Increased Risk of Parkinson's Disease in Women after Bilateral Oophorectomy

Marianne Canonico, Giancarlo Pesce, Audrey Bonaventure, Maryline Le Noan-Lainé, Isabelle Benatru, Danièle Ranoux, Frédéric Moisan, Alexis Elbaz

Increased risk of Parkinson's disease in women after bilateral oophorectomy

Marianne Canonico, PhD[1], Giancarlo Pesce, PhD[1], Audrey Bonaventure, MD, PhD[2], Maryline Le Noan-Lainé, MSc[1], Isabelle Benatru, MD[3], Danièle Ranoux, MD[4], Frédéric Moisan, PhD[5], Alexis Elbaz, MD, PhD[1]

[1] Paris-Saclay University, Paris-South University, UVSQ, Center for Research in Epidemiology and Population Health, INSERM, Villejuif, F-94807, France
[2] CRESS, Université de Paris INSERM, UMR 1153, Epidemiology of childhood and adolescent cancers team, Villejuif, France
[3] Neurology Department, University Hospital of Poitiers, Poitiers, France
[4] Pain center, CHU Dupuytren, 2 bis avenue Martin Luther King, 87000 Limoges and Pain center, Fondation Adolphe de Rothschild, 28 rue Manin, 75019 Paris
[5] Santé publique France, Direction santé environnement et travail, Saint Maurice, France

Corresponding author: Marianne Canonico, Inserm U1018, 16 av Paul Vaillant-Couturier, 94807 Villejuif Cedex, France

Word account: 1935

Running head: Bilateral oophorectomy and Parkinson's disease

Key words: Epidemiology; Women; Bilateral oophorectomy; Parkinson's disease.

Relevant Financial Disclosure/Conflict of Interest for the last 12 months: The authors have nothing to declare/report.

Funding sources : This study was supported by INSERM (Institut National de la Santé et de la Recherche Médicale) and the MSA (Mutualité Sociale Agricole), and funded by the Agence Nationale de la Recherche (ANR), Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), and France Parkinson.

Abstract

Background. Results on the association between hormonal exposure and risk of Parkinson's disease (PD) are heterogeneous.

Objectives. To investigate the association of reproductive life characteristics with Parkinson's disease among postmenopausal women.

Methods. The PARTAGE case-control included 130 female cases and 255 age-matched female controls. Information on gynaecological history was obtained from a standardized questionnaire and PD was validated by neurological examination. Odds ratios (OR) and 95% confidence intervals (CI) were computed using conditional logistic regression.

Results. After adjustment for education level, smoking status, professional exposure to pesticides, and coffee and alcohol drinking, bilateral oophorectomy (OR=3.55, 95%CI=1.75-7.20), but neither menopause before 50 years (OR=1.24, 95%CI=0.74-2.09) nor hormone therapy (HT; OR=1.07, 95%CI=0.62-1.86), was associated with PD.

Conclusion. Our findings suggest that bilateral oophorectomy is associated with increased risk of PD.

Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease, and its incidence is 1.5 to 2.0 times higher in men than women.[1] Estrogens have been shown to have neuroprotective effects, especially for nigrostriatal pathways[2] through increased dopamine synthesis, upregulation of neurotrophic factors,[3] and prevention of Lewy body formation and α-synuclein aggregation.[4] Estrogens also have anti-oxidative and anti-inflammatory properties, by decreasing levels of cytokines and other inflammatory modulators.[5]

Based on these clinical and experimental observations, it has been hypothesized that hormonal exposure could have a protective role against PD in women. However, data on the role of estrogens in PD remain conflicting, especially regarding the role of age at menopause and type of menopause.[6-13]

Using data from the PARTAGE case-control study, we investigated the association of markers of hormonal exposure (age at and type of menopause, postmenopausal hormone therapy) with PD. In particular, we attempted to disentangle the role of surgical menopause and early age at menopause, which are often correlated.

Methods

Study design and participants

PARTAGE is a population-based case-control study conducted among members of *Mutualité Sociale Agricole* (MSA) in five French districts. MSA is the French health insurance for workers in agriculture and related occupations while active and retired. The research protocol was approved by the ethics committee of *Hôpital de la Pitié-Salpêtrière* (Paris, France), and all subjects signed an informed consent.[14]

Briefly, PD cases (18-80 years) were identified between January 1, 2006, and December 31, 2007, among MSA members through two overlapping computerized databases: (*i*) reimbursements of antiparkinsonian drugs (code N04 of the Anatomical Therapeutic Chemical Classification System); (*ii*) free healthcare for PD: in France, PD belongs to a list of 30 chronic illnesses for which free medical care is granted, usually after a neurologist confirms the diagnosis. We excluded cases with free healthcare for dementia or psychiatric conditions. Potential cases were examined by a movement disorders specialist. PD was defined as the presence of ≥2 cardinal signs (rest tremor, bradykinesia, rigidity, impaired postural reflexes) in the absence of prominent or early signs of more extensive nervous system involvement and drug induced parkinsonism.[15] Only patients with confirmed PD and disease duration ≤15 years were included.

Controls were identified from MSA computerized database of all affiliates in the five districts after excluding subjects who benefited from free healthcare for PD, dementia, or psychiatric conditions, and subjects who received antiparkinsonian drugs in 2006-2007. We randomly matched 2 controls on sex, district, and age (± 2 years) to each case.

Acceptance rate was 81% for cases and 73% for controls.

Data collection and exposure assessment

Cases and controls were interviewed face-to-face by trained interviewers using a standardized questionnaire. Information on education level, smoking, alcohol and coffee drinking, and history of head trauma were collected. The Mini-Mental State Examination (MMSE) was assessed.

In women, we obtained information on menopausal status, age at menopause, type of menopause, history of hysterectomy or oophorectomy (unilateral, bilateral), and postmenopausal hormone therapy (HT) use (never/past/current).

Type of menopause was defined as natural versus artificial, which was divided into medical (after medical treatment, e.g., chemotherapy, radiotherapy) and surgical (after surgery: hysterectomy only or bilateral oophorectomy +/- hysterectomy). Women with unilateral oophorectomy before menopause were included in the natural menopause group. Age at menopause was categorized at the median in controls (≤50, > 50 years).

Statistical analysis

In controls, we defined index age as age at study minus the lag between age at onset and age at study in matched cases. Only exposures occurring before age at PD onset in cases and index age in controls were considered. Analyses were restricted to post-menopausal women at PD onset (cases) or index date (controls).

We used conditional logistic regression for matched sets to compute odds ratios (OR) and 95% confidence intervals (CI). We conducted analyses unadjusted and adjusted for covariates associated with PD in our study or the literature (education; smoking; coffee and alcohol drinking; professional exposure to pesticides). We also adjusted for MMSE to reduce a potential recall bias; however, this could lead to collider bias if MMSE was affected both by PD and exposures, and we report MMSE-adjusted results as sensitivity analyses.

Interactions were tested by including multiplicative terms in the models. Statistical significance was considered at a two-tailed value of 0.05 for main effects, and 0.10 for interactions.

Analyses were conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

We included 130 cases matched to 255 controls (Table 1). Table 2 shows the association of characteristics of menopause and hormone therapy use with PD. In adjusted analyses, artificial menopause was associated with PD (46 [35.4%] cases; 49 [19.2%] controls; OR=2.49; 95% CI=1.50-4.11). This association was significant for surgical menopause (43 [33.1%] cases; 45 [17.6%] controls; OR=2.56; 95% CI=1.53-4.26) but not for medical menopause (3 [2.3%] cases; 4 [1.6%] controls; OR=1.71; 95% CI=0.33-8.78); however, few women reported medical menopause and the ORs were not statistically different (P=0.64). For surgical menopause, the association was stronger (P=0.09) for bilateral oophorectomy (32 [24.6%] cases; 24 [9.4%] controls; OR=3.70; 95% CI: 1.95-7.02) than hysterectomy only (11 [8.5%] cases; 24 [9.4%] controls; OR=1.60; 95% CI=0.69-3.68).

Menopause before 50 years was more frequent in cases than controls (OR=1.61; 95% CI=1.01-2.56). In analyses of the independent and combined effects of bilateral oophorectomy and early menopause, compared to natural late menopause, natural early menopause was more frequent in cases than in controls but the association was not statistically significant (OR=1.30; 95% CI=0.78-2.15); few women had late bilateral oophorectomy, and the association was borderline significant (OR=5.76; 95% CI=0.95-34.9); the most significant association was observed for women with early bilateral oophorectomy (OR=4.61; 95% CI=2.22-9.56). There was no significant interaction between bilateral oophorectomy and age of menopause (P-interaction=0.91), and no significant difference between bilateral oophorectomy before and after 50 years (P=0.59).

HT use was not associated with PD (OR=1.30; 95% CI=0.78-2.15), and there was no difference between past and current users (P=0.42). Analyses restricted to women without bilateral oophorectomy led to similar results (OR=1.38; 95% CI=0.72-2.66).

In a multiadjusted model including age at menopause, bilateral oophorectomy, and HT use, bilateral oophorectomy was the only characteristic associated with PD (OR=3.55; 95% CI=1.75-7.20).

In analyses stratified by median index age or disease duration in cases, the association of bilateral oophorectomy with PD was similar in the strata (Supplementary table 1).

Sensitivity analyses after exclusion of women with unilateral oophorectomy (1 case, 5 controls) led to similar results (data not shown). Similar conclusions were also reached after further adjustment for MMSE (Supplementary table 2).

Discussion

Our findings suggest that bilateral oophorectomy is a PD risk factor among postmenopausal women. The prevalence of bilateral oophorectomy in controls from our study (~9%) is similar to that in women ≥65 years from a French population-based study (7.9%);[16] in comparison, nearly 25% of PD cases had a bilateral oophorectomy.

Our result on the association of bilateral oophorectomy with PD is consistent with findings from US studies. One study found a 68% increased risk of parkinsonism in women who underwent unilateral or bilateral oophorectomy before menopause compared to women of comparable age; findings were consistent for PD, but did not reach significance.[7] Another study reported that PD risk was 3.34-times higher in women with bilateral oophorectomy compared to women without, but the authors were cautious in the interpretation of this finding as only 4 PD cases had bilateral oophorectomy.[17] By contrast, there was no association between bilateral oophorectomy and PD incidence in the Nurses' Health Study, but the authors noted that the number of women with oophorectomy was too small to exclude a moderate association.[8] A pooled analyses of five studies (4 case-control, 1 cohort) did not find a significant association of surgical menopause with PD.[9] However, the definition of surgical menopause included oophorectomy as well as hysterectomy with ovarian conservation, which could have diluted the association.

In our study, early age at menopause was not associated with PD after taking into account oophorectomy, in agreement with one of the studies discussed above.[17] Our results are inconsistent with studies showing that early menopause was associated with PD, but they did not adjust for oophorectomy which is strongly correlated with early menopause.[6,13,18] Finally, we did not find any association of HT with PD, in agreement with other studies.[19] However, due to the limited number of women with bilateral oophorectomy, we are cautious in our conclusions about the independent role of bilateral oophorectomy, age at menopause, and HT, and larger studies are needed.

A potential neuroprotective effect of estrogens represents the main hypothesis for the association of bilateral oophorectomy with PD. During natural menopause, women are exposed to a progressive decline of circulating estrogens; alternatively, hormones decrease abruptly and more markedly after bilateral oophorectomy which causes ovarian insufficiency and a hypoestrogenic climate characterized by lower estrogens concentrations in women with bilateral oophorectomy compared to those with natural menopause.[20] In addition, women with a hysterectomy without bilateral oophorectomy present an intermediate hormonal status characterised by cessation of menses without immediate ovarian insufficiency, and women with unilateral oophorectomy without hysterectomy have similar hormonal levels than women with both ovaries.[21]

Strengths of our study include the population-based design, PD diagnosis confirmation by a neurologist, and detailed information on gynaecological history. Our study also has limitations. First, subjects were recruited through the MSA, which limits the generalizability of our findings. Second, we were unable to examine whether the cause of artificial menopause played a role. In particular, artificial

menopause may be a consequence of gynaecological cancers. Although it is generally considered that the frequency of cancers (especially smoking-related cancers) is lower in PD cases than controls,[22] we cannot exclude that ovary cancer could be a confounder of the association between oophorectomy and PD. However, although individual studies on the relation of gynaecological cancers with PD are inconsistent, one meta-analysis reported no significant association between cervical or uterine cancers and PD, while there was an inverse association for ovary cancer (OR=0.81, 95% CI=0.65-1.00, p=0.013).[23] The lower frequency of ovary cancer in PD cases than controls according to this meta-analysis suggests that ovary cancer is an unlikely explanation for the positive association between oophorectomy and PD. Third, we did not collect information on age at menarche and parity. Fourth, the sample size remained relatively modest, especially regarding participants with surgical menopause, and we cannot exclude that this sample size limited statistical power for subgroup analyses. Fifth, our study is an observational study with the potential for bias, including survival, incidence-prevalence, recall, and non-participation biases. Associations of bilateral oophorectomy with PD were of similar size in younger and older participants, and in PD cases with shorter and longer disease duration, making it unlikely that survival or incidence-prevalence bias accounted for these associations. We cannot exclude differential recall in PD cases and controls (recall bias); however the similar prevalence of bilateral oophorectomy in controls from our study and in women ≥65 years from a French population-based study is not in favour of under-report in controls.[16] It is also unlikely that higher rates of oophorectomy in PD cases than controls are due to more medical contacts due to incipient PD and subtle motor signs in the years preceding PD diagnosis, since there was an association for bilateral oophorectomy before 50 years. In addition, surgical menopause is a major health event which is likely to be reliably reported by most women. Although self-report may be less reliable for oophorectomy than for hysterectomy [24], this is unlikely to be differential. Finally, acceptance rates were high in cases and controls, and selection (non-participation bias) is unlikely to explain the results.

In conclusion, these findings suggest that women in whom menopause is due to bilateral oophorectomy represent a group at higher risk of PD.

Acknowledgements

We thank the MSA physicians and personnel who helped us for the local study coordination (Drs Jacques Aimedieu, Catherine Bolut, Albert Daniel, Christophe Fuzeau, Virginie Gaussères, Maryline Grandjean, Jean Houssinot, Marine Jeantet, Bernard Ladépèche, Didier Menu, Omar Tarsissi; Joël Gourgues, Sandrine Nogues, Emilie Richard, Pierre Vannier), the study interviewers (Véronique Dumay, Viviane Palleau, Frédérique Pellerin, Estelle Seguin, Sophie Sinibaldi), the study neurologists (Irina Balaboi, Isabelle Benatru, Julien Dumurgier, Elsa Krim, Danièle Ranoux), and Aïcha Soumaré for her help in coordinating the study.

Author contributions

(1) Research Project: A. Organization, B. Execution, C. Conception;
(2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
(3) Manuscript: A. Writing of the First Draft, B. Review and Critique

MC: 2A, AB, 2C, 3A, 3B
GP: 3B
AB: 2A, AB, 2C, 3B
MLNL: 3B
IB: 3B
DR: 3B
FM: 3B
AE: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

Financial Disclosures of all authors (for the preceding 12 months)

None

References

1. Moisan F, Kab S, Mohamed F, et al. Parkinson disease male-to-female ratios increase with age: French nationwide study and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2016;87:952-957.
2. Cerri S, Mus L, Blandini F. Parkinson's Disease in Women and Men: What's the Difference? *J Parkinsons Dis.* 2019;9:501-515.
3. Sawada H, Shimohama S. Estrogens and Parkinson disease: novel approach for neuroprotection. *Endocrine.* 2003;21:77-79.
4. Hirohata M, Ono K, Morinaga A, Ikeda T, Yamada M. Anti-aggregation and fibril-destabilizing effects of sex hormones on alpha-synuclein fibrils in vitro. *Exp Neurol.* 2009;217:434-439.
5. Brann DW, Dhandapani K, Wakade C, Mahesh VB, Khan MM. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. *Steroids.* 2007;72:381-405.
6. Ragonese P, D'Amelio M, Salemi G, et al. Risk of Parkinson disease in women: effect of reproductive characteristics. *Neurology.* 2004;62:2010-2014.
7. Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology.* 2008;70:200-209.
8. Simon KC, Chen H, Gao X, Schwarzschild MA, Ascherio A. Reproductive factors, exogenous estrogen use, and risk of Parkinson's disease. *Mov Disord.* 2009;24:1359-1365.
9. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann. Neurol.* 2012;72:893-901.
10. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *The Lancet Neurology.* 2016;15:1257-1272.
11. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. *Parkinsonism Relat Disord.* 2016;23:1-9.
12. Lv M, Zhang Y, Chen GC, et al. Reproductive factors and risk of Parkinson's disease in women: A meta-analysis of observational studies. *Behav Brain Res.* 2017;335:103-110.
13. Yoo JE, Shin DW, Jang W, et al. Female reproductive factors and the risk of Parkinson's disease: a nationwide cohort study. *Eur J Epidemiol.* 2020;35:871-878.
14. Moisan F, Spinosi J, Delabre L, et al. Association of Parkinson's Disease and Its Subtypes with Agricultural Pesticide Exposures in Men: A Case-Control Study in France. *Environ. Health Perspect.* 2015;123:1123-1129.
15. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. *Neurology.* 1999;52:1214-1220.
16. Canonico M, Scarabin-Carre V, Brailly-Tabard S, et al. High level of plasma estradiol as a new predictor of ischemic arterial disease in older postmenopausal women: the three-city cohort study. *J Am Heart Assoc.* 2012;1:e001388.
17. Liu R, Baird D, Park Y, et al. Female reproductive factors, menopausal hormone use, and Parkinson's disease. *Mov Disord.* 2014;29:889-896.
18. Benedetti MD, Maraganore DM, Bower JH, et al. Menopause, hysterctomy, and estrogen in Parkinson's disease: an exploratory case-control study. *Mov. Disord.* 2000;16:830-837.
19. Wang P, Li J, Qiu S, Wen H, Du J. Hormone replacement therapy and Parkinson's disease risk in women: a meta-analysis of 14 observational studies. *Neuropsychiatr. Dis. Treat.* 2014;11:59-66. doi: 10.2147/NDT.S69918. eCollection;%2015.:59-66.
20. Korse CM, Bonfrer JM, van Beurden M, Verheijen RH, Rookus MA. Estradiol and testosterone levels are lower after oophorectomy than after natural menopause. *Tumour Biol.* 2009;30:37-42.
21. Cooper GS, Thorp JM, Jr. FSH levels in relation to hysterectomy and to unilateral oophorectomy. *Obstet Gynecol.* 1999;94:969-972.
22. Bajaj A, Driver JA, Schernhammer ES. Parkinson's disease and cancer risk: a systematic review and meta-analysis. *Cancer Causes Control.* 2010;21:697-707.

23. Zhang P, Liu B. Association between Parkinson's Disease and Risk of Cancer: A PRISMA-compliant Meta-analysis. *ACS Chem Neurosci.* 2019;10:4430-4439.
24. Phipps AI, Buist DS. Validation of self-reported history of hysterectomy and oophorectomy among women in an integrated group practice setting. *Menopause (New York, N.Y.* 2009;16:576-581.

Table 1. Characteristics of cases and controls.

Characteristics	Cases (N=130)	Controls (N=255)
Age at study, years, mean (SD)	73.6 (5.4)	74.0 (5.4)
Age at onset of PD, years, mean (SD)	67.7 (6.4)	--
Disease duration, years, mean (SD)	5.0 (3.8)	--
Ethnicity, % (N)		
Caucasian	99.2 (129)	99.2 (253)
Other (North Africa, West Indies)	0.8 (1)	0.8 (2)
Education level, % (N)		
Primary	81.5 (106)	84.3 (215)
Secondary	12.3 (16)	10.2 (26)
High school study or more	6.2 (8)	5.5 (14)
Occupation, % (N)		
No farming	13.1 (17)	11.8 (30)
Farming without exposure to pesticides	64.6 (84)	70.2 (179)
Farming with exposure to pesticides	22.3 (29)	18.0 (46)
Ever smoker, % (N)[a]	2.3 (3)	3.6 (9)
Regular alcohol drinking, % (N)[b]	48.1 (62)	46.0 (115)
Regular coffee drinking, % (N)[c]	72.7 (93)	76.0 (193)
History of head trauma, % (N)[d]	14.7 (19)	14.7 (37)
MMSE, % (N)[e]		
<25	37.2 (48)	31.4 (80)
[25-28[	43.4 (56)	40.0 (102)
>28	19.4 (25)	28.6 (73)

PD: Parkinson's disease; SD: standard deviation; MMSE: mini mental score examination.
[a] Missing values for 1 case and 2 controls.
[b] Missing values for 1 case and 5 controls.
[c] Missing values for 2 cases and 1 control.
[d] Missing values for 1 case and 3 controls.
[e] Missing value for 1 case.

Table 2. Relation of characteristics of menopause and hormone therapy use with Parkinson's disease.

Characteristics, % (N)	Cases (N=130)	Controls (N=255)	OR (95% CI)	p	Adjusted OR[a] (95% CI)	p
Type of menopause						
Natural	64.6 (84)	80.8 (206)	1.00 (reference)	--	1.00 (reference)	--
Artificial	35.4 (46)	19.2 (49)	2.27 (1.40-3.66)	<0.01	2.49 (1.50-4.11)	<0.01
Medical	2.3 (3)	1.6 (4)	1.82 (0.39-8.61)	0.45	1.71 (0.33-8.78)	0.52
Surgical[b]	33.1 (43)	17.6 (45)	2.30 (1.41-3.75)	<0.01	2.56 (1.53-4.26)	<0.01
Hysterectomy only	8.5 (11)	7.4 (19)	1.37 (0.62-3.04)	0.44	1.60 (0.69-3.68)	0.27
Bilateral oophorectomy	24.6 (32)	9.4 (24)	3.37 (1.84-6.18)	<0.01	3.70 (1.95-7.02)	<0.01
Age at menopause[c]						
≥ 50 years	31.5 (40)	42.5 (108)	1.00 (reference)	--	1.00 (reference)	--
< 50 years	68.5 (87)	57.5 (146)	1.56 (1.00-2.44)	0.05	1.61 (1.01-2.56)	0.04
Age and type of menopause[d]						
Natural menopause ≥50y	31.0 (35)	44.1 (101)	1.00 (reference)	--	1.00 (reference)	--
Natural menopause <50y	40.7 (46)	45.4 (104)	1.30 (0.77-2.19)	0.33	1.35 (0.78-2.33)	0.30
Bilateral oophorectomy ≥50y	3.5 (4)	0.9 (2)	5.99 (1.03-34.8)	0.04	5.76 (0.95-34.9)	0.06
Bilateral oophorectomy <50y	24.8 (28)	9.6 (22)	3.84 (1.92-7.70)	<0.01	4.61 (2.22-9.56)	<0.01
Hormone therapy[e]						
Never users	69.1 (87)	74.0 (188)	1.00 (reference)	--	1.00 (reference)	--
Ever users	30.9 (39)	26.0 (66)	1.32 (0.81-2.18)	0.27	1.30 (0.78-2.15)	0.31
Past users	22.2 (28)	17.5 (44)	1.45 (0.83-2.53)	0.19	1.50 (0.85-2.66)	0.16
Current users	8.7 (11)	7.9 (20)	1.18 (0.51-2.72)	0.70	1.01 (0.42-2.43)	0.98
Multiadjusted model[f]						
Age at menopause <50y vs ≥50y	65.1 (71)	54.8 (125)	1.24 (0.75-2.06)	0.39	1.24 (0.74-2.09)	0.42
Bilateral oophorectomy vs natural	27.5 (30)	10.1 (23)	3.25 (1.66-6.36)	<0.01	3.55 (1.75-7.20)	<0.01
Ever users of hormone therapy	30.3 (33)	25.9 (59)	1.13 (0.66-1.93)	0.67	1.07 (0.62-1.86)	0.81

OR, odds ratio; CI, confidence interval.

[a] Adjusted for education level, smoking status, professional exposure to pesticides, and coffee and alcohol drinking; missing values of covariates were considered as a separate category.

[b] Type of surgical menopause missing for two controls.

[c] Age at menopause missing for 3 cases and 1 control.

[d] Cases and controls with medical menopause or hysterectomy only are excluded. Analyses were performed using unconditional logistic regression after breaking the matching and adjusted for matching variables (age at the index date, district).

[e] Hormone therapy missing for 4 cases and 3 controls.

[f] Analyses based on 109 cases and 228 controls without missing data for the three exposures. Cases and controls with medical menopause or hysterectomy only are excluded from the reference group by including dummy variables.

Supplementary Table 1. Relation of characteristics of menopause and hormone therapy with PD: multiadjusted model stratified by age at index date and disease duration

Characteristics, % (N)	Cases	Controls	Adjusted OR[a] (95% CI)	p	p-interaction[b]
Age ≤ 75 years (56 cases, 118 controls)					
Age at menopause <50y vs ≥50y	64.3 (36)	52.5 (62)	1.50 (0.68; 3.31)	0.31	--
Bilateral oophorectomy vs natural	30.4 (17)	10.2 (12)	3.73 (1.25; 11.2)	0.02	--
Ever users of hormone therapy	35.7 (20)	36.4 (43)	1.06 (0.49; 2.33)	0.88	--
Age > 75 years (53 cases, 110 controls)					
Age at menopause <50y vs ≥50y	66.0 (35)	57.3 (63)	1.16 (0.51; 2.64)	0.72	0.57
Bilateral oophorectomy vs natural	24.5 (13)	10.0 (11)	2.65 (0.99; 7.08)	0.05	0.63
Ever users of hormone therapy	24.5 (13)	14.6 (16)	2.14 (0.81; 5.61)	0.12	0.39
Disease duration ≤ 4.5 years (56 cases, 117 controls)					
Age at menopause <50y vs ≥50y	67.7 (35)	56.6 (63)	1.12 (0.53; 2.35)	0.76	--
Bilateral oophorectomy vs natural	23.8 (15)	9.60 (12)	2.85 (1.04; 7.81)	0.04	--
Ever users of hormone therapy	37.5 (20)	25.6 (31)	1.32 (0.61; 2.90)	0.48	--
Disease duration > 4.5 years (53 cases, 111 controls)					
Age at menopause <50y vs ≥50y	69.4 (36)	58.4 (62)	1.29 (0.59; 2.80)	0.52	0.95
Bilateral oophorectomy vs natural	26.6 (15)	9.7 (11)	4.45 (1.51; 13.1)	<0.01	0.52
Ever users of hormone therapy	24.2 (13)	26.4 (28)	0.80 (0.34; 1.89)	0.62	0.45

OR, odds ratio; CI, confidence interval.

[a] Adjusted for education level, smoking status, professional exposure to pesticides, and coffee and alcohol drinking; missing values of covariates were considered as a separate category. Cases and controls with medical menopause or hysterectomy only are excluded from the reference group by including dummy variables.

[b] P-values for the difference in ORs for each exposure across strata defined by median age or median disease duration in PD cases; in each strata of disease duration, cases were compared to their matched controls.

Supplementary Table 2. Relation of characteristics of menopause and hormone therapy use with Parkinson's disease, after further adjustment for MMSE.

Characteristics, % (N)	Cases (N=130)	Controls (N=255)	Adjusted OR[a] (95% CI)	p
Type of menopause				
Natural	64.6 (84)	80.8 (206)	1.00 (reference)	--
Artificial	35.4 (46)	19.2 (49)	2.35 (1.42-3.90)	<0.01
Medical	2.3 (3)	1.6 (4)	1.86 (0.36-9.71)	0.46
Surgical[b]	33.1 (43)	17.6 (45)	2.39 (1.43-4.01)	<0.01
Hysterectomy only	8.5 (11)	7.4 (19)	1.58 (0.68-3.65)	0.29
Bilateral oophorectomy	24.6 (32)	9.4 (24)	3.37 (1.78-6.42)	<0.01
Age at menopause[c]				
≥ 50 years	31.5 (40)	42.5 (108)	1.00 (reference)	--
< 50 years	68.5 (87)	57.5 (146)	1.50 (0.93-2.42)	0.10
Age and type of menopause[d]				
Natural menopause ≥50y	31.0 (35)	44.1 (101)	1.00 (reference)	--
Natural menopause <50y	40.7 (46)	45.4 (104)	1.19 (0.68-2.09)	0.53
Bilateral oophorectomy ≥50y	3.5 (4)	0.9 (2)	5.04 (0.82-31.2)	0.08
Bilateral oophorectomy <50y	24.8 (28)	9.6 (22)	4.40 (2.11-9.18)	<0.01
Hormone therapy[e]				
Never users	69.1 (87)	74.0 (188)	1.00 (reference)	--
Ever users	30.9 (39)	26.0 (66)	1.31 (0.79-2.19)	0.30
Past users	22.2 (28)	17.5 (44)	1.51 (0.85-2.69)	0.16
Current users	8.7 (11)	7.9 (20)	1.02 (0.42-2.46)	0.96
Multiadjusted model[f]				
Age at menopause <50y vs ≥50y	65.1 (71)	54.8 (125)	1.14 (0.67-1.95)	0.63
Bilateral oophorectomy vs natural	27.5 (30)	10.1 (23)	3.45 (1.70-7.03)	<0.01
Ever users of hormone therapy	30.3 (33)	25.9 (59)	1.08 (0.62-1.88)	0.80

OR, odds ratio; CI, confidence interval.

[a] Adjusted for education level, smoking status, professional exposure to pesticides, coffee and alcohol drinking, and MMSE in tertiles; missing values of covariates were considered as a separate category.

[b] Type of surgical menopause missing for two controls.

[c] Age at menopause missing for 3 cases and 1 control.

[d] Cases and controls with medical menopause or hysterectomy only are excluded. Analyses were performed using unconditional logistic regression after breaking the matching and adjusted for matching variables (age at the index date, district).

[e] Hormone therapy missing for 4 cases and 3 controls.

[f] Analyses based on 109 cases and 228 controls without missing data for the three exposures. Cases and controls with medical menopause or hysterectomy only are excluded from the reference group by including dummy variables.