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Abstract

Background: Parkinson's disease is more common in men than women by a ratio of about 1.5:1 and yet there is no consensus to date as to whether female reproductive factors including hormone use affect Parkinson's disease risk. Our objective was to examine the relationship between Parkinson's disease and female reproductive factors in the largest population-based Parkinson's disease case-control study to date.

Methods: 743 female Parkinson's disease cases diagnosed between 1996 and 2009 were selected from the Danish National Hospital Register, diagnoses confirmed by medical record review, and the cases matched by birth-year to 765 female controls randomly selected from the Danish Civil Registration System. Covariate information was collected in computer-assisted telephone interviews covering an extensive array of topics including reproductive and lifestyle factors.

Results: After adjusting for smoking, caffeine and alcohol use, education, age, and family Parkinson's disease history, we found inverse associations between Parkinson's disease and early menarche (first period at ≤11 years), oral contraceptives, high parity (≥4 children), and bilateral oophorectomy; adjusted odds ratios [aOR] and 95% confidence limits [CL] were respectively 0.68 (0.45-1.03) for early menarche, 0.87 (0.69-1.10) for oral contraceptives, 0.79 (0.59-1.06) for high parity, and 0.65 (0.45-0.94) for bilateral oophorectomy. We found little support for associations between Parkinson's disease and fertile life length, age at menopause, or post-menopausal hormone treatment.

Conclusions: Reproductive factors related to women's early- to mid-reproductive lives appear to be predictive of subsequent Parkinson's disease risk whereas factors occurring later in life seem less important.

Reproductive factors and Parkinson's disease risk in Danish women

N Greene, C Funch Lassen, K Rugbjerg, B Ritz

Introduction: Parkinson's disease (PD) is a neurodegenerative disorder involving multiple systems that affects women less than men in terms of motor and non-motor features.[1,2] Indeed, most epidemiologic studies reported an approximate male to female ratio of 1.5:1,[3] raising the possibility that female hormones such as estrogens may play a protective role and yet, to date, there is no consensus as to whether or how female reproductive factors and hormone use may affect PD risk. [4-14] Some studies suggested that conditions resulting in reduced endogenous estrogen levels increase risk while treatments with estrogen decrease risk of PD in women.[6,7,9] However, there are also reports to the contrary [8,11,12,14] and some studies found no association between post-menopausal hormone use and PD. [5,14] A recent study of the anti-estrogenic Tamoxifen treatment for breast cancer suggested a 5-fold increased rate of PD in participants shortly after receiving treatment, [15] in contrast to an animal study which suggested that Tamoxifen may be neuroprotective. [16] Results for early age at menopause,[5,6,8,9,11] age at menarche,[8,9,11] parity [5,8,9,11,14] and type of menopause [4-6,8,9,11,14] have been inconsistent with regards to their influence on women's PD risk.

In view of these inconsistencies and to gain a better understanding of the role of female reproductive factors and hormone status in association with PD and possibly help identify preventive strategies for vulnerable groups of women, we examined the relationship between women's reproductive histories and hormone use patterns and PD risk in one of the worldwide largest PD case-control studies to date in which only cases with medical record-confirmed idiopathic Parkinson's disease were included.

Materials and Methods

Study subjects: This population-based case-control study (PASIDA: Parkinson's disease in Denmark) was conceived to examine the interplay of occupational, lifestyle, and genetic factors as these relate to the risk of idiopathic PD in Denmark. Figure 1 describes the case selection process in detail. We identified 2,084 women, aged 35 years or older at diagnosis, with a PD diagnosis between 1996 and 2009 in the Danish National Hospital Register[17] and restricted our invitation to participate to those female cases from 10 of Denmark's 15 neurological centers (the catchment area of the remaining 5 centers overlapped with the included 10 centers). Inclusion criteria were having documented PD after medical record review,being alive and well enough to participate at the time of the scheduled interview (2008-2010), speaking English or Danish. We excluded women with research protection and those without contact information as well as those with dementia or a cerebrovascular disease hospital diagnosis within the 3 years preceding the PD diagnosis. Of the 1078 invited to participate, 237 declined In all, 743 medical record-confirmed female PD cases agreed to participate and were interviewed (participation rate of 75% of medical record-confirmed PD cases). Up to 10 potential controls per case were initially selected at random matched on sex and birth year from the Danish Central Population Register,[18] and alive and free of PD at the time we identified the case in the Danish National Hospital Register. We telephoned potential controls in random order until one agreed to participate. This resulted in 1651 potential female controls being invited, and, of these, 765 agreed to be interviewed (46%). When the medical record review for a case revealed

no iPD, the control already chosen and interviewed was then assigned to a different case with the same birth year. Thus, there were 743 female cases and 765 female controls with data for analysis.

The study protocol was approved by the Danish Data Protection Agency and the UCLA Institutional Review Board.

Reproductive history and covariate data: Detailed information on lifetime measures of reproductive factors and lifestyle and behaviors such as caffeine, alcohol consumption, smoking, exercise, as well as education, occupations, and a family history of PD (defined as having a first degree relative with PD) were collected in structured telephone interviews. The degree of urbanization for each case and control was determined based on the population density of the home municipality as recorded in the Central Population Register 3 years before the date of the first hospital PD diagnosis of the respective case (we chose this time because a review of Danish National Hospital Register and Danish National Prescription Register [19] data showed that on average cases received their first medication 3 years before their hospital diagnosis).

Statistical analysis: We performed descriptive, univariate, and trend analyses as well as unconditional logistic regression, adjusting for the matching factor, to examine how reproductive factors relate to PD. Use of conditional logistic regression analyses for matched pairs did not change our results, thus, to utilize all data we collected, we report only results for unconditional models below.

We constructed reproductive covariates to allow for comparison with previous research and to adequately investigate our hypotheses. In addition, guided by the existing PD literature, we constructed a model using directed acyclic graphs [20] to identify potential confounders and adjusted for these.

For the reproductive factors, age at menarche was treated as a continuous ordinal (9-11, 12-13, 14-15, ≥16), and dichotomous (≤11, >11 years) variable; use of high estrogen dose oral contraceptives (the variety available in the 1960's when our female subjects would have been initiating use) was coded as ever vs. never as well as never vs. <5, ≥ 5 years; parity as a continuous, ordinal variable (≤1, 2-3, ≥4) and dichotomous variable (≤3 vs. ≥4); type of menopause was defined as 'surgical' if the subject reported having both ovaries removed, and 'natural' otherwise. Fertile life length was defined as the number of years between menarche and menopause, subtracting time spent pregnant, and categorized as ≤36 years vs. >36 years (for comparison with other studies) and also ordinally (<30 years, 30-39, 40-49, ≥50). Post-menopausal hormone replacement therapy (HRT) was defined as having begun treatment before the first PD symptom date of the respective case (hereafter the index date) and treated as ever vs. never, and never vs. <5, ≥ 5 years. We constructed an estrogen index that is meant to represent relatively high estrogen states during the reproductive lifecourse by summing across 5 binary variables (early menarche [(≤11 years], use of high estrogen dose oral contraceptives, high parity (≥4 children), surgical menopause (both ovaries out), HRT use before onset of motor symptoms.

In addition to the matching factor (birth year as a continuous measure), we adjusted for age at a case's first motor symptom as the index date, smoking (ever vs. never, and never vs. former and current), caffeine consumption (ever vs. never consumed a caffeinated beverage at least once per week for a year or more, number of cups of coffee per day (0-2,3-6,7-10,>10)), a

family history of a first degree relative with PD (yes vs. no), education (6 levels from primary school to higher education), degree of urbanization (living in Copenhagen vs. provincial city, peripheral region or urban area), alcohol consumption (ever vs. never consumed one or more alcoholic drinks per week for at least 6 months).

Although we excluded subjects with a hospital diagnosis of cerebrovascular disease or dementia within the 3 years preceding case PD diagnosis, interviews were conducted several years after diagnosis. Thus, to assess the influence of cognitive impairment on subjects recall of exposures, we performed sensitivity analyses including only subjects with an interviewer rating of "very reliable" or "reliable" (note: our interviewers repeated some simple questions through the course of the interview and were trained in recognizing memory issues).

Results: The mean age at first symptom for cases (and birth year-matched controls) was 62 years (standard deviation = 10), the mean duration of disease from first motor symptom to first hospital diagnosis was 2 years (standard deviation = 3) and to interview it was 6.6 years (standard deviation = 5 years). Demographic and non-reproductive risk factors are distributed among cases and controls as expected from previous studies, i.e. female cases were more often never-users of alcohol, caffeine, and smoking products than controls (Table 1). Additionally a larger proportion of cases had a primary education or lower, and lived in provincial cities.

The adjusted odds ratios (aOR) with 95% confidence intervals (CI) pertaining to reproductive factors are shown in Table 2 in chronological order in terms of women's reproductive lives. An early age at menarche (≤11 years) was inversely related to PD risk (aOR = 0.68, 95% CI 0.44-1.06; p for trend with increasing age at menarche 0.04). Ever-use of high estrogen dose oral contraceptives was inversely associated with PD risk (aOR = 0.76, 95% CI 0.59-0.98). High parity (having had 4 or more children) was consistent with a 21% reduction in the aOR (95% CI 0.56-1.11). Surgical menopause (defined as having had a bilateral oophorectomy) was inversely associated with PD risk (aOR = 0.69, 95% CI 0.47-1.01). Our data offer little support for an association between PD and fertile life length (trend p-value = 0.89, aOR for a fertile life length of ≤36 years=0.98; 95% CI 0.77-1.26) or age at menopause (aOR for last period at ≥45 years] 0.96 (95%CI 0.70-1.31) and trend p-value = 0.59). With HRT use defined as having begun use before the first PD symptom date, the aOR for ever-use was 0.94 (95% CI 0.71-1.24). The median duration of HRT use before the index date was 15 years in both cases and controls. Relying on our estrogen index score, there was a monotonic decrease in the relative odds of PD with increasing estrogen index score. (trend p-value was <0.001) (Figure 2).

Restricting our analyses to only those subjects rated by interviewers as "very reliable" or "reliable", none of the point estimates changed by more than 0.1 in either direction (data not shown).

Discussion: Examining female reproductive factors and Parkinson's disease in a large population-based case-control study of 743 female cases and 765 female population controls matched on birth year, we found that while none of the reproductive factors alone was strongly associated with a reduction in PD risk, our data were consistent with the idea that higher circulating estrogen levels earlier in reproductive life may be associated with reduced odds of developing PD. For example, along with an early menarche, use of oral contraceptives and high parity were inversely associated, to varying degrees, with the relative odds of PD. The estrogen score that counted the number of reproductive factors suggesting a relatively high estrogen state was monotonically and inversely related to PD odds. We found little support for

associations between PD and factors related to longer duration of reproductive life span such as age at menopause and overall fertile life length, and the inverse association of PD risk with ever use of HRT before the first symptom date was at best weak.

Our results are partially consistent with those from previous, mostly smaller, studies each of which enrolled less than 250 cases. Tables 3 and 4 summarize results from selected studies of female reproductive factors and PD. In the US Nurses' Health Study cohort study (244 cases)[11] and the California Kaiser Permanente population-based case-control study (178 cases), [8] no associations with age at menarche were found.[7] A small Italian case-control study (131 cases) [9] reported an inverse association between PD and older age at menarche, contrary to our findings of an inverse association with an *earlier* age at menarche. Data from the Nurses Health Study were consistent with a positive relationship between PD and more than 5 years of oral contraceptive use, but this association weakened somewhat in a second study that included longer follow-up of the same women whereas our results suggest a weakly inverse association with oral contraceptive use. No clear pattern emerged from previous work regarding the association between PD and increasing parity although an Italian case-control study [9] suggested higher relative odds of PD with a larger number of months spent pregnant (included those pregnancies resulting in live births, miscarriages, and abortions). Our data offers support for an inverse association between high parity (≥4 children) with PD.

Interestingly, our data were consistent with a moderate inverse association between PD and surgical menopause (aOR = 0.69, 95%CI 0.47-1.01) and in the same direction as previously seen in the Italian study [9] (aOR = 0.30, 95%CI 0.13-0.77). In the latter study, surgical menopause was defined as having had any procedure that stopped menses (i.e. hysterectomy and/or bilateral oophorectomy) whereas in our study we did not have information regarding concomitant hysterectomy. A recent study suggests that as many as 78% of women aged 45-64 undergoing hysterectomy for benign conditions have a concomitant bilateral oophorectomy. [21] The presence of uterine fibroids is the single most common benign indication for hysterectomy (as was the case for 94% of the women with surgical menopause, see [17]) and the formation and growth of fibroids is modulated by sex steroids such as estrogen. [22] As such, it is likely that the most common surgical indication for the 143 women in our study population (8% of cases and 11% of the controls) who had their ovaries removed was hysterectomy for fibroids, and thus these women might have had relatively high estrogen levels compared to women who did not undergo bilateral oophorectomies.

Akin to the findings of some but not all studies, [6,9] our data are consistent with a weakly inverse association between use of post-menopausal HRT, defined as use beginning before the first symptom date. In other words, the HRT would need to have been in place early enough in a woman's life to have exerted its neuroprotective effects.

Although the mechanisms by which estrogens may protect against PD are not fully understood, there is some evidence regarding pathways by which estrogens influence brain development and function. For example, estrogen can influence the synthesis of dopamine in substantia nigra neurons and its release in the striatum and may also have some bearing on dopamine uptake and responsiveness to L-dopa.[reviewed in 23] Animal studies have also suggested several mechanisms by which estrogen could also be acting neuroprotectively, including through anti-oxidative, anti-inflammatory, and anti-apoptotic pathways. [24-31] Such studies documented that exogenous estrogen treatment or conditions of high endogenous estrogen concomitant with

exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, a toxic agent harmful to dopamine neurons) resulted in preservation of striatal dopamine content.[24-26] Exogenous estrogen may also exert neuroprotective qualities by decreasing the uptake of neurotoxins via the dopamine transporter or by preventing dopamine depletion.[27] Furthermore, estrogen may be important for maintenance of existing dopamine neurons, even in the absence of a neurotoxic insult. A recent primate study showed that, if not concurrently treated with estrogens, removal of both ovaries resulted in a permanent 30% reduction in mid-brain dopamine neurons while even short-term estrogen replacement within 10 days of the surgery reversed this effect.[32] Among the 143 women in our study who had both ovaries removed, 80 either never took HRT or began taking it one or more years after their oophorectomy and of these, 84% were cases and 16% controls. Fifty-five women were either already taking HRT at the time of surgery or began taking it at the time of surgery and of these 67% were controls and only 33% cases (there was missing information on the timing of HRT and/or oophorectomy for 8 women).

One could make the argument that those with lifelong lower levels of estrogens (for example men and also women with reproductive factors that suggest a lower circulating estrogen profile) may be more vulnerable in terms of their nigrostriatal dopaminergic system such that they are at a greater than average risk of losing dopamine neurons compared with individuals of the same age and sex with higher estrogen levels. In this context, our results imply that a higher estrogen state particularly in early- to mid-reproductive life may protect the dopamine system from loss of neurons and thus lower the risk of developing PD later in life. Unfortunately, this protection seems to not continue throughout the reproductive life span, which might explain some of the lack of concordance with earlier studies.

A major strength of our study is the large number of cases and the high specificity for case definition due to confirmatory medical record review for all cases included. Additionally, the extensive interviews amassed a wealth of contextual information with only small proportions of missing data.

Issues arising from survivorship during the case selection and recruitment processes may have affected our estimates. All PD cases identified in 10 neurological centers between 1996 and 2009 were eligible to participate but the interviews did not begin until January 2008. Thus those with the earliest diagnosis dates (i.e. closer to 1996) had to survive at least 12 years with their disease to reach the interview stage and be included in the study. As such, our cases may represent a select group of willing survivors with less advanced or severe disease. If the exposure distribution in the group that died or refused differs significantly from that in our participant group, our estimates may be biased. Likewise, there could be some selection bias, if the exposure distribution among controls who refused differed from those who participated. Yet, it seems unlikely that indicators of high or low estrogen levels would be related to a control's decision to participate.Bias due to differential recall may affect estimates from case-control studies, as those affected with the outcome being studied, seeking to understand why they developed the condition, may be more likely to report, or over-report, various exposures. The female reproductive factors we studied, with the possible exception of HRT use, have not been commonly thought of as risk/protective factors for PD thus exposure misclassification is probably non-differential. Due to the exhaustive case selection and confirmation process resulting high specificity of case diagnosis, exposure errors are likely independent and, as the

exposure measures are mostly dichotomous (i.e. Early Menarche vs. Other, Oral Contraceptive Use vs. Non-use, etc.), issues arising from recall may have resulted in estimates biased toward the null of no association.

In conclusion, we studied the relationship between PD and female reproductive factors in the largest case-control study worldwide. Our data suggest inverse associations with early age at menarche, oral contraceptive use, high parity, bilateral oophorectomy. Most importantly, using an estrogen score, the relative odds of PD declined with increasing score and presumably estrogen levels earlier in reproductive life.

In view of the fact that between 30% and 50% of dopamine neurons have died by the time of the onset of motor symptoms and PD diagnosis,[33-34] it seems reasonable to think that factors occurring earlier in life may contribute to, or reduce, PD risk. If replicated, our findings may suggest a method for identifying a group of women at higher risk of PD, and may inform decision-making regarding hormone replacement after removal of ovaries for benign conditions.

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Author roles:

Naomi Greene: 1) Research project: Conception, Organization, Execution; 2) Statistical Analysis: Design, Execution, Review and Critique; 3) Manuscript: Writing of the first draft, Review and Critique.

Christina Funch Lassen: 1) Research project: Organization; 2) Statistical Analysis: Review and Critique; 3) Manuscript: Review and Critique.

Kathrine Rugbjerg: 2) Statistical Analysis: Review and Critique; 3) Manuscript: Review and Critique.

Beate Ritz: 1) Research project: Conceptionn; 2) Statistical Analysis: Review and Critique; 3) Manuscript: Review and Critique.

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Beate Ritz: Employed by UCLA, supported by funding from the National Institutes of Health.

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Figure 1 title: PASIDA Female Case Selection Flowchart

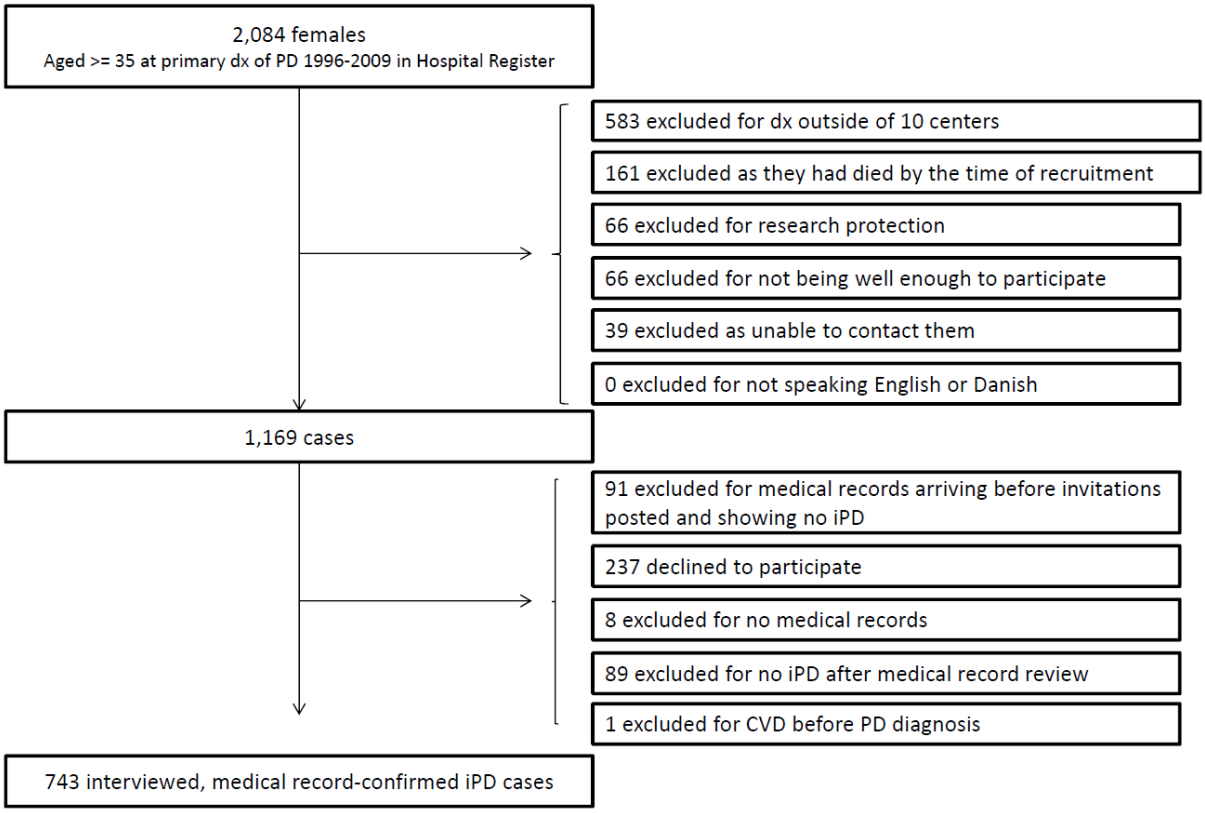

Figure 2 title: Relative Odds of PD with Increasing Estrogen Index Score in PASIDA

Figure 2 legend: Relative Odds of Parkinson's disease with Increasing Estrogen Index Score (Summation over 5 binary variables: Early Menarche + Oral Contraceptives + High Parity + Both Ovaries Out + Hormone Replacement). The y-axis is plotted on the log scale and the data labels give the antilogarithms of the odds ratio and 95% confidence limits.

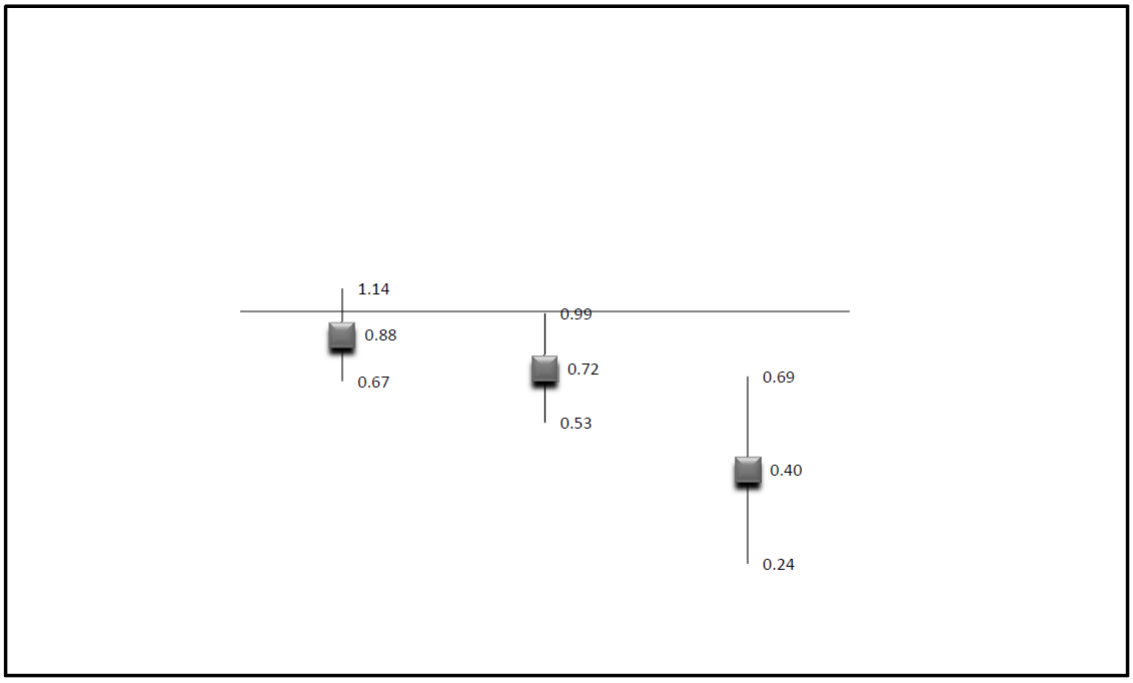

Table 1. Non-reproductive Characteristics of PASIDA Female Cases and Controls (n = 1508)

	Cases (n= 743)		Controls (n = 765)	
Variable name	N	%	N	%
1. Urbanization[1]				
Copenhagen	178	24%	232	30%
Provincial cities	467	63%	394	52%
Peripheral regions	71	10%	74	10%
Rural areas	27	4%	64	8%
2. Education[1]				
Primary	230	31%	216	28%
High School	16	2%	11	2%
Laborer/shorter education	221	30%	243	32%
Short higher education	99	13%	88	12%
Medium higher education	142	19%	162	21%
Long higher education	32	4%	40	5%
3. Family history of PD				
No	680	92%	729	95%
Yes	63	9%	36	5%
4. Alcohol consumption[1]				
Never	371	51%	322	43%
Ever	361	49%	435	58%
5. Smoking[1]				
Never	465	63%	372	49%
Former	224	30%	269	35%
Current	52	7%	119	16%
6. Caffeine consumption[1]				
Never	48	6%	28	4%
Ever	692	94%	735	96%
7. Coffee in cups/day[2]				
None	48	62%	29	38%
1-3	379	54%	323	45%
4-6	214	43%	281	39%
≥7	43	34%	83	12%
				Trend P<0.001[3]

1. Missing in ≤1%
2. Missing in 7%
3. P-value for the trend in odds of PD with increasing numbers of cups of coffee per day

Table 2. Frequencies and Relative odds of PD according to reproductive factors in female cases and controls (n = 1,508) from PASIDA Study

Variable	Cases (n = 743)		Controls (n = 765)		Adj.* Odds Ratio	Adj.** OR
	N	%	N	%	(OR) (95% CI)	(95% CI)
1. Age at Menarche[1]						
9-11 years	44	6%	64	9%	1.00 (ref)	1.00 (ref)
12-13	276	39%	294	40%	1.37 (0.90-2.07)	1.42 (0.89-2.26)
14-15	298	42%	311	42%	1.40 (0.92-2.12)	1.40 (0.88-2.23)
≥16	89	13%	73	10%	1.78 (1.09-2.92)	1.95 (1.12-3.37)
						trend p = 0.04
>11 years	663	94%	678	91%	1.00 (ref)	1.00 (ref)
≤11 years	44	6%	64	9%	0.70 (0.47-1.05)	0.68 (0.44-1.06)
2. High Estrogen Oral Contraceptives[2]						
Never used	496	74%	488	68%	1.00 (ref)	1.00 (ref)
Ever used	179	27%	230	32%	0.77 (0.61-0.97)	0.76 (0.59-0.98)
3. Duration of Oral Contraceptives[3]						
Never used	496	76%	488	69%	1.00 (ref)	1.00 (ref)
<5 years	54	8%	85	12%	0.62 (0.43-0.90)	0.62 (0.41-0.94)
≥5 years	105	16%	132	19%	0.78 (0.59-1.04)	0.73 (0.53-1.00)
						trend p = 0.09
4. Parity[4]						
≤1	145	20%	171	23%	1.00 (ref)	1.00 (ref)
2-3	501	68%	482	64%	1.23 (0.95-1.58)	1.13 (0.85-1.49)
≥4	86	12%	104	14%	0.97 (0.68-1.40)	0.86 (0.58-1.29)
						trend p = 0.79
<4	646	88%	653	86%	1.00 (ref)	1.00 (ref)
≥4	86	12%	104	14%	0.84 (0.61-1.14)	0.79 (0.56-1.11)
5. Length of Fertile Life (years) [5]						
<30	133	21%	140	21%	1.00 (ref)	1.00 (ref)
30-39	365	58%	397	58%	0.97 (0.73-1.28)	0.87 (0.64-1.18)
40-49	79	13%	89	13%	0.94 (0.64-1.37)	0.90 (0.59-1.39)
≥50	53	8%	54	8%	1.04 (0.65-1.66)	0.96 (0.57-1.61)
						trend p = 0.89
≤36 years	325	52%	339	50%	1.00 (ref)	1.00 (ref)
>36 years	301	48%	333	50%	1.03 (0.82-1.29)	0.98 (0.77-1.26)
6. Type of Menopause[6]						
Natural	664	92%	667	89%	1.00 (ref)	1.00 (ref)
Both ovaries out	58	8%	85	11%	0.69 (0.48-0.97)	0.69 (0.47-1.01)
7. Age at menopause[7]						
<45	109	17%	122	18%	1.00 (ref)	1.00 (ref)
45-49	131	20%	153	22%	0.96 (0.68-1.36)	0.92 (0.63-1.35)
50-54	239	37%	246	35%	1.09 (0.80-1.49)	0.94 (0.66-1.33)
≥55	170	26%	175	25%	1.09 (0.78-1.52)	1.02 (0.70-1.48)
						trend p = 0.59
≤44	109	17%	122	18%	1.00 (ref)	1.00 (ref)
≥45	540	83%	574	83%	1.05 (0.79-1.40)	0.96 (0.70-1.31)

Table 2. Frequencies and Relative odds of PD according to reproductive factors in female cases and controls (n = 1,508) from PASIDA Study (cont.)

Variable	Cases (n = 743)		Controls (n = 765)		Adjusted* Odds	Adjusted** OR
	N	%	N	%	Ratio (OR)	(95% CI)
8. Hormone use[7]						
None before index date	521	77%	552	75%	1.00 (ref)	1.00 (ref)
Ever before index date	152	23%	181	25%	0.89 (0.70-1.14)	0.94 (0.71-1.24)
9. Duration of HRT[7]						
None before index date[8]	524	78%	555	76%	1.00 (ref)	1.00 (ref)
<5 years	20	3%	18	3%	1.18 (0.62-2.26)	1.30 (0.61-2.76)
≥5 years	129	19%	160	22%	0.85 (0.66-1.11)	0.90 (0.68-1.21)

* Adjusted by birth year CI = Confidence Interval

** Adjusted by birth year, age at first symptom, smoking, alcohol, caffeine (cups/day), education, family PD history (1st degree relative) CI = Confidence Interval

1. Missing in 4%
2. Missing in 8%
3. Missing in 12%
4. Missing in 1%
5. Missing in 13%
6. Missing in 2%
7. Missing in 7%
8. 3 cases and 3 controls started using HRT in the same year as the index date, so calculated duration was zero

Table 3. Selected literature examining reproductive factors and Parkinson's disease risk

First author (Year)	Study design	Cases	Controls/Unaffected/ Person-Time
1. Ascherio A (2003) (Nurses Health Study)	Cohort	154	1,039,434 person-years
2. Simon K (2009) (Nurses Health Study)	Cohort	244 same group as in (1) above with an additional 4 years of followup	--
3. Rugbjerg K (2013) (Diet, Cancer and Health Study)	Cohort	77	365,698 person-years
4. Rocca W (2008) Olmstead County, MN 1950-1987	Cohort (parkinsonism)	51 with parkinsonism out of 2327 with any oophorectomy	28 with parkinsonism out of 2368 age-matched controls without any oophorectomy
5. Benedetti M (2001) Olmstead County, MN 1976-1995	Case-control	72	72 age-matched controls
6. Ragonese P (2004) Recruited outpatients from neurologic clinics Palermo and Messina	Case-control	131	131 age- and municipality matched controls
7. Popat R (2005) Kaiser Permanente in Northern California	Case-control	178	189 age-matched controls
8. Nicoletti A (2011) FRAGAMP Study- Italian movement disorder centers - recruited 2005	Case-control	200	299 female controls selected from among those accompanying the index case to clinic
9. Currie L (2004) University of VA Movement Disorder Clinic recruited in 1999	Case-control	68 all with natural menopause	72 female friend controls all with natural menopause

Table 4. Reproductive factors and PD risk in selected literature

Study	Age at Menarche		Oral Contraceptives		Parity		Type of Menopause	
1. Ascherio (2003)	Not examined		<5yrs vs. Never	0.99 (0.64-1.53)	2-3 vs. ≤1	1.00 (0.61-1.65)	Hyst + ≤1 ovary	1.29 (0.78–2.15)
			≥5yrs vs. Never	1.63 (1.03-2.58)	≥4 vs. ≤1	1.10 (0.66,1.83)	Hyst + 2 ovaries	1.07 (0.65–1.77)
2. Simon (2009)	12 vs. <12	1.06 (0.73, 1.55)	Ever vs. Never	1.02 (0.77, 1.36)	2-3 vs. ≤1	1.20 (0.78, 1.83)	Hyst + ≤1 ovary	0.79 (0.69, 1.36)
	13 vs. <12	1.02 (0.70, 1.46)	<5yrs vs. Never	0.84 (0.59, 1.19)	≥4 vs. ≤1	1.22 (0. 78, 1.89)	Hyst + 2 ovaries	0.97 (0.44, 1.44)
	>13 vs.<12	1.07 (0.73, 1.58)	≥5yrs vs. Never	1.35 (0.93, 1.96)				
3. Rugbjerg (2013)	Not examined		Ever vs. Never	1.30 (0.81,2.09)	0 vs. ≥3	0.88 (0.39,1.99)	Hyst Yes vs. No	1.10 (0.60,1.99)
					1 vs. ≥3	0.75 (0.33,1.71)	Ooph Yes vs. No	0.45 (0.16,1.24)
					2 vs. ≥3	1.24 (0.73,2.11)		
4. Rocca (2008)	Not examined		Not examined		Not examined		≥1 ovary vs. none	1.75 (1.04–2.95)
5. Benedetti (2001)	Not examined		Not examined		Not examined		Surgical vs. Natural	2.23 (0.90,5.54)
							Hyst + ≤1 ovary	3.36 (1.05,10.77)
6. Ragonese (2004)	>13 vs. ≤13	0.63 (0.33,1.20)	Not examined		Cumulative pregnancy length in months		Surgical vs. Natural	0.30 (0.13,0.77)
					>30 vs. ≤30	2.19 (1.22,3.91)		

Table 5. Reproductive factors and PD risk in selected literature (continued)

Study	Age at Menarche		Oral Contraceptives		Parity		Type of Menopause	
7. Popat (2005)	13-14 vs. <13	0.8 (0.5,1.3)	Not examined		1-3 vs. 0	0.9 (0.4,1.8)	Hyst + 0 ovaries vs. no hyst	1.2 (0.6,2.4)
	>14 vs. <13	0.9 (0.5,1.8)			>3 vs. 0	1.1 (0.5,2.5)	Hyst + ≥1 ovaries vs. no hyst	0.7 (0.4–1.3)
							Don't know procedure	1.3 (0.3,4.9)
8. Nicoletti (2011)	>13 vs. <13	1.02 (0.70,1.48)	Ever vs. Never	3.27 (1.24,8.59)	Cumulative pregnancy length in months ≤23 vs. ≥24	1.24 (0.86,1.78)	Hyst vs. no hyst	1.5 (0.30,7.52)
9. Currie (2004)	Case mean = 13±2 years		Ever vs. Never	19% of cases vs.	Number of pregnancies		Excluded women with hysterectomy	
	Control mean= 13±1 years			33% of controls	Cases: 3±2	Controls: 3±2		
	P-value for mean diff = 0.19			P < 0.08	P < 0.39			

Additional Reproductive Factors

Study	Age at Menopause		Post-menopausal hormone use		Fertile life
1. Ascherio (2003)	45-49 vs. <45	0.95 (0.46–1.99)	Past vs. Never	0.88 (0.58,1.35)	Not examined
	50-54 vs. <45	0.76 (0.38–1.51)	Current vs. Never	1.02 (0.69,1.52)	
	≥55 vs. <45	0.58 (0.21–1.60)	<5 vs. Never	0.91 (0.61,1.36)	
			≥5 vs. Never	1.00 (0.64,1.58)	
2. Simon (2009)	45-49 vs. <45	0.89 (0.51, 1.57)	Past vs. Never	1.08 (0.78, 1.50)	Not reported
	50-54 vs. <45	0.74 (0.44, 1.25)	Current vs. Never	1.18 (0.88, 1.59)	
	≥55 vs. <45	0.60 (0.28, 1.28)	<5 vs. Never	1.14 (0.83, 1.57)	
			≥5 vs. Never	1.14 (0.84, 1.54)	

Table 5. Reproductive Factors and PD Risk in Selected literature (continued)

Study	Age at Menopause		Post-menopausal hormone use		Fertile life	
3. Rugbjerg (2013)	Not examined		Ever vs. Never	1.42 (0.91,2.23)	>37 vs. ≤37	1.17 (0.70,1.96)
			Current vs. Never	1.36 (0.68,2.71)		
			Former vs. Never	1.67 (0.92,3.03)		
4. Rocca (2008)	Not examined		Not examined		Not examined	
5. Benedetti (2001)	≤46 vs. >46	2.18 (0.88,5.39)	All women		Not examined	
			≥6 mos vs. never	0.47 (0.12,1.85)		
			Natural menopause			
			≥6 mos vs. never	0.08 (0.004,1.58)		
6. Ragonese (2004)	≤46 vs. >46	1.90 (0.84,4.23)	Ever vs. Never	0.45 (0.13,1.50)	≤36 vs. >36	2.07 (1.00,4.30)
7. Popat (2005)	≤44 vs. >44	0.5 (0.3,0.9)	All women		Not examined	
			Ever vs. Never	1.3 (0.8,2.1)		
			Former vs. Never	1.8 (1.0,3.3)		
			Current vs. Never	1.0 (0.6,1.8)		
			Women with hysterectomy			
			Ever vs. Never	2.6 (1.1,6.1)		
			Former vs. Never	3.0 (1.1,8.5)		
			Current vs. Never	2.4 (1.0,6.0)		
			Women with natural menopause			
			Ever vs. Never	0.9 (0.5,1.7)		
			Former vs. Never	1.4 (0.7,3.1)		
			Current vs. Never	0.7 (0.3,1.4)		
8. Nicoletti (2011)	≤46 vs. >46	0.87 (0.57,1.32)	Ever vs. Never	0.99 (0.27,3.57)	<36 vs. >36	0.95 (0.66,1.35)
9. Currie (2004)	Case mean = 49±6 years		Ever vs. Never	25% of cases vs.	Not examined	
	Control mean = 50±5 years			50% of controls		
	P < 0.21			P < 0.003		