Whooping Cough and Parkinson's Disease

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Background. We reported high levodopa use and prevalences of Parkinson's Disease (PD) in periodically, time-clustered, Icelandic cohorts born after major whooping cough epidemics (MWCE).

Methods. In order to quantify a possible relationship between age at first post-birth MWCE and risk of PD we: 1) calculated cumulative incidences of PD during the period 1954-1963 in one-year Icelandic cohorts born between 1869 and 1927, using raw material from a reported survey; 2) identified MWCE from 1869 onwards in Iceland; 3) estimated cohort ages at onset of incidence period and at first MWCE; and 4) combined the above-mentioned information using log-linear models. In addition, we studied the prevalence of levodopa users in Icelandic birth cohorts during a recent period.

Results. The curves of the above-mentioned incidences and prevalences in one-year birth-cohorts showed: 1) a similar, age-related, inverted V profile; and 2) a systematic notchy pattern, with peak values for one or both measurements for cohorts born during or after each of nine MWCE identified during the period 1869-1927. When 13 cohorts born in years with MWCE were excluded from the analysis, the risk of PD rose with age at first defined MWCE, with the linear increase being 8.4% per year (95% CI : -0.1-18.3%).

Conclusions. These results are consistent with reported effects of age at exposure in animal models of toxic parkinsonism, age-related changes in the dopamine receptor-GPT-binding protein-adenylatecyclase system observed in rats treated with pertussis toxin, and some PD epidemiological features. They suggest that pertussis neurotoxicity could be causally related to PD worldwide.

Keywords: dopamine, drug use, epidemiology, aetiology, Parkinson's disease, pertussis

Parkinson's disease (PD) is a disorder characterized by progressive Lewy-body neuronal degeneration, located mainly in substantia nigra (SN) and other brainstem nuclei. This lesion might precede the onset of clinical symptoms by several decades. The disease appears to be ubiquitous, is not present in animals, and may have undergone similar historical changes worldwide linked to modernization. The highest reported PD incidence and prevalence for ages under 70 years and Parkinsonism-related mortality are to be found in Iceland.

The causes of PD are unknown. Nowadays, the most plausible aetiological hypothesis is a combination of hereditary—most probably polygenic—and toxic environmental factors. However, while a two- to threefold risk of PD associated with a genetic defect linked to cytochrome P450 mono-oxygenase activity, a protective factor against toxic environmental compounds, has been reported, environmental toxins potentially linked to PD remain unidentified.

In the West, recent studies report that 76–83% of all prevalent diagnosed patients are being treated with levodopa (LD). Furthermore, LD use (LDU) is highly specific for PD treatment. Geographical evaluation of sales of LD in 92 regions from Denmark, Iceland, Greece, Spain, and Sweden pointed to highest LDU
in Greenland, the Faroe Islands and Iceland, which historically constituted small-sized, geographically isolated populations. Results of a survey of LD prescriptions in 1990–1991, reanalysis of raw data on PD prevalence in 1963 plus historical reports on several childhood infections in Iceland suggested that cohorts born after whooping cough epidemics (WCE) might account, at least in part, for the high prevalence of PD and high LDU level. The purpose of this paper was to quantify a possible relationship between age at whooping cough infection and risk for PD in Iceland.

METHODS

Parkinson's Disease Frequency

The raw material produced by the late K R A Gudmundsson, generated from the PD survey he conducted as a PhD Thesis in Iceland in the mid-1960s (reported in 1967), was retrieved. The numbered, 29-page document, entitled 'Parkinsonism 1954–1963. All cases', was undated. It consisted of a manuscript listing dates of birth and death, diagnostic category—idiopathic (IP), postencephalitic, post-traumatic or arteriosclerotic (AP) parkinsonism—and age at clinical onset for 470 patients. All the information, was legible. Interpretation of the data did not prove problematic, except for one patient classified as having both IP and AP, and one patient for which death was quoted but not dated. Data for three patients, one of them deceased in 1966, had been appended on the last page. The calendar year of clinical onset for patients with IP or AP, an item of information crucial for inclusion in incidence counts for the above-mentioned period, had not been recorded. Hence, this was calculated from the date of birth and age at onset of clinical manifestations. Sixteen cases with post-encephalitic parkinsonism and one classified as post-traumatic were excluded from this analysis. Information on the Icelandic population at 31 December 1950, 1960, 1965 and 1990, was obtained from the Icelandic National Office for Statistics. The Icelandic populations by one-year groups as at I January 1954 and 31 December 1963 were estimated by taking the average of the above-mentioned population figures for 1950 and 1960, and 1960 and 1965. Cumulative incidences during the period 1954–1963 for IP+AP were calculated for one-year birth cohorts born during the period 1860–1940.

Identification of WCE

The earliest summary reports on WCE in Iceland refer to outbreaks in 1792, 1826, 1839 and 1841 but documents are only available for certain years. Systematic, annually compiled reports on relevant epidemics in this population were published in Danish official statistics for the period 1854–1914. The quality of the information on WCE from the annual 1854–1914 health reports varied considerably. The text printed in Gothic lettering was sometimes difficult to read. The information from reports for the period between 1854 and 1870 was brief and incomplete. From 1881 onwards notification data on WC were collected annually. Reports for the period 1881–1950 were compiled in 1961. The examiners—AL, GG and HT—found the reported data for the period 1869 onwards to be reliable for purposes of identification of major WCE (MWCE). After verifying that the notification data were in accordance with the reported graphs, we identified major WC outbreaks, which were denoted as defined major WCE (DMWCE) when they were reported: 1) as massive, in the time prior to notification, or at least when one annual count of notified cases numbered 400 or higher; and 2) as successively affecting populations resident in distant regions of the island, including always the most populated region in the South. The nationwide spread of each DMWCE was ascertained by identifying the residence of reported WC cases in a minimum of four areas, namely, Reykjavik and three selected counties, Thingeyri, Hofn and Faskrúdsfjördur (whose names changed with time), located in the northwestern, central-northern and eastern regions of the country, respectively. Calendar years with DMWCE were defined as those when peaks of a DMWCE were judged to have occurred prior to 1890, or those with 400 or more notified WC cases.

Age at Clinical Onset, Age at Infection and Modelling Strategies

Data from 59 one-year birth cohorts, those for the period 1869–1927 which generated the majority of the IP+AP cases, were taken as a preliminary selection for analytical purposes. For each cohort, age at 1 January 1954 was calculated, taken as a surrogate for age at clinical onset for said cohort and denoted for our purposes as cohort age. The cohorts were further classified into categories, taken as surrogates of age at infection according to the number of years elapsed between year of birth and 1 January of the first year with a DMWCE. This measurement would correspond to a minimum average age at first possible, i.e. post-birth, pertussis infection (PI). A considerable shortcoming of the age at first DMWCE measurement in this ecological approach—particularly if the WCE started in the early months of the birth year—is its low validity as a proxy of age at PI for cohorts born in years with DMWCE. This is because many individual members of such cohorts could have been born after the epidemic had affected the population in the residential area of their
mothers, and so conceivably remained uninfected during such an epidemic. In fact, the minimum possible age at PI for this proportion—non-existent in cohorts born in periods free of WCE—would be much higher than a few months since, at the very least, they ought to have become infected after the immediate inter-epidemic interval. The analysis was therefore run on a subset of the above birth cohort data, namely, that resulting after exclusion of all cohorts born in years with DMWCE.

The relationship between age at first DMWCE and risk of PD was assessed using a log-linear Poisson model where the predictor variables were cohort age and cohort age at first DMWCE, and the dependent variable the cumulative incidence of IP+AP for each cohort. In the model, the following steps were carried out: 1) cohort age was categorized into nine age intervals (0–44, seven 5-year intervals, and 80 years and over), and cohort age at first DMWCE into five categories, from one to five and more years; 2) both factors were then coded as dummy; and lastly, 3) introduced into the final model, since the relationship of PD incidence with age is well established. With regard to effect of age at first DMWCE, the reference for comparison of risks were the cohorts born in the year immediately preceding that for the first post-birth DMWCE. An interaction term was then introduced but the model did not converge; hence, interaction was not tested. Output values from this model for effect of age at first DMWCE would be interpretable as RR, with effect of age at onset of clinical manifestations being controlled for. Goodness-of-fit was evaluated by comparing the deviance of the two-factor ‘cohort age + age at first DMWCE’ model against that of: 1) the base model with the intercept term; and 2) the model with cohort age as the only independent variable.

Prevalence of LD Users
In order to verify whether the birth-cohort pattern found for reported prevalences of LD users in Icelandic birth cohorts for the period 1 October 1990 to 31 March 1991 (based on data obtained from a drug prescription survey) fitted the findings for PD incidence during the period 1954–1963 and for MWCE, the three data sets were plotted on the same graph.

RESULTS
The differences between reported and reanalysed data from the Icelandic PD survey, grouped in diagnostic and epidemiological categories, are shown in Table 1. There were 272 reported versus 270 retrieved IP+AP patients incident during the study period, the youngest being born in 1925. The variations with possible impact in the analysis were small.

The age-specific, reported and reanalysed incidences and cumulative incidences of IP or AP in Iceland during the period 1954–1963, as well as the age-specific prevalences of LD recipients during the 6-month period, October 1990-March 1991, are listed in Table 2. Rates and proportions increase with age, particularly so in the case of prevalences of LD users. With regard to differences between reported and recalculated counts, a slight variation in the distribution of incidences of IP+AP by age at clinical onset is observed.

During the period 1869–1927, nine major WC outbreaks were identified, with the duration of DMWCE-free intervals ranging from 4 to 8 years. The first WCE reported for this period was that in 1871–1872. Details regarding spread were sparse in some cases, particularly for the early epidemics with onset in 1871 and 1880, for which a lack of reported cases from some counties was observed. At that time, physicians were scarce, their reporting habits varied and they might have been absent from some places just when the resident population was affected. The 1871–1872 epidemic affected the capital and, subsequently, the southern regions—where most infants aged below one year died—reaching western and northern Iceland the following year. The 1880–1882 outbreak traced a similar pattern, with deaths reported solely in 1881. For each of the seven remaining DMWCE recorded over the period 1869–1927, WC case notification came, at the minimum,
Table 2: Reported and reanalysed occurrence of PD, and use of LD in Iceland. Number of patients in parentheses

| Age groups | Incidence density per 10^5 | Levodopa prescription |
|------------|---------------------------|-----------------------|
|            | Reported | Reanalysed |                  | Prevalence of LD recipients per 10^3 in Iceland, Oct 1990-March 1991 |
| 0-29       | 0 (0)    | 0 (0)      | 89 626             | 1.1 (1) |
| 30-39      | 1.4 (3)  | 0.9 (2)    | 21 075             | 38.0 (8) |
| 40-49      | 5.6 (10) | 5.6 (10)   | 17 327             | 109.7 (19) | 0.0 (0) |
| 50-59      | 32.9 (48) | 31.5 (46) | 14 245             | 610.7 (87) | 368.1 (77) |
| 60-69      | 97.2 (112) | 98.1 (113) | 10 124            | 1135.8 (115) | 1065.8 (206) |
| 70-79      | 136.2 (82) | 136.2 (82) | 5651              | 654.7 (37) | 1982.6 (250) |
| 80+        | 69.2 (17) | 69.2 (17) | 2348              | 127.4 (3) | 1817.2 (130) |
| All ages   | 16.0 (272) | 15.8 (270) | 160 408           | 168.3 (270) | 272.3 (691) |

*Reported 6*

Figure 1a: Period prevalence of recipients of LD prescriptions issued from 1 October 1990 to 31 March 1991 and cumulative incidence of PD for the period 1954–1963 in Icelandic one-year birth cohorts, and number of notified cases of WC or year of major outbreaks (arrows) from 1860 to 1950 in Iceland from the above-mentioned four-area cross-section, namely Reykjavik and three specific counties.

Figure 1 provides a view of IP+AP and LDU measurements for birth cohorts plus annual WC activity registered over a protracted period (1860–1950). Figure 1a depicts: 1) the period prevalences of LD-prescription recipients from 1 October 1990 to 31 March 1991, and the cumulative incidences of IP+AP during the period 1954–1963 in one-year birth cohorts; 2) the years with DMWCE identified from non-numerically described, massive, WC outbreaks (arrows); and 3) the annual number of notified cases of WC in Iceland from 1890.
onwards. The incidences and prevalences in birth cohorts are unstable and show similar variations: a) an inverted V-skewed shape linked to cohort age; and b) notchy profiles, where peak birth-cohort values are suggested for calendar time-clustered cohorts born consecutively and immediately after 1870, 1880, 1889, 1901, 1908 and 1912 for incidences, and 1896, 1902, 1910, 1912, 1919 and 1926 for prevalences. The indentations overlapping the age-related pattern are more clearly perceived when plotting smoothed incidences and prevalences in the form of 3-year, centred, one-step-ahead moving averages (Figure 1b). In the Figure, most peak values for PD occurrence or prevalence of LD users corresponded to cohorts born consecutively, during or immediately after WCE. For some cohorts, such as those born after 1896 and 1903, peak values for both measurements are seen. To sum up: 1) the notchy pattern described in periodically time-clustered Icelandic cohorts for LD use in 1990–1991, and prevalences of PD in 1963 shown elsewhere, with peaks in cohorts born immediately after MWCE years, is observed from IP+AP cumulative incidences during an earlier period; and 2) followed-up cohorts, surveyed at time points approximately 30 years apart, present parallel, overlapping peak frequencies for IP+AP and LD users.

The information on 59 cohorts born and WCE registered during the period 1869–1927, taken as a preliminary selection for analytical purposes, is presented in Table 3. More specifically, the Table lists detailed annual information for the period 1869–1927 on: 1) numerators and denominators of cumulative incidences of IP+AP in birth cohorts; 2) identified DMWCE years; 3) cohort age at 1 January 1954 and; 4) the estimated age at first DMWCE for each birth cohort. Some epidemics, such as those with onset in 1896 and 1902—years of birth for cohorts with a considerable contribution to incidence counts—started in the spring. Since 13 out of the above-mentioned 59 cohorts were born in years with DMWCE, the remaining 46 cohorts were selected for analysis. Because WC epidemics quite often spread during years immediately preceding or following those with DMWCE, pertussis infective activity in Iceland was observed to a remarkable extent during years free of DMWCE, such as 1870, 1882, 1902 and 1910. This phenomenon particularly affected those cohorts born one and five-or-more years before DMWCE.

The results of the model and goodness-of-fit tests are shown in Table 4. When compared with cohorts born in years immediately preceding those with DMWCE, and effect of cohort age was controlled for, the risk of IP+AP increased moderately with age at first DMWCE. In general, the 95% CI of RR for categories of age at DMWCE were wide. The increase was highest for cohorts born 4 years before a DMWCE (RR 1.64; 95% CI: 1.00–2.68). When a linear trend of RR, as determined by age in years at first DMWCE, was calculated,
| Calendar and birth year | WC data | Estimated pop. at 1 Jan 1954 | No. of cases of IP or AP | Age at 1 January 1954 | Estimated age at first major outbreak |
|-------------------------|---------|-----------------------------|------------------------|----------------------|--------------------------------------|
|                         | Notified no. of cases | Reported onset and spread of outbreak | No of individuals | | |
| 1869                    | –       | –                           | 215                    | 0                    | 84                                   | 2                                   |
| 1870                    | –       | –                           | 268.5                  | 0                    | 83                                   | 1                                   |
| 1871                    | –       | Started in Oct               | 282                    | 1                    | 82                                   | 0\*                                 |
| 1872                    | –       | In northern zone, Jan-July   | 299                    | 1                    | 81                                   | 8                                   |
| 1873                    | –       | –                           | 337                    | 0                    | 80                                   | 7                                   |
| 1874                    | –       | –                           | 332                    | 2                    | 79                                   | 6                                   |
| 1875                    | –       | –                           | 373                    | 2                    | 78                                   | 5                                   |
| 1876                    | –       | –                           | 439                    | 2                    | 77                                   | 4                                   |
| 1877                    | –       | –                           | 567.5                  | 3                    | 76                                   | 3                                   |
| 1878                    | –       | –                           | 602.5                  | 7                    | 75                                   | 2                                   |
| 1879                    | –       | –                           | 629.5                  | 3                    | 74                                   | 1                                   |
| 1880                    | –       | Started                     | 611.5                  | 0                    | 73                                   | 0\*                                 |
| 1881                    | –       | Continued                   | 672                    | 3                    | 72                                   | 0\*                                 |
| 1882                    | –       | Continued                   | 722                    | 12                   | 71                                   | 8                                   |
| 1883                    | –       | –                           | 702                    | 3                    | 70                                   | 7                                   |
| 1884                    | –       | –                           | 842.5                  | 7                    | 69                                   | 6                                   |
| 1885                    | –       | –                           | 832.5                  | 12                   | 68                                   | 5                                   |
| 1886                    | –       | –                           | 909.5                  | 16                   | 67                                   | 4                                   |
| 1887                    | –       | –                           | 996.5                  | 9                    | 66                                   | 3                                   |
| 1888                    | –       | –                           | 1060                   | 5                    | 65                                   | 2                                   |
| 1889                    | –       | –                           | 1059                   | 9                    | 64                                   | 1                                   |
| 1890                    | 797     | Latter months               | 1051.5                 | 10                   | 63                                   | 0\*                                 |
| 1891                    | 672     | First half                  | 1098                   | 19                   | 62                                   | 0\*                                 |
| 1892                    | 59      | –                           | 1127                   | 13                   | 61                                   | 4                                   |
| 1893                    | 0       | –                           | 1148                   | 15                   | 60                                   | 3                                   |
| 1894                    | 0       | –                           | 1258                   | 12                   | 59                                   | 2                                   |
| 1895                    | 0       | –                           | 1308                   | 13                   | 58                                   | 1                                   |
| 1896                    | 407     | May–Dec                     | 1365                   | 14                   | 57                                   | 0\*                                 |
| 1897                    | 1256    | All months                  | 1420                   | 6                    | 56                                   | 0\*                                 |
| 1898                    | 33      | Jan–June                    | 1420                   | 13                   | 55                                   | 5                                   |
| 1899                    | 0       | –                           | 1501                   | 4                    | 54                                   | 4                                   |
| 1900                    | 12      | Oct–Nov                     | 1451.5                 | 7                    | 53                                   | 3                                   |
| 1901                    | 0       | –                           | 1467                   | 2                    | 52                                   | 2                                   |
| 1902                    | 238     | May–Dec                     | 1511                   | 5                    | 51                                   | 1                                   |
| 1903                    | 1660    | All months                  | 1544.5                 | 11                   | 50                                   | 0\*                                 |
| 1904                    | 5       | Jan–Feb                     | 1562                   | 5                    | 49                                   | 4                                   |
| 1905                    | 3       | –                           | 1618.5                 | 2                    | 48                                   | 3                                   |
| 1906                    | 0       | –                           | 1651                   | 2                    | 47                                   | 2                                   |
| 1907                    | 0       | –                           | 1744.5                 | 1                    | 46                                   | 1                                   |
| 1908                    | 1086    | –                           | 1699.5                 | 1                    | 45                                   | 0\*                                 |
| 1909                    | 1180    | –                           | 1787.5                 | 2                    | 44                                   | 0\*                                 |
| 1910                    | 239     | –                           | 1762                   | 3                    | 43                                   | 4                                   |
| 1911                    | 1       | –                           | 1793.5                 | 0                    | 42                                   | 3                                   |
| 1912                    | 0       | –                           | 1812                   | 2                    | 41                                   | 2                                   |
| 1913                    | 0       | –                           | 1897.5                 | 1                    | 40                                   | 1                                   |
| 1914                    | 1829    | –                           | 2006                   | 3                    | 39                                   | 0\*                                 |
| 1915                    | 329     | –                           | 1981                   | 2                    | 38                                   | 5                                   |
| 1916                    | 0       | –                           | 2006                   | 0                    | 37                                   | 4                                   |
| 1917                    | 3       | –                           | 2032                   | 0                    | 36                                   | 3                                   |

Continued
### Table 3

| Calendar and birth year | Notified no. of cases | Reported onset and spread of outbreak | Estimated pop. at 1 Jan 1954 | No. of cases of IP or AP | Age at 1 January 1954 | Estimated age at first major outbreak |
|-------------------------|-----------------------|--------------------------------------|-----------------------------|-------------------------|----------------------|-------------------------------------|
| 1918                    | 0                     | -                                    | 2042.5                      | 2                       | 35                   | 2                                   |
| 1919                    | 288                   | -                                    | 2096.5                      | 0                       | 34                   | 1                                   |
| 1920                    | 2767                  | -                                    | 2149.5                      | 1                       | 33                   | 0*                                 |
| 1921                    | 137                   | -                                    | 2194                        | 0                       | 32                   | 6                                   |
| 1922                    | 0                     | -                                    | 2137                        | 0                       | 31                   | 5                                   |
| 1923                    | 0                     | -                                    | 2430.5                      | 0                       | 30                   | 4                                   |
| 1924                    | 0                     | -                                    | 2369.5                      | 0                       | 29                   | 3                                   |
| 1925                    | 4                     | -                                    | 2318                        | 1                       | 28                   | 2                                   |
| 1926                    | 91                    | -                                    | 2280                        | 0                       | 27                   | 1                                   |
| 1927                    | 6645                  | -                                    | 2295                        | 0                       | 26                   | 0*                                 |

* Year with DMWCE.

### Table 4

| Independent variables | Relative risk |
|-----------------------|---------------|
|                       | Point estimate | 95% CI | Point estimate | 95% CI |
| Year of birth in relation to first DMWCE | | |
| Year preceding DMWCE | 1             | -     | 1.08           | 0.99-1.18 |
| 2 years preceding DMWCE | 1.12     | 0.67-1.87 |
| 3 years preceding DMWCE | 1.30     | 0.78-2.16 |
| 4 years preceding DMWCE | 1.64     | 1.00-2.68 |
| 5–8 years preceding DMWCE | 1.31     | 0.81-2.10 |
| 8 one-year ordinal levels | 1        | 3.62-10.72 |
| Cohort age at 1 Jan 1954 | | |
| 0–44                  | 1             | -     | 1.04           | 0.99-1.18 |
| 45–49                 | 4.37          | 1.85-10.31 | 4.54        | 1.93-10.72 |
| 50–54                 | 8.65          | 4.07-18.38 | 9.04       | 4.28-19.18 |
| 55–59                 | 29.95         | 15.03-59.68 | 27.67      | 14.14-54.16 |
| 60–64                 | 30.33         | 15.28-60.20 | 32.48      | 16.55-63.73 |
| 65–69                 | 28.66         | 14.84-55.34 | 28.07      | 14.55-54.17 |
| 70–74                 | 26.06         | 11.91-57.03 | 19.99      | 9.06-44.14 |
| 75–79                 | 18.89         | 8.74-40.82  | 18.67       | 8.65-40.30 |
| 80+                   | 2.30          | 0.34-21.01  | 2.14        | 0.27-16.77 |
| Goodness-of-fit tests: | | |
| Base model with intercept term | 333.65(45) | Likelihood ratio (d.f.) | P-value |
| Model with cohort age | 53.52(37) | <0.001 |
| Model with two dummy variables | 48.98(33) | 0.338 |
| Versus base model with intercept term | 284.67(12) | 0.001 |
| Versus model with cohort age | 4.54(4) | 0.001 |
| Model with two variables for linear trend | 50.19(36) | 0.001 |
| Versus base model with intercept term | 283.47(9) | 0.001 |
| Versus model with cohort age | 3.34(1) | 0.068 |
with such variable being coded as an ordinal value from 1 to 8 years, and the effect of cohort age was controlled for, the risk of PD increased by 8.4% per year of age at DMWCE (95% CI : -0.1–18.3). The goodness-of-fit of the two models improved when age at first DMWCE was added.

**DISCUSSION**

The results of this study suggest a relationship in Iceland between age at events closely linked to WC infection and incidence of parkinsonism, and that this factor underlies recently reported differences in prevalences of LD users among birth cohorts. The pattern revealed by PD incidence and prevalence of LD users could hardly be determined by events underlying the above-mentioned disparity between reported and reanalysed data, or by random or systematic error present in the different studies and specific for certain birth cohorts, such as might result from 1) under- and misdiagnosis of PD, most likely present in the raw material from the 1954–1963 survey, 2) use of diagnostic criteria, 3) choice of drug for PD treatment or 4) mistakes in our calculations. However, the ‘age-at-exposure’ categories consist of calendar time-aggregated measurements and the underlying facts at the individual level are unknown. Therefore, although we have failed to identify any health-related phenomena matching the pattern of WCE in Iceland, confounding by simultaneous phenomena causally related to parkinsonism cannot be ruled out.

The independent variables for cohorts represent impure operative categories of age at WC infection and age at onset of clinical manifestations. The effect of such a misclassification appears to be particularly relevant for age at first DMWCE in cohorts born five or more years prior to DMWCE. This would give rise to underestimation of the magnitude of an underlying association for this exposure category and of the linear trend. The expected magnitude of the association in studies based on individual age at infection would be higher too because, whereas the ecological measurements here computed correspond to 8 1-year categories of age at WCE, actual age at exposure for individuals ranged from 0 to at least 14 years in Iceland, despite neonates and very young infants being highly susceptible to the disease.

The distribution of 138 incident cases of parkinsonism in Rochester, Minnesota for the period 1967–1979 was: 85.5% IP, 1.4% AP, 7.2% drug-induced and 5.8% parkinsonism-plus syndromes (PPS). Some PPS cases might have been classified as IP by K R A Gudmundsson or, despite poor response to LD recorded for some PPS variants, have been on LD by 1990–1991, hence accounting for the notchy pattern in both data sets. However, since the variability in age at PI is determined by endemcity, closely related to demography, (population size and concentration), geographical isolation, and duration of the interpandemic intervals (particularly long in Iceland, and population density was proposed 8 years ago as a major common determinant of LD use and PD, this pattern could be attributable to a phenomenon in which PD is implicated. An inverse relationship between population concentration/density and PD was suggested from a recent reanalysis of PD incidence in Europe (where most such surveys have been conducted), because incidence at ages below 70 years was lowest in the Netherlands, and significantly higher in southwest Finland and, above all, in Iceland. With regard to risk factors for PD, while multiple interpretations have been given to the well-established, modest, negative association with smoking, this and other (sometimes inconsistent) associations such as those with residence in rural environment (particularly in the first decades of life), well-water drinking, neoplasm incidence and mortality, plus a trend with age at measles infection, could all be interpreted as confounding by effects of population density, such as age at PI, since they may merely constitute population-density-associated factors linked to modernization. In addition, results of a similar pilot analysis conducted in December 1992 in the Azores (San Miguel Island) suggest that, a hypothesis positing a causal link between PD aetiology and age at PI would also apply outside Iceland. This interpretation of our results would imply some reasonable assumptions, namely that: 1) there is an absence of a protective effect or early-in-life PI, as suggested by the historically high lethality of WC in infants; 2) the high PD incidences present in Iceland are not due to high inbreeding rates, relevant for diseases (dissimilar to PD) which display a recessive pattern; and 3) PD behaves in populations and calendar time following a unitarian pattern.

It has been argued that the geographically widespread PD distribution calls for a non-toxic aetiology and alternative hypotheses. However, information available at the present time allows for an eclectic view and synthesis of different proposals. Age-at-infection determinants of effect are a common characteristic of laboratory infections by neurotropic agents. Infective and toxic agents can be linked in the same causal process, and an L-dopa responsive disorder has been described following Nocardia infection in mice. Infectious agents whose reservoir is the human host might underlie ubiquitous environmental neurotoxicity. We are not aware of any reports suggesting a possible
relationship between exposure to WC agents and neurodegenerative diseases. An odds ratio of 0.88 (95% CI: 0.60–1.3) for unreported PI at college entrance was found by Sasco and Paffenbarger, but this proportion—42% among cases—was disproportionately high, suggesting recall deficit; age at infection was not studied.

While there is extensive biological evidence of acute neuronal pertussis toxicity, we are not aware of reported extrapyramidal symptoms during PI in humans. PI-related diseases can be generated from an array of *B. pertussis* virulence factors, pertussis toxin (PT), heat-labile toxin, adenylate cyclase toxin and tracheal cytotoxin. PT, perhaps the most studied of these, is an ADP-ribosyltransferase capable of inactivating many eukaryotic G proteins involved in cellular metabolism, and determines virulence and immunogenicity. Over the last 7 years, evidence of the short-term effects of PT in striatal dopaminergic function has been accumulated from approximately 100 laboratory reports (because PT has been routinely used to study said neuronal function but the long-term effects are not known. PT interacts in vivo with the Ni regulatory protein coupled with the striatal D2-dopamine receptor, involved in the receptor-adenyl cyclase system. Age-related changes in the dopamine receptor-GPT-binding protein-adenylate cyclase system have been identified using PT, and differences were shown between adult and infant rats in which the striatal function of said system is low. Latencies of considerable duration for exposure-related effects are not uncommon in developmental neurotoxicology. PT injected intracerebrally into mice induced a durable motor neurological abnormality after a log period of one week. However, this could be due to a non-specific effect.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) selective nigral neuronal toxicity in laboratory animals is highest for the older rats and macaca and, in the mouse, can be inhibited pretreatment by specific enzymatic action or with a nerve growth factor, BDNF. Age-related changes in melanin content or metabolic impairment of SN neurons BDNF growth factor availability, or individual variations in cytochrome P450 expression might constitute individual conditions determining a neuronal substrate sensitization for PT, potentially resulting, in the long run, in a dying-back SN degenerative process. If, as seen in the animal models of MPTP toxic Parkinsonism, there is a more extensive aspect (not age-at-exposure-related) of the SN toxic lesions, the foregoing might indicate that the relevance of PI as a factor, potentially implicated in a subtle, preventable lesion of the dopaminergic system, could be high in terms of PD aetiological fraction.

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APPENDIX
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