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Prenatal and Early Life Factors and Risk of Parkinson's Disease

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Abstract

Few studies have investigated the relation between early life factors and risk of Parkinson's disease (PD), although a potential role of exposures during pregnancy and childhood has been hypothesized. The study population comprised participants in two prospective cohorts: the Nurses' Health Study (121,701 female nurses followed from 1976–2002) and the Health Professionals Follow-up Study (51,529 male health professionals followed from 1986–2002). PD risk was examined in relation to season of birth, birthweight, parental age at birth, preterm birth, multiple birth, ever having been breast-fed, and handedness. We identified 659 incident PD cases. No significant relation with PD was observed for birthweight, paternal age, preterm birth, multiple birth, and having been breast-fed. A modest non-significant association was suggested for season of birth (30 percent higher risk of PD associated with spring vs. winter birth), and for older maternal age at birth (75 percent increased risk among those with mothers age 30 and over vs. less

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than 20). Left-handedness was associated with a 62 percent increased risk of PD in women, but not in men. Further investigation of the relation between prenatal, perinatal, or neonatal factors and PD in other study populations is suggested.

Keywords

Birth weight; Epidemiology; Functional laterality; Maternal exposure; Parkinson disease; Prenatal exposure delayed effects; Risk factors

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease of later life, characterized by tremor, rigidity, bradykinesia, and postural instability that result from the progressive loss of dopamine-producing neurons in the substantia nigra. The primary cause of PD is still unknown. Familial forms of PD have been described, but the majority of cases appear to be sporadic and largely determined by environmental factors (1, 2).

In animal models of PD, early life exposure to neurotoxins is associated with increased disease frequency in adult life (3, 4). Toxic exposures in the pre-/perinatal periods may decrease the number of dopaminergic neurons in critical brain areas or increase the vulnerability of surviving neurons. These lesions may become manifest only decades later when compounded by the neuronal attrition that comes with normal aging (5), or early life insults may potentiate the effects of later life environmental factors inducing dopaminergic cell loss, consistent with a two-hit model of pathogenesis (4). Whether such mechanisms are relevant to PD in humans remains unknown.

Therefore, we examined whether early life factors relate to the risk of PD among participants in two large ongoing prospective cohorts, the Nurses' Health Study (NHS), comprising over 100,000 female nurses (6), and the Health Professional Follow-up Study (HPFS), comprising over 50,000 male health professionals (7). Available information on early life factors included season of birth, birthweight, and handedness and, in the NHS only, having been breastfed, preterm birth, multiple birth, and maternal and paternal age at birth.

METHODS

Study Population

The NHS cohort began in 1976 with 121,701 female nurses age 30–55 identified by the nursing boards of 11 US states. Following the initial questionnaire in 1976, these nurses receive a follow-up questionnaire every two years to collect information on demographic factors, lifestyle factors and diet, in addition to newly diagnosed disease outcomes. The HPFS includes 51,529 male health professionals age 40–75 at baseline. Like the NHS, a baseline questionnaire in 1986 was followed by questionnaires sent every two years which collect information on disease diagnosis and health-related behaviors. A participation rate of over 90 percent has been achieved over time in both cohorts.

Outcome Assessment

Ascertainment of PD in these cohorts has been described in detail previously (8). Briefly, cases were initially identified by self-report on the NHS and HPFS biennial questionnaires, and then confirmed by obtaining a diagnostic report from the treating neurologists or reviewing a copy of the medical records. In the rare instances when a neurologist was not

involved in diagnosis or failed to respond, the individual's internist was contacted for confirmation of diagnosis. A case was confirmed if the diagnosis was considered definite or probable by the treating neurologist/internist or by medical record review if the medical record included either a final diagnosis of PD made by a neurologistor clinical evidence of at least two of thecardinal signs (rest tremor, rigidity, and bradykinesia) in the absence of an alternative diagnosis for the Parkinsonian symptoms. Eighty-five percent of the diagnoses were confirmed by the treating neurologists.

Exposure assessment

Information regarding birthweight, season of birth and hand preference was assessed in both the NHS and HPFS cohorts. Additional information regarding maternal and paternal age at birth, preterm birth, multiple birth, and breastfeeding exposure during infancy was only available in the NHS.

In 1992 the NHS participants were asked to report their birthweight (<5, 5–5.5, 5.5–7, 7–8.5, 8.5–10, 10+ lbs), whether they were born two or more weeks preterm (vs. fullterm), whether they were part of a multiple birth, and whether they were breastfed in infancy. Maternal and paternal age at birth were calculated from NHS baseline information on maternal and paternal year of birth. Season of birth was assessed using baseline data on month of birth for both the NHS as well as the HPFS (winter: December-February, spring: March-May, summer: June-August, fall: September-November). Birthweight was also assessed categorically (<5.5, 5.5–6.9, 7–8.4, 8.5–9.9, 10+ lbs) in the HPFS in 1994.

In 1992 the NHS and HPFS participants were asked the following question: "Which of the following describes you? (mark all that apply)", with the following possible responses: naturally right-handed, naturally left-handed, forced to change, ambidextrous. Anyone who reported being ambidextrous or both naturally left- and right-handed was coded as ambidextrous. Of the remaining, those who reported being left-handed, including those who *also* reported being forced to change, were coded as left-handed. Likewise, anyone who reported being naturally right-handed, excluding those who were ambidextrous, were coded as right-handed. And those who reported being forced to change handedness but did not report being either naturally left- or right-handed or ambidextrous were coded as "forced to change with unknown innate handedness". The risk of PD among individuals who were naturally left-handed was compared to that among individuals who were naturally right-handed, excluding individuals who were forced to change handedness with unreported innate hand preference or were ambidextrous. In the NHS 6.0 percent were naturally left-handed, and in the HPFS 6.5 percent were naturally left-handed. The percentage of left-handed individuals in this cohort is consistent with similar US study populations (9, 10).

In 538 randomly selected members of the NHS-II cohort, a younger cohort of female US nurses, self-reports of birthweight and breast feeding were both shown to have a high degree of validity when compared with their mothers' reports (Spearman correlation r=0.75 for birthweight, r=0.74 for duration of breast feeding) (11). For the report of ever having been breast fed, the sensitivity was 82 percent and the specificity was 86 percent.

Covariates

The baseline questionnaires in both cohorts included a detailed assessment of lifetime smoking history and smoking behavior was updated in each subsequent biennial questionnaire. Cumulative exposure to cigarette smoking, defined in pack-years, was calculated by multiplying the number of packs smoked per day (1 pack=20 cigarettes) by the number of years over which that amount was smoked (12). Caffeine consumption was

calculated using information on average consumption of food and beverages from a semiquantitative food frequency questionnaire (SFFQ), as previously described (13).

Use of post-menopausal hormones was assessed biennially starting at baseline in NHS (14). Lastly, family history of PD in parents and siblings was assessed in the NHS in 1994.

Data analysis

Each cohort member contributed person-time of follow-up from the return date of the baseline questionnaire to the date of first PD symptoms, death, or end of follow-up (2002), whichever came first. Univariate Cox proportional hazards models were used to estimate rate ratios (RR) and 95 percent confidence intervals (CI) for each prenatal factor stratified by age in months and calendar year. All p-values are two sided.

Multivariate adjusted Cox models were used to estimate the rate ratios adjusting for other significant risk factors, including age (months), calendar year, cigarette smoking (never, <10 packs/year, 10–24 packs/year, 25+ packs/year), and caffeine consumption (cumulative average quintile). Analyses in women were further adjusted for family history of PD (yes/no) post-menopausal estrogen exposure (PMH: ever/never) and the interaction between PMH and caffeine consumption (8, 12, 14). The missing indicator method, which involves the inclusion of a dichotomous variable in the model that indicates missingness (yes vs. no) of the covariate, was used when controlling for covariates with missing data (15).

Parental age at birth and birthweight were assessed categorically and linear tests of trend were conducted. For the trend tests birthweight was assessed as an ordinal categorical variable and parental age at birth was assessed continuously. We also examined the possibly non-linear relation between birthweight and parental age at birth and the RR of PD non-parametrically with stepwise restricted cubic splines (16, 17), adjusting for covariates. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

For the factors examined in both the NHS and the HPFS, a summary effect estimate was calculated using a random effects model after pooling the results from both cohorts using inverse-variance weighting (18). Tests of heterogeneity of the main exposures by cohort were performed by using the Q statistic. Statistical analyses were performed by using SAS software version 9 (SAS institute, Cary, NC).

As mentioned, birthweight, preterm birth, and having been breastfed were assessed in the NHS in 1992 and birthweight was assessed in the HPFS in 1994. These analyses were partly retrospective as cases accrued both prior to and following exposure data collection. Due to the possibility of recall bias with these factors, sensitivity analyses were conducted that were restricted to person-time and case accrual following exposure assessment through 2002. These analyses included 65 percent of the NHS cases (N=212) and 53 percent of the HPFS cases (N=174).

This research was approved by the Institutional Review Boards at Brigham and Women's Hospital and the Harvard School of Public Health in Boston, Massachusetts.

RESULTS

Table 1 shows the association between prenatal/neonatal factors and smoking and caffeine consumption, two important risk factors for PD. Table 1a indicates the age-adjusted mean pack-years of smoking at baseline (1976) and daily caffeine consumption (mg) in 1980 across categories of the prenatal/neonatal variables in the NHS. Likewise, table 1b indicates

the age-adjusted mean pack-years of smoking and daily caffeine consumption (mg) at baseline across categories of the prenatal/neonatal variables in the HPFS. Individuals with birthweight over 10 pounds appear to have smoked more and consumed more caffeine, and those with paternal age at birth less than 20 years also appear to have smoked more.

During the follow-up until 2002, we documented 659 incident cases of PD, 328 in women and 331 in men.

Table 2 shows the summary effect estimates for the age-adjusted and multivariate adjusted analyses of the relationship between PD and those early life variables collected in both cohorts, including birthweight, season of birth, and handedness. No significant heterogeneity was observed between the two cohorts for any of the factors examined (P>0.05). None of these factors were significantly associated with PD risk. Although in the pooled analysis there was a marginal increased risk among those born in the spring (multivariate-adjusted RR, compared to winter birth =1.30, 95 percent CI: 0.97, 1.74, P=0.08), in the NHS alone, an 82 percent higher risk of PD (multivariate-adjusted 95 percent CI: 1.17, 2.81) was observed for women born during the summer as compared to those born during the winter.

For birthweight, there was neither a linear nor non-linear trend, and there was no significant difference in risk of PD between those in the highest and lowest categories of birthweight. Additionally, a sensitivity analysis restricted to person-time and cases that accrued after exposure assessment in 1992 (NHS) and 1994 (HPFS) showed no association between birthweight and risk of PD (multivariate-adjusted RR and 95 percent CI vs. 5.5–8.4 lbs: 0.94 (0.58 1.52) for <5.5 lbs; 0.80 (0.52, 1.22) for 8.5–9.9 lbs; 1.37 (0.77, 2.46) for 10+ lbs).

Although there was no observed relation between natural hand preference and risk of PD in the pooled analysis of the HPFS and NHS (left-handed vs. right-handed RR=1.31, 95% percent CI: 0.84–2.06), in the multivariate-adjusted analysis restricted to the NHS a significant 62 percent increased risk of PD was observed among those who were left-handed as compared to those who were right-handed (95 percent CI: 1.06, 2.50). A secondary analysis examining the potential association between handedness and age of onset of PD also showed no association (data not shown).

Results for early life exposures available only in women are shown in table 3. In the NHS no significant association was observed between PD and paternal age at birth, preterm birth, multiple birth, or exposure to breastfeeding during infancy. A sensitivity analysis restricted to person-time and cases that accrued after exposure assessment in 1992 also showed no association for preterm birth (multivariate-adjusted RR=0.92, 95 percent CI: 0.43, 1.95) and not having been breastfed during infancy (multivariate-adjusted RR=0.82, 95 percent CI: 0.56, 1.20). Although there was no significant difference observed between the extreme categories of paternal age at birth (data not shown), when those with mothers age 30 and older at birth were combined and compared to those with mothers less than 20 years old the RR was 1.75 (95 percent CI: 0.94, 3.25, P=0.08). However, there was no significant linear nor nonlinear trend for maternal age at birth.

DISCUSSION

In summary, in this large cohort study with 659 PD cases we found no relation between the risk of PD and paternal age at birth, birthweight, preterm birth, multiple birth, and exposure to breast-feeding during infancy. While an increased risk of PD was observed among the female NHS participants born during the summer months, in the pooled analysis of both males and females a marginal increased risk was only observed in relation to birth during the spring. Although there was no relation between hand preference and risk of PD among the male health professionals, an increased risk of PD was found among the left-handed NHS

participants. Lastly, the data suggested a possible increased risk of PD associated with older maternal age at birth, particularly age 30 and older, although a dose-response relationship was not evident.

The primary strengths of this study are the use of large cohorts (total N=173,230) with high follow-up rates and comprehensive data on other established risk factors for PD. Despite these important strengths, limitations to the current study are noted. Most importantly, there is the potential for inaccurate report of prenatal and perinatal factors by the nurses, resulting in misclassification of birthweight, prematurity, and breastfeeding. Any misclassification is most likely nondifferential and would thus bias relative risk estimates towards the null. However, because exposure information was collected both before and after the onset of PD we cannot exclude the potential for differential misclassification. Also, because of the relative rarity of some exposures, such as low birthweight and preterm birth, the power of our study was modest, and was further reduced because a substantial proportion of participants were unable to report their perinatal exposures. For these reasons, the negative findings should be interpreted cautiously.

An increased risk of PD associated with birth during the summer months (June-August) was observed in the female NHS cohort, but not among men in the HPFS cohort, and in the pooled analysis a modest association with spring birth (March-May) was observed. Results of previous studies on season of birth and PD risk have been inconsistent. A small study in Japan found an increased risk associated with births in winter and spring (19). A larger study with 517 cases in England and Whales also showed an excess of births between March and June, peaking in May (20). However, a third study conducted in Aberdeen, UK showed no season of birth trend associated with Parkinsonism (21). These studies were not stratified by sex. Season of birth has been used as a proxy with which to examine the potential role of intrauterine viral infections. However, there are many factors and environmental exposures (e.g. vitamins) that show seasonal variation and might account for this relationship. Further evidence for the role of intrauterine influenza exposure in the etiology of PD comes from one study that found an increased risk of PD among individuals born during the years surrounding the influenza pandemics or in years of high influenza mortality (20). It is also interesting to note that one study suggested that adult dopamine turnover peaks in association with birth during November–December, with a nadir associated with birth in May–June (22).

The data suggested a possible, marginally significant, association between PD risk and older maternal age at birth, particularly over the age of 30 as compared to under the age of 20. The mechanism underlying this potential relationship is unclear, but could be due to the increased risk of chromosomal abnormalities in older ova. While advanced maternal age has been shown to be associated with an increased risk of obstetrical complications (23, 24), it is unknown which, if any, of these complications may affect the risk of PD. A significant positive association between maternal age at birth and PD has been suggested in other smaller studies, but results have been inconsistent. Zorzon and colleagues compared 136 PD cases with 272 age- and sex-matched controls and found that maternal age at birth was significantly higher among those with PD (mean=27.4 years) than among the controls (mean=25.1 years) (25). A study in Spain also found a negative correlation between age at onset of PD and maternal age at birth but not paternal age at birth (adjusted for age and sex) (26). Of note, we also examined the potential association between maternal age at birth (assessed continuously) and age of onset of PD and observed no association (data not shown). A third study comparing 177 PD cases and 177 sex-matched controls reported no difference in maternal age at birth between cases and controls (27). One case-control study with 172 cases and 343 matched controls also failed to find an association between PD risk and birthweight (28).

The potential relationship between handedness and the risk of PD has not been previously investigated. Handedness has been studied in relation to several other chronic diseases including breast cancer, diabetes, and autoimmune diseases as a marker for *in utero* exposure to steroid hormones (29, 30). However, the empirical evidence for a relation between handedness and prenatal steroid hormone exposure has been limited and inconclusive, and the causes of hand preference remain unknown. While some studies have indicated a positive relationship between left-handed preference and surrogate markers for prenatal steroid hormone exposure (e.g. low 2D:4D digit ratio (31, 32), diethylstilbestrol exposure (33), congenital adrenal hyperplasia (34)), other studies have not (35–38). Although effect modification by sex was not expected, differential effects of testosterone on lateralization in males and females have been reported (35).

While the current study provides modest support for a potential relation between left hand preference and risk of PD particularly among females, further examination is recommended in other study populations. More importantly, direct examination of the relation between prenatal hormone exposure and risk of PD is needed in both males and females. Research on the role of hormone exposure during adulthood has been motivated by the increased incidence of PD among males (39) as well as evidence that estrogen exposure may be neuroprotective and may influence dopaminergic functioning (40). Earlier menopause and longer cumulative length of pregnancies have been shown to increase risk, while the association with post-menopausal hormone use and oral contraceptives has been inconsistent (41).

A hypothesis also persists that left-handedness may be a marker for in-utero brain injury. Prenatal stress and distress has been observed as a risk factor for non-right-handedness in several studies (42–44), and some evidence suggests that left-handedness may be associated, albeit weakly and inconsistently, with high risk pregnancy, birth stress, low birthweight, prematurity and physical anomalies (45–48).

In this study, handedness was simply classified as left-handed, right-handed, or ambidextrous based on the response to a single question. Although multi-item questionnaires and performance tools have been developed to measure laterality on a range of tasks including writing, brushing teeth, throwing a ball, and using utensils, and can incorporate measurements of both preference and performance (49,50), a level of agreement greater than 95% has been reported between a single global question of hand preference and a 10-item performance battery given to 1223 individuals (51). The positive predictive value among self-reported left-handers was 70% in males and 68% in females (51). Therefore, misclassification is likely to be modest and, if present, would most likely be nondifferential, biasing the estimate towards the null.

In conclusion, in this large cohort study we found suggestive evidence that season of birth and increased maternal age at birth may be associated with risk of developing PD, and that left-handed females may experience a slightly elevated risk. Those factors that were not associated with PD in the current study, such as birthweight and preterm birth, are very crude measures of prenatal health, and are affected by many exposures, only some of which may be etiologically relevant. Therefore, the relationship between obstetrical and perinatal/neonatal complications and PD requires further investigation in other study populations. Most importantly, future studies are recommended to examine more specific indicators of prenatal health (e.g. infectious exposures, preeclampsia, gestational diabetes, nutrition, medication use, maternal occupation during pregnancy, placental abnormalities, labor complications, etc.) in relation to PD risk.

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Table 1a

Association between early life factors and smoking (baseline) and caffeine consumption (1980) in the NHS

Exposure variable	Pack-years of smoking	Daily caffeine consumption (mg)
Birthweight		
<5.5 lbs	23.6	387
5.5–8.4	22.0	387
8.5–9.9 lbs	24.2	398
10+ lbs	25.7	422
Season of birth		
Spring (March–May)	24.7	388
Summer (June–August)	24.1	391
Fall (September–November)	25.4	391
Winter (December–February)	25.0	392
Maternal age at birth		
14–20	24.7	400
20–24	24.6	394
25–29	24.2	386
30–34	23.4	389
35–49	24.9	394
Paternal age at birth		
14–20	27.8	392
20–24	24.7	395
25–29	23.3	389
30–34	23.7	390
35–39	25.3	388
40+	23.1	398
2+ weeks premature		
Yes	23.4	390
No	23.0	390
Multiple birth		
Yes	20.4	383
No	24.7	391
Breastfed		
Yes	22.1	389
No	24.0	391
Handedness		
Left	24.1	397
Right	23.0	390

Table 1b

Association between early life factors and smoking and caffeine consumption at baseline in the HPFS

Exposure variable	Pack-years of smoking	Daily caffeine consumption (mg)
Birthweight		
<5.5 lbs	12.8	229
5.5–8.4	12.6	224
8.5–9.9 lbs	13.9	230
10+ lbs	15.1	249
Season of birth		
Spring (March–May)	13.2	226
Summer (June–August)	13.5	225
Fall (September–November)	13.9	233
Winter (December–February)	14.0	225
Handedness		
Left	12.9	234
Right	13.1	227

Table 2

Prenatal/neonatal factors and PD in the NHS and HPFS cohorts combined

Variable	# Participants*	# Cases*	Age-adjusted Rate Ratio and 95% CI.		Multivariate-adjusted† Rate Ratio and 95% CI	
Birthweight (lbs)						
<5.5 lbs	8932	28	0.88	0.59, 1.30	0.89	0.60, 1.31
5.5–8.4	69678	261	1.0 (ref)		1.0 (ref)	
8.5–9.9	11857	43	0.83	0.60, 1.16	0.84	0.61, 1.17
10+ lbs	3417	22	1.06	0.68, 1.66	1.12	0.72, 1.74
			test for linear trend	P=0.81‡	test for linear trend	P=0.91‡
Season of birth						
Spring	42335	157	1.31	0.98, 1.76	1.30	0.97, 1.74
Summer	44630	175	1.41	0.89, 2.25	1.42	0.88, 2.29
Fall	44299	173	1.26	0.94, 1.70	1.27	0.94, 1.71
Winter	41459	153	1.0 (ref)		1.0 (ref)	
Handedness						
Left	8290	40	1.31	0.86, 1.98	1.31	0.84, 2.06
Right	113070	494	1.0 (ref)		1.0 (ref)	

*For each factor, the number of cases and participants may not add up to the total number in the study due to missing values

†Controlling for age in months, calendar year, PMH use, quintile of caffeine consumption, the interaction between PMH use and caffeine consumption, pack-years of smoking, and family history of PD (for NHS only)

‡No significant non-linear trend observed

Table 3

Prenatal/neonatal factors and the risk of PD in the Nurses' Health Study

Variable	# Participants*	# Cases*	Age-adjusted Rate Ratio and 95% CI		Multivariate-adjusted† Rate Ratio and 95% CI	
Maternal age at birth						
14–19	7038	11	0.59	0.32, 1.10	0.61	0.32, 1.13
20–24	32892	95	1.16	0.90, 1.54	1.18	0.88, 1.57
25–29	36858	91	1.0 (ref)		1.0 (ref)	
30–34	24669	72	1.17	0.89, 1.59	1.16	0.85, 1.58
35–49	17173	50	1.12	0.79, 1.58	1.13	0.80, 1.60
			test for linear trend	P=0.41‡	test for linear trend	P=0.46‡
Paternal age at birth						
14–19	1430	1	0.25	0.04, 1.84	0.25	0.03, 1.81
20–24	16680	44	1.06	0.73, 1.52	1.07	0.74, 1.54
25–29	33973	85	1.0 (ref)		1.0 (ref)	
30–34	29526	78	1.06	0.78, 1.44	1.05	0.77, 1.43
35–39	17903	53	1.18	0.84, 1.66	1.17	0.83, 1.65
40+	14003	43	1.13	0.78, 1.63	1.12	0.78, 1.62
			test for linear trend	P=0.52‡	test for linear trend	P=0.58‡
2+ weeks premature						
Yes	3903	10	0.90	0.48, 1.68	0.89	0.47, 1.67
No	81926	268	1.0 (ref)		1.0 (ref)	
Multiple birth						
Yes	1380	5	1.39	0.57, 3.38	1.24	0.51, 3.00
No	120180	323	1.0 (ref)		1.0 (ref)	
Breastfed						
No	26279	57	0.90	0.67, 1.22	0.92	0.68, 1.25
Yes	47784	181	1.0 (ref)		1.0 (ref)	

*For each factor, the number of cases and participants may not add up to the total number in the study due to missing values

†Controlling for age in months, calendar year, pack years of smoking, family history of PD, PMH use, quintile of caffeine consumption, and the interaction between PMH use and caffeine consumption

‡No significant non-linear trend observed