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Female reproductive factors, menopausal hormone use, and Parkinson's disease

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Abstract

Objective—To examine the associations of reproductive factors and exogenous hormone use with risk of Parkinson's disease (PD) among postmenopausal women.

Methods—The study comprised 119,166 postmenopausal women ages 50–71 years in the NIH-AARP Diet and Health Study, who completed a baseline questionnaire in 1995–1996 and a follow-up survey in 2004–2006. A total of 410 self-reported PD diagnoses were identified between 1995 and 2006. Multivariate odds ratios (OR) and 95% confidence intervals (CI) were derived from logistic regression models.

Results—PD risk was not significantly associated with female reproductive factors including age at menarche, age at first live birth, parity, and age at menopause. For example, compared with women with natural menopause at ages 50–54 years, the ORs were 1.18, (95% CI 0.78–1.79) for women with natural menopause at ages <45, 1.19 (0.88–1.61) for ages 45–49, and 1.33 (0.91–1.93) for ages 55 or later. We found that oral contraceptive use for ≥10 years (vs. never use) was associated with lower PD risk (OR=0.59; 0.38–0.92) but shorter use showed no association. Use of menopausal hormone therapy showed inconsistent results. Compared with non-hormone users at baseline, current hormone users of <5 years showed a higher risk of PD (OR=1.52; 1.11–2.08). However, no associations were observed for past hormone users or current users of ≥5 years.

Conclusions—Overall, this large prospective study provides little support for an association between female reproductive factors and PD risk. Our findings on long-term oral contraceptive use and current hormone therapy warrant further investigations.

Keywords

Reproductive factors; Parkinson's disease; cohort studies; menopausal hormone therapy

Gender differences in Parkinson's disease (PD) have been indicated..[1,2] More men are diagnosed with PD than women with an approximate ratio of 2:1.[3,4] Moreover, compared to men, women tend to have a slightly later age at onset, better Unified Parkinson's Disease Rating Scale (UPDRS) motor scores with PD progression, and fewer reported parkinsonian symptoms among those with PD.[2]

Even though the precise nature and mechanisms that underlie the gender differences in PD remain unclear, estrogen has been speculated to be neuroprotective. In animal studies of PD, estrogen showed neuroprotective properties against neurotoxins when administered prior to, or coinciding with, the neurotoxins.[5] However, when administered immediately or several days after the neurotoxin, the neuroprotective effects of estrogen within the nigrostriatal dopaminergic system were no longer present.[6,7] The suggestive beneficial effects of estrogen reported in animal models of PD, however, have not been consistently observed in human studies.

Four clinical trials have examined postmenopausal estrogen supplementation in PD patients, three found no benefits in ameliorating parkinsonian symptoms.[8–10] One double-blind trial showed a significant improvement on the motor UPDRS among the estrogen-treated group.[11] The few observational studies on hormone use and PD risk generated inconsistent

results. Postmenopausal hormone use in these studies has been associated with either higher,[12] lower,[13] or null risk[14–20] of PD. Moreover, only one study had a sample size greater than 300 PD cases. We therefore examined the role of reproductive factors and exogenous hormone use on risk of PD among a large prospective cohort of postmenopausal women enrolled in the NIH-AARP Diet and Health Study.

MATERIALS AND METHODS

Study population

The NIH-AARP Diet and Health study was initiated in 1995–1996 by the National Cancer Institute to investigate roles of diet and lifestyle in cancer etiology.[21] The cohort comprised 566,398 AARP members ages 50–71 from six US states and two metropolitan areas. Approximately 40% of the participants are women (n=226,732). Participants completed a baseline questionnaire on diet, demographic characteristics, health-related behaviors, and reproductive and medical history.[21] In 1996–1997, a second questionnaire was sent to respondents of the baseline questionnaire to collect additional information on diet, physical activity, and use of menopausal hormones. A follow-up survey was conducted in 2004–2006 among surviving participants of the original cohort to update lifestyle exposures and to ascertain the occurrence of major chronic diseases, including PD. A total of 130,761 female participants returned the follow-up survey. After excluding 8,712 women who were premenopausal or had unknown menopausal status at enrollment and 2,686 women with missing information on PD status, 119,363 potential eligible women remained.

Exposure assessment

At baseline, participants were asked about their age at first live birth (nulliparous, <16, 16–19, 20–24, 25–29, 30–34, 35–39, ≥40 years); number of live-born children (none, 1,2,3–4, 5–9, ≥10); age at first (≤10, 11–12, 13–14, ≥15 years) and last menstrual period (<40, 40–44, 45–49, 50–54, ≥55 years, still menstruating). The latter was defined as age of menopause. They were also asked whether their menopause was natural or due to surgery, radiation or chemotherapy; history of hysterectomy and oophorectomy; oral concentrative use (never or <1 year, 1–4, 5–9, ≥10 years); menopausal hormone therapy use (never, former, current) and duration of menopausal hormone use (never, <5, 5–9, ≥10 years). The second questionnaire, sent within 6 months of the baseline questionnaire, elicited more detailed information about the type of menopausal hormone therapy (e.g. estrogen only or estrogen plus progestin), recency, and duration of use (ranging from ‘1 years or less’ to ‘≥10 years).

PD case identification

Participants in the follow-up survey reported whether they had ever received a physician diagnosis of PD and the year of their first diagnosis in the following categories: before 1985, 1985–1994, 1995–1999, or in or after 2000. Of the 119,363 women eligible for the current study, 607 (0.5%) reported a PD diagnosis. Since exposure information was collected at the baseline survey in 1995–1996, we excluded from our analyses 120 cases who reported a PD diagnosis before 1995. We further excluded 77 self-reported cases whose diagnosis was later denied by patients themselves (n=59) or denied (n=8) or deemed uncertain (n=10) by their

treating physicians or medical record reviews in the diagnostic confirmation effort described below. After these exclusions, we had a total of 410 postmenopausal women with self-reported PD diagnosis in or after 1995 and 118,756 postmenopausal women without PD in the primary analyses.

We validated the accuracy of self-reported PD diagnoses in conjunction with DNA collection for PD genetic research.[22] Briefly, we asked surviving self-reported cases to confirm their diagnosis and to give us permission to contact their treating physicians. We then asked the treating physicians, mostly neurologists, to complete a diagnostic questionnaire and to send us a copy of the patient's medical records pertaining to PD diagnosis. The medical records were subsequently reviewed by a movement disorder specialist (XH). The self-reported diagnosis was considered valid if: 1) the treating neurologist confirmed the diagnosis; or 2) if the medical record included a final PD diagnosis or evidence of two or more cardinal signs of PD (with one being rest tremor or bradykinesia), a progressive course, responsiveness to dopaminergic treatments, and absence of features that suggested an alternative diagnosis. Overall, of the 1,069 physician responses received for the entire cohort, 940 (87.9%) PD diagnoses were confirmed.

Statistical analysis

We estimated multivariate odds ratios (OR) and 95% confidence intervals (CI) from unconditional logistic regression models. Linear trend tests were conducted by modeling categorical values as ordinal terms. Some categories were combined in the tables to preserve the stability of the OR estimates. All models were adjusted for age in years at baseline, race (whites vs. non-whites), smoking status (never smokers, past smokers [years since quitting: ≥35, 30–34, 20–29, 10–19, 1–9], and current smokers [cigarettes per day: 1–10, 11–20, >20]), and caffeine intake (quintiles). In addition to examining all reproductive and hormonal factors individually in separate models, we also ran models where they were mutually adjusted for each other.

Our analysis was carried out in two parts. First, all exposure variables of interest collected at the baseline questionnaire, except for type of menopausal hormone therapy, were evaluated. This analysis included 119,166 women among whom 410 had a diagnosis of PD. In the second portion of the analysis, detailed information regarding type of menopausal hormone therapy use was examined. This analysis was based on a subset of 84,834 postmenopausal women (287 cases) who responded to the second questionnaire. In this latter analysis, we used women who reported not using menopausal hormone therapy as the reference group. For menopausal hormone use, we conducted additional sensitivity analyses by restricting to PD participants diagnosed after the year 2000 (278 cases) to examine the possibility that lifestyle change before or around PD diagnosis might have affected the analysis (i.e. reverse causality). All statistical analyses were conducted using SAS, version 9.1 (SAS Institute Inc., Cary, NC). Significance tests were 2-tailed with $\alpha = 0.05$.

Standard protocol approvals, registrations, and patient consents

Participants consented to the study by returning survey questionnaires. The study protocol was approved by the Institutional Review Board of the National Institute of Environmental

Health Sciences and the Special Studies Institutional Review Board of the National Cancer Institute.

RESULTS

Baseline characteristics of the study population according to PD diagnosis are presented in Table 1. Compared with those without PD, PD cases were older at baseline, were more likely to be non-Hispanic white, were less likely to be past or current smokers, and had lower caffeine intake.

Risk of PD was not associated with age at menarche, parity, or age at first live birth (Table 2). Long-term oral contraceptive use was associated with a lower PD risk. Compared with never oral contraceptive use, the multivariate OR for ≥10 years of oral contraceptive use was 0.62 (95% CI, 0.40–0.96). Additional adjustments for other hormonal factors slightly strengthened the association, with a borderline significant trend test.

Type of menopause and ages at natural menopause or hysterectomy with bilateral oophorectomy were not significantly associated with risk of PD (Table 3). Women with natural menopause between ages 50–54 years was used as the reference category to compare effects associated with each of the other menopause categories; the reference age range was chosen as it represents when most women experience natural menopause. Younger age (<40 years) at hysterectomy not involving removal of both ovaries was associated with a slightly higher PD risk (OR=1.45, 95% CI 1.00–2.10), compared to women with natural menopause at ages 50–54 years. However, no significant trends were observed. Further, a history of bilateral oophorectomy alone was associated with a higher PD risk (OR=3.34, 95% CI 1.22–9.12), although this finding was based on a small number of cases (n=4). Additional sensitivity analysis was carried out comparing the surgical categories to a reference group of all women who reported a natural menopause, and results were essentially unchanged (data not shown).

Current menopausal hormone use at baseline was associated with a slightly higher risk of PD (Table 4). Compared with nonusers, the multivariate-adjusted OR of PD risk for current users was 1.29 (95% CI 1.03–1.61). When former or current hormone users were further classified according to duration of use (<5 years and ≥5 years), only current users of <5 years showed a higher risk of PD (OR=1.52, 95% CI 1.11–2.08). No associations were observed for past users or current users of ≥5years. In subgroup analyses, the association between menopausal hormone use and PD risk did not vary by type of menopause (data not shown). In further sensitivity analysis limited to PD cases after 2000, the OR for current users of <5 years reduced to 1.29 (0.87–1.92), suggesting possible reverse causality.

Further analyses on type of menopausal hormone therapy use and PD risk were based on the subset of postmenopausal women who completed the second questionnaire (Table 5). We found no evidence of an association with PD risk in the analyses of estrogen use only. However, in the analysis on estrogen plus progestin use, we observed a statistically significant higher PD risk for ever-use (OR=1.47, 95% CI 1.09–1.98), current use (OR=1.63, 95% CI 1.16–2.31) and a duration of use of <5 years (OR=1.53, 95% CI 1.05–

2.22). The strengths of these associations attenuated when we restricted the analysis to PD diagnosed after 2000, the OR decreased to 1.31 (95% CI 0.91–1.88) for ever-use of estrogen plus progestin, 1.45 (95% CI 0.94–2.23) for current estrogen plus progestin use, and 1.19 (95% CI 0.74–1.93) for estrogen plus progestin use of <5 years.

DISCUSSION

In this large prospective study of postmenopausal women, overall, we found little evidence for an association between reproductive factors or exogenous hormone use and PD risk. Contrary to most previous studies that reported no association,[12,13,16,17] in our data, long-term oral contraceptive use was associated with a lower risk of PD and current menopausal hormone therapy with a higher risk. However, the latter association was attenuated and became non-significant when cases were limited to those diagnosed after 2000, suggesting possible reverse causation.

Few epidemiologic studies have investigated hormonal and reproductive factors in relation to PD risk and results are mixed. Most studies reported null associations between age at menarche,[13,15,16,20] parity,[12–14,16,17] age at menopause,[13–18,20] or type of menopause[12,14–17] and risk of PD. One case-control study related hysterectomy to a higher risk of PD, [18] but another linked surgical menopause to a lower risk.[20] One population-based study reported a higher risk of parkinsonism and PD among women who underwent oophorectomy, although the association for PD alone did not reach statistical significance.[23] Our results on bilateral oophorectomy is in line with this finding, however, the analysis was based on a small number of cases and therefore should be interpreted with caution. Studies with other reproductive factors also generated inconsistent results. For example, lower levels of endogenous estrogen was suggested to be protective of PD in one study showing early age at final menstrual period (<44 years) to be associated with a 50% lower PD risk;[12] however, another study speculated the opposite: decline in endogenous estrogen levels during the perimenopausal period leads to the neurodegenerative process to PD.[20] In this latter study, a more than 2-fold higher PD risk was associated with a fertile life length (years between menarche and menopause) shorter than 36 years and having a cumulative length of pregnancy greater than 30 months.[20] A recent multicenter case-control study however, observed no association with either fertile life duration or cumulative duration of pregnancies and PD risk.[15]

Contrary to most previous studies that reported no association,[12,13,16,17] we observed that long-term oral contraceptive use was associated with a lower risk of PD. On the other hand, the Nurses' Health Study reported a higher PD risk with oral contraceptive use of more than 5 years.[14] Similar results were reported in a recent multicenter case-control study for oral contraceptive use of 6 months or longer.[15] Formulation and usage differences over time[24] might play a role in the discrepancies observed across studies with varying age groups of postmenopausal women.

Epidemiological data on menopausal hormone use and PD are also largely null [14–16,18–20] with few exceptions[13,17]. Interestingly, Popat et al.[12] reported that the association was dependent on type of menopause. For women who had hysterectomy with or without

oophorectomy, estrogen use was associated with a 2.6-fold increased risk, and the risk increased with increasing duration of estrogen use but was not influenced by recency. On the other hand, women with natural menopause who had used postmenopausal hormone for more than 10 years had a 60% reduced PD risk compared with never users. This reduction in risk however was only observed among women who had used hormone therapy within 5 years of reference date. The timing of estrogen treatment in relation to type or stage of menopause, referred to as the "timing hypothesis", has been suggested to be critical for evaluating potential effects of estrogen on cognitive decline and dementia.[25,26] In our study, although our results suggested a higher risk of PD with bilateral oophorectomy and hysterectomy alone at younger age, as well as current use of postmenopausal hormone less than 5 years, we lack data to fully investigate the timing hypothesis because we did not have information on age at hormone initiation relative to type or stage of menopause.

Within the subset of women who completed the second questionnaire, we observed a higher PD risk for current use of estrogen plus progestin, although there was no evidence of a trend with increasing years of use. We however could not rule out the possibility of chance or reverse causality, as indicated in our sensitivity analysis limited to PD cases diagnosed after 2000. Only one prior cohort study explored different types of postmenopausal hormone use in relation to PD risk[16] and found a 3-fold increased risk of PD with use of progestin-only hormones. However, their finding was based on a small number of cases. One experimental study supported the neuroprotective potential of progesterone,[27] however, depending on dose and method of infusion, progesterone can either enhance or inhibit dopaminergic activity.[28] Yet, synthetic progestin commonly found in postmenopausal hormones may not exert neuroprotective effect;[29] and estrogens plus progestin therapy have shown to reverse the positive effects of estrogen alone.[30]

Our study had a number of strengths compared to previous epidemiologic investigations. A key strength is the substantially larger sample size: we have nearly double the number of postmenopausal women with PD than the previous largest prospective epidemiologic study.[17] Other important strengths of the current study include the prospective study design and detailed statistical analyses accounting for various confounding variables such as smoking and caffeine intake.

Our study also had several limitations. First, all of the reproductive history and hormone use variables were based on self-report and therefore were subject to recall errors. Further, self-reported age at last menstrual period is not a precise assessment for menopausal age, although self-reported age at menopause has been positively associated with total and free serum estradiol concentrations.[31] This is particularly a concern for women who had hysterectomy without bilateral oopherorectomy. Second, misclassification with regard to type of menopause is possible since we did not collect information on the precise age at menopause and timing and indication for surgical menopause. Third, we lacked detailed information on age at initiation of hormone therapy in relation to type and stage of menopause. As these exposure data were collected years prior to outcome assessment, exposure misclassifications were likely to be non-differential with respect to the outcome and might have contributed to the null associations observed.

Another major limitation of the study is the fact that PD case identification was based on self-reports. It is inevitable that some cases were missed and some were misdiagnosed. However, our validation study validated 88% of self-reported diagnosis among those with medical information available and we excluded from the analysis cases with erroneous reports. This confirmation rate is comparable to other cohorts with similar case-confirmation protocol[32] and to a study in which detailed clinical examinations were carried out.[33] Diagnostic errors were also likely; however, in recent large clinicopathological studies, the accuracy of the clinical diagnosis of PD was found to be 90% or higher by neurologists or movement disorder specialists.[34,35] Finally, although our cohort was relatively large, we still had only modest numbers of PD cases in some analyses; this, together with potential measurement errors in exposure and outcome assessments, may have limited our ability to detect moderate associations.

In conclusion, overall, the results of our study do not support a major role of female hormonal and reproductive factors in PD risk. Although we observed that long-term oral contraceptive use and current postmenopausal hormone use are associated with risk of PD, these associations are not internally consistent and could be due to chance or reverse causality. Future large prospective studies are needed to clarify the roles of female reproductive and hormonal factors in PD etiology, preferably with more accurate assessments of age and type of menopause and the timing of hormone therapy. Future studies should also consider the complex interplay of environmental factors, genetic predisposition, and other sex hormones in addition to estrogen to disentangle the nature and biological mechanisms behind the gender difference in PD.

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TABLE 1

Selected baseline characteristics of postmenopausal women in the NIH-AARP Diet and Health Study according to Parkinson's disease diagnosis after 1995

	No PD	PD
N	118,756	410
Mean age in years (SD)	61.6 (5.2)	63.5 (5.0)
Caffeine intake (mg/day), Median (IQR)	210.7 (510.3)	120.8 (498.9)
Race, %		
Non-Hispanic Whites	91.0	93.2
Others	7.9	5.9
Smokers, %		
Never	46.5	55.9
Past	40.6	34.9
Current	12.0	8.8

Abbreviations: IQR = interquartile range (25%–75%); PD = Parkinson disease.

TABLE 2

Association between reproductive factors and Parkinson's disease among 119,166 postmenopausal women, NIH-AARP Diet and Health Study, 1995–2006

Characteristic	PD / No PD[a]	OR[b]	95% CI	OR[c]	95% CI
Age at menarche, y					
≤10	24/7,941	0.93	0.61–1.42	0.93	0.61–1.43
11–12	177/50,435	1.00	Referent	1.00	Referent
13–14	174/49,571	0.96	0.78–1.19	0.96	0.78–1.19
15+	35/10,534	0.91	0.64–1.31	0.91	0.63–1.31
P_{trend}		*0.736*		*0.738*	
Parity					
Nulliparous	63/18,261	1.00	Referent	1.00	Referent
1	35/12,005	0.87	0.57–1.31	0.88	0.58–1.33
2	102/31,160	0.94	0.68–1.28	0.95	0.69–1.31
3–4	168/43,950	1.04	0.77–1.39	1.06	0.79–1.42
5+	42/12,642	0.86	0.58–1.28	0.89	0.60–1.32
P_{trend}		*0.978*		*0.855*	
Age at first live birth, y					
Nulliparous	58/17,745	1.00	Referent	1.00	Referent
<20	61/18,757	1.04	0.73–1.50	0.95	0.66–1.37
20–24	176/51,679	0.97	0.72–1.30	0.93	0.69–1.26
30+	111/29,605	1.02	0.74–1.40	0.98	0.71–1.36
P_{trend}		*0.964*		*0.937*	
Duration of oral conceptive use, y					
Never	282/71,251	1.00	Referent	1.00	Referent
1–4	62/20,645	0.99	0.75–1.32	0.98	0.74–1.31
5–9	42/14,603	0.96	0.69–1.34	0.94	0.67–1.30
≥10	22/11,529	0.62	0.40–0.96	0.59	0.38–0.92
P_{trend}		*0.075*		*0.045*	

Abbreviations: CI = confidence interval; OR = odds ratio; PD = Parkinson disease.

[a] Numbers may not sum to total due to missing values.

[b] All adjusted for age (continuous), race, smoking and caffeine.

[c] Additionally adjusted for age at menopause, type of menopause, use of hormone therapy, and duration of oral contraceptive use, when applicable.

TABLE 3

Association between menopausal factors and Parkinson's disease among 119,166 postmenopausal women, NIH-AARP Diet and Health Study, 1995–2006

Characteristic	PD / No PD[a]	OR[b]	95% CI	OR[c]	95% CI
Type of menopause					
Natural	246/69,757	1.00	Referent	1.00	Referent
Surgery/radiation/chemo	164/48,999	0.98	0.80–1.19	0.83	0.64–1.08
Age at different types of menopause[d]					
Age at natural menopause					
<45	29/7,581	1.18	0.78–1.79	1.18	0.78–1.79
45–49	69/19,170	1.19	0.88–1.61	1.19	0.88–1.61
50–54	111/34,946	1.00	Referent	1.00	Referent
≥55	37/7,837	1.34	0.92–1.94	1.33	0.91–1.93
Age at surgically induced menopause, hysterectomy only					
<40	40/9,194	1.58	1.10–2.27	1.45	1.00–2.10
40–44	12/4,921	0.75	0.41–1.37	0.71	0.39–1.29
45–49	9/2,959	0.92	0.46–1.81	0.86	0.44–1.71
≥50	3/1,093	0.75	0.24–2.36	0.70	0.22–2.19
Age at surgically induced menopause, hysterectomy with bilateral oophorectomy					
<40	20/7,422	0.93	0.58–1.50	0.84	0.52–1.36
40–44	22/6,081	1.15	0.72–1.81	1.05	0.66–1.67
45–49	20/6,614	0.96	0.60–1.55	0.88	0.54–1.43
≥50	12/4,297	0.83	0.46–1.51	0.76	0.41–1.38
Bilateral oophorectomy only	4/353	3.48	1.28–9.52	3.34	1.22–9.12
Unknown type of menopause	22/5,887	1.23	0.77–1.94	1.16	0.73–1.84

Abbreviations: CI = confidence interval; OR = odds ratio; PD = Parkinson disease.

[a] Numbers may not sum to total due to missing values.

[b] All adjusted for age (continuous), race, smoking and caffeine.

[c] Additionally adjusted for use of hormone therapy and duration of oral contraceptive use.

[d] Natural menopause at ages 50–54 years was used as the reference group for both natural and surgically induced age at menopause.

TABLE 4

Association between menopausal hormone use and Parkinson's disease among 119,166 postmenopausal women, NIH-AARP Diet and Health Study, 1995–2006

Characteristic	PD / No PD[a]	OR[b]	95% CI	OR[c]	95% CI
Menopausal hormone use					
Never User	176/52,841	1.00	Referent	1.00	Referent
Former User	41/12,159	1.03	0.73–1.45	1.06	0.75–1.50
Current User	193/53,523	1.20	0.98–1.48	1.29	1.03–1.61
P_{trend}		*0.331*		*0.217*	
Recency and duration of menopausal hormone use					
Never	168/50,839	1.00	Referent	1.00	Referent
Past <5 years	25/8,537	0.94	0.62–1.43	0.96	0.63–1.47
Past ≥5 years	16/3,591	1.26	0.76–2.12	1.32	0.78–2.22
Current <5 years	55/14,850	1.47	1.07–2.01	1.52	1.11–2.08
Current ≥5 years	138/38,655	1.14	0.91–1.43	1.23	0.96–1.57
P_{trend}		*0.105*		*0.029*	

Abbreviations: CI = confidence interval; OR = odds ratio; PD = Parkinson disease.

[a] Numbers may not sum to total due to missing values.

[b] All adjusted for age (continuous), race, smoking and caffeine.

[c] Additionally adjusted for age at menopause, type of menopause, and duration of oral contraceptive use.

TABLE 5

Association between type of exogenous menopausal hormone therapy and Parkinson's disease among a subset of 84,834 postmenopausal women responded to the 1996–1997 risk factor survey, NIH-AARP Diet and Health Study, 1995–2006

Characteristic	PD / No PD[a]	OR[b]	95% CI	OR[c]	95% CI
N	287/84,547				
Menopausal hormone type					
No HT	95/31,364	1.00	Referent	1.00	Referent
Estrogen only	83/24,866	1.18	0.87–1.58	1.27	0.90–1.78
Estrogen/Progestin	91/24,529	1.44	1.07–1.93	1.47	1.09–1.98
Other/Unknown type	17/3,734	1.65	0.98–2.77	1.71	1.01–2.89
Recency of ET only use					
No HT	95/31,364	1.00	Referent	1.00	Referent
Former	16/6,723	0.79	0.47–1.35	0.81	0.47–1.41
Current	67/17,885	1.36	0.99–1.87	1.47	0.98–2.20
Duration of ET only use, y					
Never	95/31,364	1.00	Referent	1.00	Referent
1–9 years	34/12,222	1.07	0.72–1.58	1.10	0.72–1.68
≥10 years	47/12,269	1.25	0.88–1.78	1.31	0.84–2.05
Recency of EPT only use					
No HT	95/31,364	1.00	Referent	1.00	Referent
Former	28/9,722	1.07	0.70–1.64	1.10	0.71–1.70
Current	60/14,361	1.61	1.15–2.25	1.63	1.16–2.31
Duration of EPT use					
No HT	95/31,364	1.00	Referent	1.00	Referent
<5 years	43/11,502	1.50	1.04–2.18	1.53	1.05–2.22
5–9 years	19/6,605	1.15	0.69–1.89	1.14	0.69–1.89
≥10 years	24/5,514	1.39	0.88–2.19	1.42	0.89–2.25

Abbreviations: CI = confidence interval; ET = unopposed estrogen therapy; EPT = estrogen plus progestin therapy; HT = hormone therapy; OR = odds ratio; PD = Parkinson disease.

[a] Number may not sum to total due to use of other or unknown hormone therapy, and missing data.

[b] All adjusted for age (continuous), race, smoking and caffeine.

[c] Additionally adjusted for age at menopause, type of menopause, and duration of oral contraceptive use.