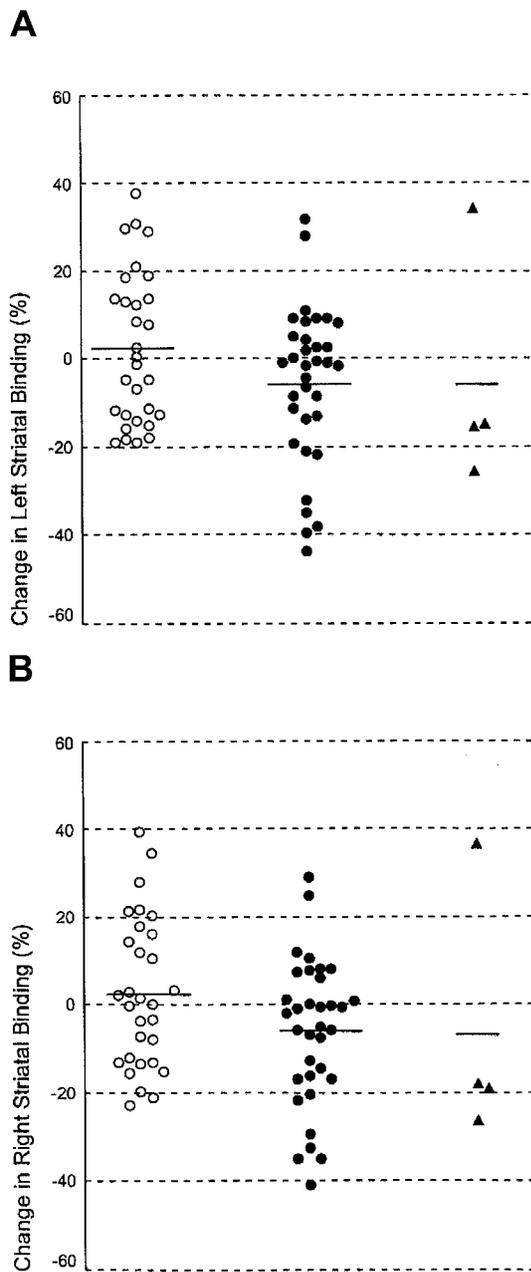


Fig 4. Scatterplots of the rate of change in left (A) and right (B) striatal [ $^{123}\text{I}$ ] $\beta$ -CIT binding ratios over the 2-year follow-up period. Normosmic relatives (open circles;  $n = 30$ ); hyposmic relatives (filled circles;  $n = 34$ ); hyposmic relatives who developed clinical parkinsonism (filled triangles;  $n = 4$ ); mean change in [ $^{123}\text{I}$ ] $\beta$ -CIT binding values (solid lines).

develop clinical signs of PD. Note also that the risk of PD associated with hyposmia strongly depends on the operational definition of hyposmia used and therefore may further increase with more exact cutoff values for the olfactory tests used.

Predating the diagnosis of PD and identifying subjects at risk is an important and young research topic.<sup>18</sup>

With the development of neuroprotective treatment strategies,<sup>30–32</sup> an earlier diagnosis will allow a more timely application of such treatments and also increase the time window available for neuroprotection. On the basis of these results, the olfactory approach to the early diagnosis of PD appears to be particularly promising. Other potentially useful methods to detect pre-clinical PD include ultrasound imaging of the substantia nigra aimed at demonstrating increased echogenicity of the substantia nigra<sup>33</sup> and the use of a battery of clinical tests designed to detect subtle (non)motor manifestations of PD.<sup>34,35</sup> However, the predictive value of these other methods for the subsequent development of clinical PD remains to be determined.

Recent neuropathological observations show extensive extranigral neuropathological changes in idiopathic PD, including the olfactory bulb and related portions of the anterior olfactory nucleus.<sup>17,36,37</sup> In the novel and challenging pathological staging system for PD put forward by Braak and colleagues, Lewy body pathology in these anterior olfactory structures actually precedes involvement of the substantia nigra. The authors hypothesize that the anterior olfactory system may be one of the induction sites of the neuropathological process in PD. The presence of high numbers of dopaminergic neurons in the olfactory bulb might lead to the assumption that olfactory dysfunction in PD might well be related to a loss of dopaminergic neurons. Quite to the contrary, a recent study in postmortem brain tissue showed a doubling of the number of dopaminergic neurons in the olfactory bulb of PD patients relative to age-matched controls.<sup>38</sup> Although the precise pathophysiology of the olfactory deficits in PD remains to be elucidated, the early pathological involvement of the olfactory system in PD is quite in line with our observation that hyposmia may precede clinical motor signs in PD.

In conclusion, our results indicate that olfactory dysfunction in first-degree relatives of PD patients is associated with an increased risk of developing clinical PD of at least 10%. In contrast, in individuals with intact olfactory function the risk appears to be lower than in the general population. Considering the increased rate of decline in dopamine transporter binding in the group of hyposmic relatives, extending the follow-up period of this cohort of relatives may reveal that the risk of PD associated with idiopathic hyposmia is actually considerably higher.

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