An inverse association between Parkinson’s disease and smoking has often been described.¹ However, the debate as to whether this is due to a genuine protective effect of components in cigarette smoke, to methodologic artefacts, or to a variety of other explanations remains unresolved.¹⁻⁵

We carried out a large case-control study investigating the possible relationship between PD and certain environmental exposures. Here, we present a detailed analysis and discussion of the data on smoking habits.

METHODS
The methods of this study have been described in detail.⁶ Briefly, PD patients were recruited in nine neurologic clinics from different regions of Germany. All cases with a clinical diagnosis of PD between 1987 and 1992 and 65 years of age or less were identified. Three clinics included a total of four patients up to 67 years of age. Older patients were not recruited in order to minimize memory deficits, and patients with a longer disease duration were excluded to minimize recall bias. All patients were under the care of experienced neurologists, who were asked to verify inclusion and exclusion criteria according to the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria.⁷ Patients with secondary parkinsonian syndromes or PD patients with dementia were excluded. Of 533 PD patients identified, 377 (71%) agreed to

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Hellenbrand W (Institute of Social Medicine, Faculty of Medicine, Otto-von-Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany), Seidler A, Robra B-P, Vieregge P, Oertel W H, Joerg J, Nischan E, Schneider E and Ulm G. Smoking and Parkinson’s disease: A case-control study in Germany. International Journal of Epidemiology 1997; 26: 328–339.

Background. In a hospital based case-control study, we investigated the role of environmental factors in the aetiology of Parkinson’s disease. This paper describes our results on smoking habits.

Methods. The smoking histories of 380 Parkinson’s disease (PD) patients recruited from nine German clinics were compared to those of age- and sex-matched control subjects (379 neighbourhood controls and 376 controls from the same region). Detailed information on smoking behaviour was collected in structured personal interviews in order to calculate the number of pack-years smoked up to the time of diagnosis. Conditional logistic regression was used to calculate odds ratios (OR) and control for potential confounders.

Results. Among PD patients, 44% had ever smoked, as compared to 59% in both control groups. Among ever-smoking patients, 74% quit prior to the date of diagnosis, as compared to roughly 45% of the ever-smoking control subjects. The OR for ever having smoked was 0.5 (95% confidence interval [CI] : 0.3–0.7), P trend < 0.00005).

Conclusions. The results are considered in terms of criteria for causality. Plausible explanations for the observed inverse association between smoking and PD include:
1. A genetic predisposition that increases the risk for PD (such as defective detoxification enzymes) simultaneously decreases the likelihood of smoking.
2. Inherently lower dopamine levels in predestined PD patients cause them to be less prone to addiction.
3. Smoking is neuroprotective.

Keywords: smoking, Parkinson’s disease, case-control study, epidemiology, causation

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participate. Five additional patients were recruited from neurologic practices affiliated with two of the centres, resulting in a total of 382 participating PD patients. Of 26 patients who provided reasons for declining an interview, 13 stated poor health.

Two controls were recruited for each patient on a random route basis. The first control was recruited within the patient’s immediate neighbourhood and the second control from the same urban or rural region. The random route scheme instructed interviewers to contact personally every second household starting with the patient’s (first control) or a predetermined ‘regional’ (second control) address in order to find a person of the same sex and age (± 3 years) as the patient. The regional address was selected randomly from a list of all addresses in the patient’s voting district. In rural regions, this meant that the control person might be in a nearby small town or village. If the potential control person was not at home at the time the initial contact was made, the interviewer requested to return at a mutually convenient time. On average, 21 household contacts were required to find an appropriate neighbourhood control and 22 contacts to find a regional control willing to participate. No controls could be found for two cases, no neighbourhood control could be found for one case and no regional controls could be found for four cases, leaving 380 patients with at least one control, 376 neighbourhood controls and 379 regional controls for the analysis.

Experienced interviewers were contracted with Infratest/Epidemiologische Forschung Berlin, a sociologic and health research institute. The interviewers were professionally trained in standardized interview techniques and a non-differential approach to patients and controls. The same person interviewed the case and the corresponding controls. Interviewers elicited detailed information regarding onset of smoking and quitting, as well as the quantity of cigarettes, cigars, and pipes smoked in 10 year age-intervals. Pack-years were calculated for cigarettes by dividing the average number of cigarettes smoked per day in a given time interval by 20 and multiplying by the number of years smoked. Five cigars or cigarillos, and 2.5 pipes were considered equivalent to one pack of cigarettes.

Data were compiled in a relational databank using the SIR 3.1 Database System. Basic data analysis was carried out using SPSS/PC. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression with BMDP Statistical Software. Tests for trend were calculated with the interval-scaled data based on logistic regression. All calculations were performed separately for both sets of matched pairs. Analyses consider information up to the date of diagnosis. For this purpose, controls were assigned the date of diagnosis of their matched patient.

As results for the two comparisons were similar, odds ratios presented in the text refer to the comparison with regional controls only.

RESULTS

The mean age of patients was 56.2 ± 6.6 years, of neighbourhood controls, 56.2 ± 7.0 years and of regional controls, 56.5 ± 6.8 years. Mean age at diagnosis (as reported by patients) was 52.5 ± 6.6 years. Mean age at symptom onset was 50.5 ± 7.2 years. Disease duration (from date of diagnosis) was 3.7 ± 1.8 years (min <1, max 8). Of the 380 patients, 251 were men and 129 were women.

Educational level was assessed by years of schooling (general or academic level) in three categories that took into account differences between East and West German education systems. In general, cases were more highly educated than controls, although this difference was not statistically significant (P = 0.07, cases versus neighbourhood controls; P = 0.08, cases versus regional controls, Mann-Whitney test). The results are adjusted for educational status.

Forty-four per cent of patients had ever smoked (56% of men and 21% of women), as compared to 59% among the control groups (71% of men and 33% of women). Less than 5% of subjects among the patient as well as both control groups reported ever having smoked cigars or pipes, with no difference between groups. Among ‘ever-smokers’, there was a markedly higher proportion of ‘ex-smokers’ among patients than controls: 74.4% of ‘ever-smoking’ patients had quit, while only 44.8% of neighbourhood and 46.6% of regional ‘ever-smoking’ controls had quit prior to the date of diagnosis.

The age of onset of smoking did not differ between cases (20.3 ± 6.6 years), neighbourhood (19.5 ± 6.0 years) and regional controls (19.6 ± 5.2 years). In agreement with the larger proportion of ex-smokers in the patient group, smoking duration up to the date of diagnosis differed significantly between the patients and both control groups (Table 1). The dynamics of starting and quitting smoking among patients and controls prior to the patients’ diagnosis are graphically shown in Figures 1 and 2. Figure 1 shows that the maximum smoking rate was reached at roughly the same age in patients and controls, but that controls reached a significantly higher maximum and tended to start quitting at an older age than patients. Figure 2 illustrates smoking patterns according to time before diagnosis. It shows that the larger proportion of quitters...
among the ‘ever-smoking’ patients as compared to ‘ever-smoking’ controls was not due to a higher rate of quitting close to the date of diagnosis in patients. Patients quit a median of 17 years prior to the date of diagnosis; the corresponding figure for neighbourhood controls was 15 years and for regional controls, 12 years.

Smoking controls smoked for significantly more pack-years than patients who smoked (patients, 16.9 ± 15.5; neighbourhood controls: 23.6 ± 19.4 [P < 0.0005]; regional controls, 22.4 ± 17.1 [P = 0.001], Student’s t-test). As shown in Table 2, the OR (95% CI) for ‘ever’ versus ‘never’ smokers was 0.5 (0.3–0.7) (men: 0.4 [0.3–0.7], women: 0.6 [0.3–1.0]), and for ‘current’ (at the date of diagnosis) versus ‘never’ smokers, 0.2 [0.1–0.4] (men: 0.2 [0.1–0.3], women: 0.3 [0.1–0.9]). A strong dose-response relationship was seen for the number of pack-years smoked (P trend <0.00005, Table 3). The OR for ex-smokers did not differ significantly from unity, which is explained mathematically by the proportionately higher number of ex-smokers among ever-smoking PD patients.

The association between smoking and PD long before the diagnosis was examined. When only the amount smoked by patients and controls up to 20 years

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**Table 1. Smoking duration up to the time of diagnosis of patients and controls**

<table>
<thead>
<tr>
<th></th>
<th>Smoking duration ex-smokers</th>
<th>Smoking duration all ever-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>19.3 ± 11.5</td>
<td>20.9 ± 11.7</td>
</tr>
<tr>
<td>Neighbourhood controls</td>
<td>22.3 ± 12.3*</td>
<td>26.3 ± 11.7***</td>
</tr>
<tr>
<td>Regional controls</td>
<td>24.2 ± 11.0**</td>
<td>27.0 ± 10.3***</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P = 0.001, *** P < 0.0005 (compared to patients; Student’s two-sided T-test).
prior to the diagnosis was considered, a statistically significant inverse association was still found (Table 4). When the analysis was stratified according to the patients’ disease duration, a similarly strong inverse dose-response relationship was found between pack-years smoked and PD in each stratum (Table 5). This was also true for stratification according to age at disease onset (Table 6).

The results show that adjustment for education had a minimal effect on the inverse association between smoking and PD. Likewise, there was no evidence for confounding by coffee or alcohol consumption (Table 7). Inclusion of interaction terms did not lead to improvement in the models.

DISCUSSION
In this study, we found a strong inverse relationship between the history of smoking and PD. As epidemiological study designs can rarely establish causality, the results will be discussed using Hill’s Criteria as a framework. According to these criteria, the causality of a relationship is supported (although not proven) by a strong association, a dose-response gradient, consistency with other studies, specificity of the association, a clear temporal relationship, biological plausibility, and experimental evidence in support of a causal effect.

**Strength of the Association and Dose-Response Relationship**
In addition to the strong inverse association, a significant dose-response relationship was found between PD and both the duration of smoking as well as for the total number of pack-years smoked. As described above, the OR for ex-smokers was close to unity, as the proportion of ex-smokers among patients was much higher than among controls. However, prospective data support an intermediate incidence of PD in ex-smokers, thus also suggesting a dose-response relationship. This suggests that the association is not spurious, and would be especially relevant if there were a substance that protected people from PD in cigarette smoke (see below).

### Table 2
**Crude and adjusted odds ratios for Parkinson’s disease according to smoking status**

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Patients versus neighbour controls</th>
<th>Patients versus regional controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1 N2 crude ORa adj. ORb</td>
<td>N1 N3 crude ORa adj. ORb</td>
</tr>
<tr>
<td>Never</td>
<td>212 156 1.0 – 1.0 –</td>
<td>210 159 1.0 – 1.0 –</td>
</tr>
<tr>
<td>Ever</td>
<td>167 223 0.5 (0.4–0.7) 0.5 (0.4–0.7)</td>
<td>166 217 0.5 (0.4–0.7) 0.5 (0.3–0.7)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>125 100 0.9 (0.6–1.3) 0.9 (0.6–1.3)</td>
<td>125 102 0.8 (0.5–1.2) 0.8 (0.5–1.2)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>42 123 0.2 (0.1–0.3) 0.2 (0.1–0.3)</td>
<td>41 115 0.2 (0.1–0.4) 0.2 (0.1–0.4)</td>
</tr>
</tbody>
</table>

NI = number of patients, N2 = number of neighbourhood controls, N3 = number of regional controls.
a OR = odds ratio, with 95% confidence interval shown in brackets.
b Adjusted for education.

### Table 3
**Crude and adjusted odds ratios for Parkinson’s disease according to amount smoked in pack-years**

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Versus neighbour controls</th>
<th>Versus regional controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1 N2 crude ORa adj. ORb</td>
<td>N1 N3 crude ORa adj. ORb</td>
</tr>
<tr>
<td>&lt;0.1</td>
<td>218 160 1.0 – 1.0 –</td>
<td>216 166 1.0 – 1.0 –</td>
</tr>
<tr>
<td>&gt;0.1–10</td>
<td>66 56 0.8 (0.5–1.2) 0.8 (0.5–1.2)</td>
<td>67 58 0.8 (0.5–1.2) 0.7 (0.5–1.1)</td>
</tr>
<tr>
<td>&gt;10–20</td>
<td>37 48 0.5 (0.3–0.8) 0.5 (0.3–0.9)</td>
<td>37 43 0.6 (0.3–1.0) 0.6 (0.3–0.9)</td>
</tr>
<tr>
<td>&gt;20–30</td>
<td>28 45 0.4 (0.2–0.7) 0.4 (0.2–0.7)</td>
<td>26 46 0.3 (0.1–0.5) 0.3 (0.1–0.5)</td>
</tr>
<tr>
<td>&gt;30–40</td>
<td>12 37 0.2 (0.1–0.4) 0.2 (0.1–0.4)</td>
<td>12 37 0.2 (0.1–0.4) 0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>16 32 0.3 (0.2–0.6) 0.3 (0.2–0.6)</td>
<td>16 26 0.3 (0.1–0.6) 0.3 (0.1–0.6)</td>
</tr>
</tbody>
</table>

NI = number of patients, N2 = number of neighbourhood controls, N3 = number of regional controls. Two patients and one neighbourhood control reported having been smokers, but had missing information on quantity or duration.
a OR = odds ratio, with 95% confidence interval shown in brackets.
b Adjusted for education.
c Number of pack-years smoked.
Consistency with Other Studies
Other studies have reported a similar inverse relationship between PD and smoking, although there are exceptions. The first studies to report a negative association between PD and smoking were large prospective studies based on mortality data.\textsuperscript{12-16} The British Doctor’s study cohort has now been followed for over 40 years, and the latest analysis continues to show an inverse relationship between PD mortality and smoking, although only for current smokers.\textsuperscript{16} Nonetheless,
these studies have been criticized, because PD is often not recorded as the primary cause of death. This may be especially so in smoking PD patients, who presumably die of other, smoking-related causes more often than non-smoking patients. Furthermore, the total number of PD patients involved in these studies is quite small.

However, this inverse relationship has also been found in two prospective follow-up studies, one making use of data from the Framingham cohort and the other from the Honolulu Heart Study cohort. Case-control studies have shown a negative association between PD and smoking as well, although there have been some exceptions. A comprehensive review of these and some additional, smaller studies addressing strengths, weaknesses and possible biases has recently been published, and will not be repeated here.

The fact that different study designs have led to similar results suggests that design-specific biases are not an adequate explanation for the observed association. Nonetheless, due to a higher than expected unemployment rate among the male controls, we were concerned about a possible selection effect.

### Table 6
Crude and adjusted odds ratios for Parkinson’s disease according to amount smoked in pack-years stratified for age at diagnosis

<table>
<thead>
<tr>
<th>Smoking in pack-years</th>
<th>N1</th>
<th>N2 (crude OR&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>adj. OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P for trend&lt;sup&gt;c&lt;/sup&gt;</th>
<th>N1</th>
<th>N2 (crude OR&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>adj. OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P for trend&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis ≤50 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>80</td>
<td>61</td>
<td>1.0 –</td>
<td>1.0 –</td>
<td>78</td>
<td>61</td>
<td>1.0 –</td>
<td>1.0 –</td>
</tr>
<tr>
<td>&gt; 0.1–20</td>
<td>41</td>
<td>35</td>
<td>0.9 (0.5–1.6)</td>
<td>0.9 (0.5–1.6)</td>
<td>42</td>
<td>37</td>
<td>0.9 (0.5–1.6)</td>
<td>0.9 (0.5–1.6)</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>14</td>
<td>40</td>
<td>0.3 (0.1–0.6)</td>
<td>0.3 (0.1–0.6)</td>
<td>13</td>
<td>36</td>
<td>0.2 (0.06–0.5)</td>
<td>0.2 (0.06–0.5)</td>
</tr>
<tr>
<td>Age at diagnosis &gt;50 years and ≤55 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>68</td>
<td>43</td>
<td>1.0 –</td>
<td>1.0 –</td>
<td>68</td>
<td>50</td>
<td>1.0 –</td>
<td>1.0 –</td>
</tr>
<tr>
<td>&gt; 0.1–20</td>
<td>25</td>
<td>33</td>
<td>0.5 (0.2–0.9)</td>
<td>0.5 (0.2–1.0)</td>
<td>25</td>
<td>24</td>
<td>0.7 (0.3–1.4)</td>
<td>0.6 (0.3–1.3)</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>13</td>
<td>30</td>
<td>0.3 (0.1–0.6)</td>
<td>0.3 (0.1–0.6)</td>
<td>13</td>
<td>32</td>
<td>0.1 (0.03–0.4)</td>
<td>0.1 (0.03–0.4)</td>
</tr>
<tr>
<td>Age at diagnosis &gt;55 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>70</td>
<td>56</td>
<td>1.0 –</td>
<td>1.0 –</td>
<td>70</td>
<td>55</td>
<td>1.0 –</td>
<td>1.0 –</td>
</tr>
<tr>
<td>&gt; 0.1–20</td>
<td>37</td>
<td>36</td>
<td>0.7 (0.3–1.4)</td>
<td>0.6 (0.3–1.3)</td>
<td>37</td>
<td>40</td>
<td>0.6 (0.3–1.1)</td>
<td>0.6 (0.3–1.1)</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>29</td>
<td>44</td>
<td>0.5 (0.2–0.9)</td>
<td>0.5 (0.2–0.9)</td>
<td>28</td>
<td>41</td>
<td>0.4 (0.2–0.8)</td>
<td>0.4 (0.2–0.8)</td>
</tr>
</tbody>
</table>

NI = number of patients, N2 = number of neighbourhood controls, N3 = number of regional controls.

<sup>a</sup> OR = odds ratio, with 95% confidence interval shown in brackets.

<sup>b</sup> Adjusted for education.

<sup>c</sup> Number of pack-years smoked.

### Table 7
Crude and adjusted odds ratios for Parkinson’s disease according to amount smoked in pack-years: multivariate analysis including potential confounders

<table>
<thead>
<tr>
<th>Smoking in pack-years</th>
<th>N1</th>
<th>N2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>crude OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt; adj. for ethanol intake</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt; adj. for coffee intake</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt; adj. for ethanol and coffee intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>194</td>
<td>141</td>
<td>1.0 –</td>
<td>1.0 –</td>
<td>1.0 –</td>
<td>1.0 –</td>
</tr>
<tr>
<td>1–10</td>
<td>66</td>
<td>49</td>
<td>0.9 (0.6–1.4)</td>
<td>0.9 (0.5–1.4)</td>
<td>0.9 (0.5–1.4)</td>
<td>0.9 (0.5–1.4)</td>
</tr>
<tr>
<td>10–20</td>
<td>34</td>
<td>42</td>
<td>0.5 (0.3–0.9)</td>
<td>0.6 (0.3–1.0)</td>
<td>0.6 (0.3–1.0)</td>
<td>0.6 (0.4–1.1)</td>
</tr>
<tr>
<td>20–30</td>
<td>23</td>
<td>43</td>
<td>0.3 (0.2–0.6)</td>
<td>0.3 (0.2–0.6)</td>
<td>0.4 (0.2–0.7)</td>
<td>0.4 (0.2–0.7)</td>
</tr>
<tr>
<td>30–40</td>
<td>10</td>
<td>37</td>
<td>0.2 (0.1–0.4)</td>
<td>0.2 (0.08–0.4)</td>
<td>0.2 (0.1–0.4)</td>
<td>0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>15</td>
<td>30</td>
<td>0.3 (0.1–0.6)</td>
<td>0.3 (0.1–0.6)</td>
<td>0.4 (0.2–0.9)</td>
<td>0.4 (0.2–0.9)</td>
</tr>
</tbody>
</table>

N1 = patients, N2 = controls.

<sup>a</sup> The food frequency questionnaire was administered to only one control per patient, in general the neighbourhood control. As described elsewhere the dietary data could be analysed for only 342 case-control pairs.

<sup>b</sup> OR = odds ratio, with 95% confidence interval shown in brackets.
described previously, we therefore reanalysed our data after excluding controls who were unemployed but younger than retirement age at the time of the interview and patients who were unemployed but younger than retirement age at the time of diagnosis (results not shown). This did not alter our finding of a strong inverse association between smoking and PD. The possibility of a patient selection bias was minimized by selecting both ambulatory and in-patients and by selecting all patients seen at each clinic fulfilling the selection criteria. There was some evidence that more impaired patients declined to participate, and we cannot rule out that there may have been a higher percentage of smokers in this group.

Specificity of the Association

Specificity refers to the situation in which a cause leads to only one outcome, and that outcome results from only the one cause. This is a rarely observed phenomenon, which, when present, is a strong argument for causality. The inverse association between cigarette smoking and PD found in this study is, of course, not specific; first, because not all smokers were ‘protected’ from PD, and, secondly, because smoking leads to a number of other well-defined ‘effects’, which complicate the interpretation of the results.

One of these effects is an elevated mortality risk from smoking-related diseases, such as coronary heart disease and lung cancer. It has been proposed that smoking PD patients might die earlier from such diseases than smoking controls, perhaps due to the debilitating nature of their underlying illness. In a given age group, this would lead to a deficit of smokers among PD patients. However, apart from the fact that no data are available as to whether smoking PD patients do, in fact, have a higher mortality from smoking-related diseases, such an interaction effect would have to be extremely strong to lead to the observed deficit of smokers in the space of only a few years (the average disease duration of the patients participating in this study was 3.7 years). Furthermore, stratification of the case-control pairs according to disease duration (≤3 years, 3 years, Table 5) did not affect our findings, making selective mortality a less likely explanation (the association should then be stronger in the group with a longer disease duration, although this argument might be stronger if patients with a longer disease duration had been included). In addition, Baumann et al. investigated the smoking history of patients who died before their planned interview in a large case-control study by interviewing family members. Smoking had not been more common among the deceased patients than among the patients who participated in the study.

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Pack-years smoked up to age 35 (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By ever smokers</td>
</tr>
<tr>
<td>≤50 years</td>
<td>11.3 ± 8.7</td>
</tr>
<tr>
<td>&gt;50 years and ≤55 years</td>
<td>12.1 ± 9.1</td>
</tr>
<tr>
<td>&gt;55 years</td>
<td>10.7 ± 8.5</td>
</tr>
<tr>
<td>Total</td>
<td>156</td>
</tr>
</tbody>
</table>

N = number of patients: 14 patients were aged <40 years at diagnosis. Of these, five were smokers. Seven additional smokers started smoking after the age of 35, leaving 156 ‘ever-smokers’ for this analysis.

A related explanation would be the presence of an elevated mortality secondary to smoking among predestined PD patients prior to clinical disease, again through a potentiation effect. Although there is little evidence for this, it would not be possible to recognize such an effect using available epidemiological study designs, mainly because it is not (yet) possible to diagnose predestined PD patients. The finding of a lower average age of onset in ‘ever’ cigarette smokers has been interpreted as being supportive of such an effect. However, our data show that it is problematic to make inferences based on age-of-onset data. In our study, the age of PD onset was identical in ever- and never-smoking PD patients, although current smokers in our study had a significantly younger age of PD onset (49.3 ± 8.2 years) than ex-smokers (53.6 ± 5.8 years) or non-smokers (52.5 ± 6.5 years, \( P = 0.009 \) (ANOVA). A possible explanation for this observation unrelated to any aetiological arguments is the decreasing smoking rate in older people in general—thus people developing PD at a higher age are statistically more likely to have already quit than younger people.

The observation that heavy smokers in this study developed PD at a significantly older age (54.9 years in those having smoked >20 pack-years versus 51.6 years for those smoking ≤20 pack-years \( P = 0.009 \)) would tend not to support selective mortality as an explanation for the findings in our study. However, older people may simply have had more time to accrue pack-years. When we looked only at the amount smoked up to the age of 35 in the 366 patients who developed the disease at age 40 or thereafter, we did not find differences according to age at diagnosis (Table 8). Similarly, in their
prospective study, Grandinetti et al.\textsuperscript{11} did not find a difference in age at disease onset between non-smoking and smoking PD patients, nor between heavier and lighter smokers, although they did not report on differences between current and ex-smokers. This illustrates that it is difficult to use age-of-onset data to support or refute a possible protective effect of smoking on the development of PD in general or selective mortality in particular: These data will be affected not only by the actual relationship between PD and smoking, but also by the relationship between smoking habits and age, and therefore also by the age structure of the smoking and non-smoking study population (particularly in case-control studies).

Our finding that a higher proportion of ‘ever-smoking’ predestined PD patients quit smoking earlier in life than corresponding controls may have implications for the theory of ‘preclinical’ selective mortality: Because the total number of years smoked is lower and more time has elapsed since quitting, smoking related mortality should theoretically be lower among ‘ever-smoking’ predestined patients than among ‘ever-smoking’ controls. In the long run, this could theoretically lead to a positive association between PD and ‘ever smoking’, the opposite of what is actually observed.

Riggs\textsuperscript{2} takes a slightly different approach to the possibility of a selective survival bias as an explanation for the inverse association between smoking and PD. He postulates that because smokers have a higher mortality than non-smokers, the gene pools of smokers and non-smokers may become increasingly different as people get older. This could lead to different levels of risk for acquiring neurodegenerative diseases such as PD especially among older smokers and non-smokers.\textsuperscript{2} However, in this case one would expect to see a stronger inverse association between smoking and PD with increasing age at diagnosis, which we did not observe in our study (Table 6).

Another ‘effect’ of smoking is its association with a certain lifestyle, which brings us to the consideration of potential confounders. In our study, we also observed an inverse association between PD and the intake of both alcohol and coffee. This is discussed in detail elsewhere.\textsuperscript{38} Inclusion of either alcohol intake, coffee intake or both in a multivariate model with smoking did not, however, weaken the association with smoking.

Lack of specificity of the inverse association between smoking and PD, then, may be a reflection of these multiple effects of smoking. None of these ‘effects’, however, seem to provide an adequate explanation for the association. This lack of specificity may also reflect the likely multifactorial aetiology of this disease, in which smoking or factors related to smoking may be one important aspect.

Temporal Relationship

In chronic diseases with long latencies, it is not always easy to prove that a possible ‘cause’ actually precedes the disease, potentially leading to a ‘cause and effect’ bias. The chronicity of the disease per se is unlikely to have been a problem in this study, as patients had a fairly short disease duration. However, the latent period of this disease remains controversial.\textsuperscript{39} Extrapolations of pathologic studies suggest that the presymptomatic phase of the disease could be as short as 4.7 years\textsuperscript{40} or as long as 30 years.\textsuperscript{41} In twins concordant for the disease, the age of onset has varied by as much as 26 years,\textsuperscript{42} suggesting that the latent period could vary strongly and possibly be quite long. Of course, toxic or environmental insults as possible determinants of PD could occur at different ages in different people, leading to heterogeneity in age of onset, with or without a genetic predisposition.\textsuperscript{43}

Because an inverse association was found between smoking long before onset of the disease and PD (Table 4) and because the higher proportion of quitters among ever-smoking PD patients did not cluster within a time interval close to the date of diagnosis (Figure 2), it appears that preclinical symptom induced quitting, as postulated by Mayeux et al.\textsuperscript{35} is not an adequate explanation for our results. That is, a high proportion of PD patients who stopped smoking, stopped long before their disease onset. This would argue against a cause and effect bias, especially if the latent period should, in fact, be relatively short.

It has been proposed that PD patients could have inherently lower dopamine levels as compared to controls.\textsuperscript{44} As dopamine pathways play an important, although probably not the sole, role in reward mechanisms important in addiction,\textsuperscript{45,46} this could make predestined PD patients less prone to becoming addicted to smoking. Lower dopamine levels prior to clinical disease onset could be genetically determined, or, alternatively, the result of a toxic insult early in life, which could lead to an increased risk for PD. They could also be the direct result of a prolonged subclinical disease process, which would be consistent with a long latent period. This explanation for the inverse association between PD and smoking is difficult to prove, but would also be consistent with our data.

Reduced dopamine levels long before disease onset might also explain why the premorbid personality of PD patients is frequently described as being more serious, rigid, introverted, quiet and pedantic than controls.\textsuperscript{47-50} It has frequently been discussed that such a
personality profile could lead to abstinence from smoking.\cite{1,22,27,29}

Another possible explanation for less smoking among later PD patients would be an inherent inability to metabolize certain toxins, which could influence the inclination to smoke. This would also be a type of ‘cause and effect’ bias. Both enzymatic and molecular genetic studies have found a higher prevalence of poor homozygous and heterozygote debrisoquine metabolizers among PD patients than controls.\cite{51-54}

Debrisoquine hydroxylase is a P450 enzyme involved in the detoxification of numerous xenobiotics. Among these are N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),\cite{55} which is known to cause a clinical syndrome almost identical to PD in humans and animals.\cite{56} Cholerton et al.\cite{57} found that healthy homozygous poor metabolizers of debrisoquine (but not heterozygotes) were less able to convert nicotine to cotinine. Unfortunately, in our study detailed data are lacking to look for a possible genetic interaction; however, Barbeau et al.\cite{52} reported that PD patients in their study who were heterozygotes or homozygous poor metabolizers of debrisoquine had either never smoked or had smoked for a shorter time period than normal metabolizers.

Sulphur oxidation and conjugation, and thiolmethyltransferase activity have also been reported to be defective more frequently among PD patients as compared to controls.\cite{58,59} In addition, there is evidence that N-methylated pyridines tend to accumulate in PD patients as compared to controls, possibly due to a block in further metabolism by P450 oxidation reactions or oxidation through monoamine oxidase B.\cite{60} Nicotine is also metabolized to an N-methylated pyridine derivative, which might theoretically be perceived as unpleasant and lead to less smoking in predestined PD patients. Alternatively, accumulation of this metabolite could saturate the system completely and thereby reduce the formation of other more toxic N-methylated pyridines, thus having a true protective effect.\cite{60}

**Biological Plausibility and Experimental Evidence**

The latter point brings us to the final two criteria of biological plausibility and experimental evidence for a true causal, in this case protective, effect. There are various lines of evidence, such as the one just mentioned, supportive of a direct protective mechanism for cigarette smoking. The fact that smoking appears to protect patients taking neuroleptics from drug-induced parkinsonism\cite{61,62} is also evidence in this direction.

Janson and Moller\cite{63} found that chronic nicotine treatment in rats at concentrations similar to those found in smokers counteracted nigral cell loss induced by partial mesodiencephalic hemitransection. The authors suggest that this protective effect could be the result of a functional desensitization of nicotinic cholinoreceptors located on dopaminergic neurons, which could lead to reduced burst firing of nigral dopaminergic neurons\cite{64} as well as reduced dopamine utilization.\cite{65} This would lead to decreased calcium ion influx into the cells, which might explain their decreased vulnerability. In addition, decreased dopamine turnover could lead to less free radical formation and thus less oxidative stress during dopamine oxidation.\cite{66}

Smoking also induces cytochrome P450 enzymes that may be involved in the metabolism and detoxification of possible neurotoxins such as MPTP.\cite{67} Shahi et al.\cite{67} observed that cigarette smoke exposure partially protected against MPTP-induced striatal dopamine depletion in mice, while at the same time causing cytochrome P450 induction. P450 induction alone through beta-naphthoflavone treatment also had a protective effect. In addition, these authors and others\cite{68-70} have observed that cigarette smoke exposure inhibits monoamine oxidase-B (MAO-B) in mouse brain and liver, rat lung and human platelets. Although post-mortem studies have not revealed differences in MAO-B activity between PD patients and controls,\cite{68,71} Fowler et al.\cite{72} showed that smoking reduced levels of MAO-B in humans in various brain regions (including the basal ganglia) *in vivo* using positron emission tomography techniques. As oxidation of dopamine by MAO-B leads to the formation of hydrogen peroxide,\cite{73} its inhibition might lead to less oxidative stress. MAO-B is also required for the conversion of MPTP to the active neurotoxin MPP+. The presence of the MAO-B allele I has been associated with PD, thus also suggesting that a particular variant of this enzyme may be important in a predisposition to the disease.\cite{74}

In addition, cigarette smoke\cite{70} or nicotine itself\cite{75} has been found to reduce the toxicity of MPTP in some, but certainly not all,\cite{76-78} animal experiments. Some of this discrepancy may be explained by the method of nicotine administration.\cite{79} Other substances in cigarette smoke may also exert a neuroprotective effect: 4-phenyl-pyridine\cite{80} and hydrazine\cite{68} have been shown to protect from MPTP-induced neurotoxicity, possibly through a competitive mechanism. Other quaternary N-methylated nicotine derivatives may have a similar effect.\cite{81} Calne and Langston\cite{82} proposed that carbon monoxide in cigarette smoke could act as a radical scavenger and thereby reduce PD risk.

Kessler and Diamond\cite{19} hypothesized that nicotine could be converted to nicotinic acid by an as yet unidentified pathway. To our knowledge, this has never
been confirmed, however, in our dietary investigation, we found a strong inverse association between niacin intake and PD.83

Our results, then, together with other epidemiological and experimental research, provide evidence for a ‘causal’ relationship between smoking and PD according to a number of Hill’s Criteria (strength of the association, dose-response relationship, consistency with other studies, biological plausibility and experimental evidence), at least to some extent. There is less evidence for specificity of the association, and a clear temporal relationship cannot be established beyond doubt.

To summarize, in this study fewer PD patients than their age- and sex-matched controls ever started smoking, and they quit smoking sooner and more often than controls. Thus, we found a strong, statistically significant inverse association between PD and smoking prior to disease onset with a strong dose-response gradient. This finding was unaffected by disease duration or age at disease onset, and we present evidence against the postulation that the inverse relationship is simply due to quitting induced by early unrecognized symptoms of the disease. Although methodological artefacts cannot be entirely ruled out, it seems unlikely that they could account for the strength of the association and its dose-response relationship, especially in light of the consistency with most other epidemiological studies, including those based on prospective data. We also present evidence against the frequently postulated explanation of selective mortality.

Thus, we are left with several plausible explanations for the observed relationship between smoking and PD:

1. Predestined PD patients have a genetic predisposition, such as poorly functioning detoxifying enzymes, which makes them less likely to smoke.
2. Predestined PD patients have inherently lower dopamine levels, which causes them to be less prone to addictive behaviour.
3. The association is truly (neuro)protective.

The evidence for and against these possibilities is discussed in detail above. A definitive explanation would be facilitated by the availability of a preclinical marker, and will likely contribute to the uncovering of the aetiology of this disease, perhaps simultaneously increasing understanding of mechanisms underlying addiction.

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