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Coffee Consumption, Gender, and Parkinson's Disease Mortality in the Cancer Prevention Study II Cohort: The Modifying Effects of Estrogen

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Caffeine consumption is associated with a reduced risk of Parkinson's disease in men but not in women. This gender difference may be due to an interaction between caffeine and use of postmenopausal estrogens. The authors prospectively assessed the relation between coffee consumption and Parkinson's disease mortality among participants in the Cancer Prevention Study II, a cohort of over 1 million people enrolled in 1982. Causes of deaths were ascertained through death certificates from January 1, 1989, through 1998. Parkinson's disease was listed as a cause of death in 909 men and 340 women. After adjustment for age, smoking, and alcohol intake, coffee consumption was inversely associated with Parkinson's disease mortality in men (p_{trend} = 0.01) but not in women (p = 0.6). In women, this association was dependent on postmenopausal estrogen use; the relative risk for women drinking 4 or more cups (600 ml) of coffee per day compared with nondrinkers was 0.47 (95% confidence interval: 0.27, 0.80; p = 0.006) among never users and 1.31 (95% confidence interval: 0.75, 2.30; p = 0.34) among users. These results suggest that caffeine reduces the risk of Parkinson's disease but that this hypothetical beneficial effect may be prevented by use of estrogen replacement therapy.

coffee; estrogens; mortality; Parkinson disease

Abbreviations: CI, confidence interval; RR, relative risk.

Studies in twins have provided strong evidence for an important role of environmental factors in the etiology of typical Parkinson's disease (1). In addition, a growing number of large epidemiologic investigations have identified cigarette smoking and coffee consumption as strong inverse predictors of Parkinson's disease (2). The adverse effects of cigarette smoking on health and the difficulty in determining whether nicotine or other tobacco chemicals may be potentially beneficial in preventing Parkinson's disease have tempered the enthusiasm for pursuing the investigation of the potential neuroprotective effects of tobacco. In contrast, the identification of caffeine as the explanatory molecule for the reduced risk of Parkinson's disease among coffee drinkers (3) and the parallel discovery that caffeine reduces the dopaminergic neurotoxicity in animal models of Parkinson's disease (4) appear promising. The central nervous system effects of caffeine are mediated primarily by its antagonistic actions at the A_1 and A_{2A} subtypes of adenosine receptors (5). The action of caffeine on A_{2A} receptors is more likely to be relevant to Parkinson's disease because expression of these receptors is restricted to the striatum, and because genetic inactivation of the A_{2A} receptors or selective A_{2A} antagonists, like caffeine, reduces the dopaminergic neurotoxicity in animal models of Parkinson's disease (4). Exactly how blockade of these receptors might protect dopaminergic neurons remains unknown (4).

An important caveat in the hypothesis that caffeine reduces the risk of Parkinson's disease is that, whereas the risk of Parkinson's disease is markedly reduced among men who regularly consume caffeine (3, 6), a similar association has not been found in prospective studies among women (3, 7). This gender difference could be explained if the effect of

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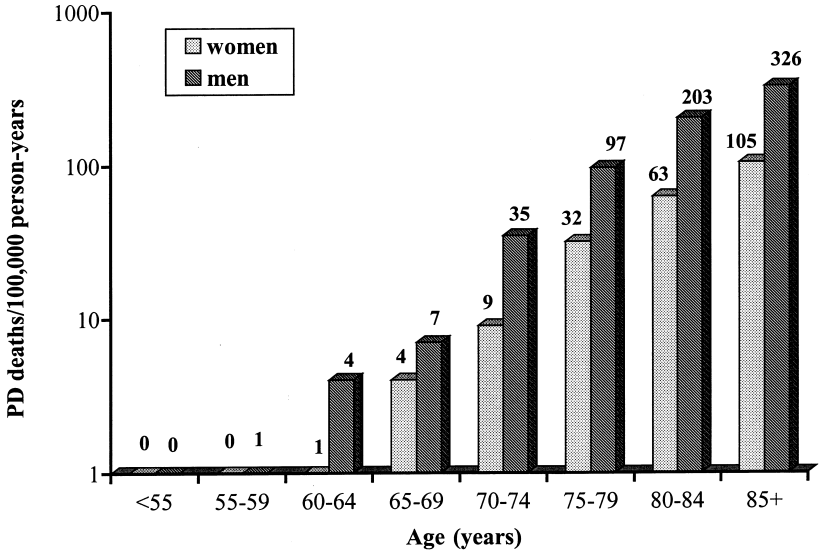

FIGURE 1. Parkinson's disease (PD) mortality rates by age and sex, Cancer Prevention Study II, 1982–1998.

caffeine on risk of Parkinson's disease depended on the level of estrogen. Consistently, in a large prospective investigation, we found that caffeine is associated with a reduced risk of Parkinson's disease among postmenopausal women who do not take estrogen replacement therapy but with an increased risk among estrogen users (8). The existence of an interaction between caffeine and estrogen in modulating the risk of Parkinson's disease could provide new clues on their possible mechanisms of action. Estrogen has potent but still incompletely understood effects on the nigrostriatal dopaminergic system (9, 10) and is a competitive inhibitor of caffeine metabolism (11). Further, the fact that both caffeine and estrogen are being considered as candidates in clinical trials among individuals with Parkinson's disease (12) gives to their potential interaction an immediate practical importance. We have therefore examined the relation between coffee intake and Parkinson's disease mortality in the Cancer Prevention Study II.

MATERIALS AND METHODS

Study population

The Cancer Prevention Study II, which began in 1982, is a prospective cohort study of nearly 1.2 million US men and women. Participants were recruited by American Cancer Society volunteers in 50 states, the District of Columbia, and Puerto Rico (13). Families with at least one member over the age of 45 years, and other family members over the age of 30 years, were invited to participate. The median age at cohort entry in 1982 was 57 years for men and 56 years for women. In total, 508,334 men and 676,288 women completed a four-page questionnaire. Because deaths from Parkinson's disease before 1989 were not coded separately, we included in the study only the 459,360 men and 639,366 women who were alive as of January 1, 1989. In the baseline self-administered questionnaire, participants were asked whether they had a diagnosis of selected diseases (not including Parkinson's disease), followed by a question on "any other serious illness." We excluded men and women who reported a history of stroke at baseline, because the diagnosis of Parkinson's disease may be difficult in patients with stroke, and also those who reported "any other serious illness" (about 11 percent of the cohort), because they may have had Parkinson's disease at the time of completing the baseline questionnaire. One or both exclusion criteria were met by 49,873 men and 70,840 women. Since our primary interest was the role of coffee consumption and reproductive variables, we further excluded 107,519 men and 180,578 women with missing coffee consumption; 807 men and 1,302 women who reported "occasional" coffee consumption (the lowest amount of coffee that participants were asked to report was 3 cups (450 ml) per week, all lower amounts being thus coded as "occasional use"); and women who were not postmenopausal (n = 122,788) or with missing information on use of estrogen replacement therapy (n = 25,616). On average, participants excluded a priori from the analyses because of missing values were 2 years older (68 vs. 66 years), less educated (18 percent college graduate vs. 25 percent), and more likely to be widows (20 percent vs. 15 percent) or Black (8 percent vs. 3 percent) than those retained in the analyses. These differences, however, are unlikely to bias the results of this prospective study. Thus, the final population for analyses included a total of 301,164 men and 238,058 women aged 30 or more years. The follow-up period extended from January 1, 1989, to December 31, 1998.

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TABLE 1. Selected characteristics of coffee drinkers and nondrinkers, Cancer Prevention Study II, 1982–1998

	Coffee consumption (cups*)					
	0	3–6/week	1/day	2–3/day	4–5/day	≥6/day
Men						
No.	38,788	19,778	42,996	111,647	52,754	3,501
Current smokers (%)	10	18	15	20	29	38
Past smokers (%)	26	28	31	32	30	25
Alcohol consumption (mean, g/day)	9.9	12.9	16.2	19	20	22.7
Body mass index (mean, kg/m^2)	25.9	26.1	26	26	25.9	25.9
Women						
No.	32,419	18,880	37,730	93,884	34,614	20,531
Current smokers (%)	13	17	13	21	31	39
Past smokers (%)	20	20	21	23	21	18
Alcohol consumption (mean, g/day)	4.4	6.1	8.1	10	10.1	10.7
Estrogen use						
Current (%)	14	12	13	13	11	11
Past (%)	26	26	25	26	26	25
Years of use (mean)	6.5	6.2	6.4	6.3	6	5.9
Oral contraceptive use (ever, %)	20	19	20	21	20	20
Menopause type						
Natural (%)	61.2	63	63.1	64.1	66.1	65.7
Surgical (%)	33.5	30	31.1	30.2	28.7	28.7
Unknown (%)	5.4	7	5.8	5.6	5.1	5.7
Age at natural menopause (years)	48.7	48.5	48.7	48.7	48.7	48.4
Body mass index (mean, kg/m^2)	24.9	25	24.8	24.5	24.3	24.3

* One cup = 150 ml.

Case ascertainment

Vital status of the study participants has been determined by automated linkage with the National Death Index through December 31, 1998 (14). Death certificates or codes for cause of death have been obtained for over 98 percent of known deaths. The underlying and contributing causes of death were coded from death certificates according to the *International Classification of Diseases*, Ninth Revision; all individuals with code 332.0 (idiopathic Parkinson's disease) listed as either the underlying or a contributing cause of death were considered as cases.

Assessment of exposure

Coffee drinking, cigarette smoking, and (in women) menopausal status, use of estrogen replacement therapy, and other reproductive variables were assessed in the baseline questionnaire in 1982. Separate questions were used to assess the usual consumption of caffeinated and decaffeinated coffee in cups usually consumed per day. Participants were also asked to report their consumptions of tea and sodas, but since no distinction was made between caffeinated and noncaffeinated products, we have not used these questions in the present analyses. Cigarette smoking status was ascertained by the question, "Do you now or have you ever smoked cigarettes, at least one a day for one year's time?" Ever smokers were then asked questions on the average number of cigarettes smoked per day, the age when they started smoking, and the total number of years they smoked. Reproductive history included questions on parity, current menopausal status, age at menopause, type of menopause (natural or surgical), and use and duration of use of oral contraceptives and estrogen replacement therapy.

Statistical analyses

Participants contributed follow-up time from January 1, 1989, to the date of death or December 31, 1998, whichever came first. Age-adjusted (in 5-year age groups) relative risks were calculated by dividing the death rate of Parkinson's disease among participants in each category of coffee drinking by the corresponding death rate in nondrinkers, using Mantel-Haenszel weights (15). Similar analyses were conducted for the other exposures of interest. We used Cox proportional hazards regression to estimate relative risks and 95 percent confidence intervals when adjusting for additional variables. To obtain a better age adjustment, we stratified the Cox models by age in single years. Significance of trends was assessed by including in the regression model the median coffee intake in cups per day as a continuous vari-

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TABLE 2. Relative risk of Parkinson's disease mortality by coffee intake at baseline, Cancer Prevention Study II, 1982–1998

Variables	Men				Women			
	No. of person-years	No. of cases	Relative risk*,†	95% confidence interval	No. of person-years	No. of cases	Relative risk*,†	95% confidence interval
All subjects								
Regular coffee								
0 cups‡	337,353	172	1.0	Referent	286,366	62	1.0	Referent
3–6 cups/week	170,459	65	0.66	0.49, 0.88	167,221	29	0.78	0.49, 1.22
1 cup/day	368,028	166	0.75	0.60, 0.93	330,789	69	0.81	0.57, 1.16
2–3 cups/day	968,880	342	0.73	0.60, 0.89	837,013	126	0.77	0.56, 1.07
4–5 cups/day	462,124	105	0.68	0.52, 0.87	310,928	31	0.69	0.44, 1.08
≥6 cups/day	304,375	59	0.63	0.46, 0.86	182,957	23	0.90	0.55, 1.48
p_{trend}			0.011				0.57	
p_{trend}§			0.26				0.91	
Never smokers								
Regular coffee								
0 cups	157,108	100	1.0	Referent	180,981	47	1.0	Referent
3–6 cups/week	55,452	25	0.55	0.35, 0.86	95,704	18	0.61	0.35, 1.07
1 cup/day	116,494	56	0.55	0.41, 0.83	201,885	46	0.67	0.44, 1.04
2–3 cups/day	229,487	83	0.52	0.38, 0.71	430,030	85	0.73	0.50, 1.08
4–5 cups/day	75,219	27	0.70	0.45, 1.10	131,721	15	0.52	0.28, 0.94
≥6 cups/day	36,072	7	0.34	0.16, 0.75	65,474	17	1.09	0.61, 1.93
p_{trend}			0.0067				0.87	
p_{trend}§			0.63				0.25	

* Relative risk for all subjects adjusted for age, smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day), and alcohol (0, <5, 5–<15, 15–<30, ≥30 g).

† Relative risk for never smokers adjusted for age and alcohol (0, <5, 5–<15, 15–<30, ≥30 g).

‡ One cup = 150 ml.

§ p_{trend} excluding noncoffee drinkers.

able. Interactions were entered as multiplicative terms in the Cox models, and their significance was ascertained on the basis of the Wald test or the likelihood ratio test. SAS version 8.2 software (SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

RESULTS

During the follow-up, 60,631 men and 37,486 women died from any cause. Parkinson's disease was listed as an underlying or contributory cause of death in 909 (1.5 percent of all deaths) men and 340 (0.91 percent) women. As expected, Parkinson's disease mortality was higher in men than in women, and it increased with age (figure 1). Further, in both men and women, we confirmed the previous finding that cigarette smokers have a lower Parkinson's disease risk than do never smokers. The relative risks of Parkinson's disease death were 0.79 in men (95 percent confidence interval (CI): 0.67, 0.93) and 0.90 in women (95 percent CI: 0.68, 1.18) for past smokers and 0.69 in men (95 percent CI: 0.54, 0.87) and 0.60 in women (95 percent CI: 0.41, 0.88) for current smokers. Coffee consumption was associated with cigarette smoking and alcohol consumption (in men and women) but not with use of postmenopausal estrogen or other reproductive factors (table 1) or with education, race, or marital status (data not shown).

Men who regularly drank caffeinated coffee had a significantly lower risk of Parkinson's disease death than did noncoffee drinkers (table 2). Although the overall test for linear trend was significant (p = 0.011), there was no evidence of dose response; the reduction in risk was similar in men who consumed 3–6 cups (1 cup = 150 ml) per week (relative risk (RR) = 0.66, 95 percent CI: 0.49, 0.88) and in men who consumed 6 or more cups per day (RR = 0.63, 95 percent CI: 0.46, 0.86). To eliminate possible residual confounding by cigarette smoking, we repeated the analyses among men who never smoked. The results were similar. In contrast, we found no significant association between intake of caffeinated coffee and risk of Parkinson's disease death among women (table 2). No relation in either men or women was present between consumption of decaffeinated coffee and Parkinson's disease death (data not shown).

To examine whether the difference in the results obtained in men and women could be attributed to use of postmeno-

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TABLE 3. Relative risk of Parkinson's disease by coffee intake stratified across estrogen use, Cancer Prevention Study II, 1982–1998

Variables	Estrogen use							
	Never (n = 169)				Ever (n = 171)			
	No. of person-years	No. of cases	Relative risk*	95% confidence interval	No. of person-years	No. of cases	Relative risk*	95% confidence interval
Regular coffee								
0 cups†	148,066	39	1.0	Referent	138,300	23	1.0	Referent
3–6 cups/week	88,413	11	0.42	0.21, 0.84	78,808	18	1.43	0.76, 2.67
1 cup/day	175,319	30	0.50	0.30, 0.83	155,470	39	1.37	0.81, 2.34
2 cups/day	254,270	40	0.59	0.37, 0.94	241,362	41	1.08	0.64, 1.84
3 cups/day	180,404	26	0.62	0.37, 1.05	160,976	19	0.92	0.49, 1.71
≥4 cups/day	271,056	23	0.47	0.27, 0.80	222,829	31	1.31	0.75, 2.30
p_{trend}			0.11				0.93	
$p_{interaction}$‡							0.20	
Any amount	969,462	130	0.53	0.36, 0.79	859,445	148	1.21	0.76, 1.91
$p_{interaction}$§							0.02	

* Adjusted for age, smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day), and alcohol (0, <5, 5–<15, 15–<30, ≥30 g).
† One cup = 150 ml.
‡ Interaction is the product of coffee intake (cups per day) and estrogen use (never/ever coded as 0, 1).
§ Interaction is the product of coffee drinker (no/yes coded as 0, 1) and estrogen use (never/ever coded as 0, 1).

pausal estrogens, we compared the association between consumption of caffeinated coffee and Parkinson's disease mortality in women who did or did not use these hormones (table 3). Among women who never used estrogens, the risk of Parkinson's disease death was lower in women who habitually drank caffeinated coffee than in never drinkers. As in men, a significantly reduced risk was already present for women consuming 3–6 cups of coffee per week (RR = 0.42, 95 percent CI: 0.21, 0.84), and no further reduction was associated with increasing amounts (4 or more cups per day: RR = 0.47, 95 percent CI: 0.27, 0.80). Because of the lack of a dose response, the overall trend was not significant (p = 0.11), but a highly significant difference in risk was evident when comparing women drinking 3 or more cups of coffee per week with noncoffee drinkers (RR = 0.53, 95 percent CI: 0.36, 0.79; p = 0.004). In contrast, among women who ever used postmenopausal estrogen, there was no relation between consumption of caffeinated coffee and Parkinson's disease mortality (table 3). The test of interaction between coffee consumption in cups per day and use of estrogens (ever vs. never) was not significant; however, a significant interaction was found between regular consumption of caffeinated coffee (drinkers vs. nondrinkers) and use of estrogens (p = 0.022). The results were not materially changed by further adjustment for type of menopause, and no significant interaction was observed between type of menopause and coffee intake. The association between coffee consumption and Parkinson's disease risk was similar among women who were former users of postmenopausal estrogen (4 or more cups per day vs. none: RR = 1.27, 95 percent CI: 0.61, 2.62) or current users (RR = 1.36, 95 percent CI: 0.34, 5.50) and did not vary significantly with duration of estrogen use, but the power of this analysis was too low to exclude a potentially important interaction. Since body mass index is also related to hormonal status in postmenopausal women, we also examined the interaction between body mass index and coffee consumption (drinkers vs. nondrinkers); no significant interaction was found (p = 0.75).

Without coffee consumption, use of postmenopausal estrogens was associated with a higher risk of death from Parkinson's disease; the multivariate relative risk comparing ever users and never users was 1.33 (95 percent CI: 1.07, 1.67) (table 4). Except for an elevated risk in women whose menopause was not identified as either natural or surgical, other reproductive variables were not significantly associated with risk of Parkinson's disease (table 4). The estimated combined effect of coffee intake and estrogens on risk of Parkinson's disease death is shown in figure 2 using women who did not drink coffee and never used estrogens as the referent.

DISCUSSION

In this large cohort, we found that consumption of caffeinated coffee was associated with a reduced Parkinson's disease mortality among men and among women who never used postmenopausal estrogens. In contrast, Parkinson's disease mortality was independent of coffee consumption among women who used estrogens. These results are consistent with those obtained in incidence studies of Parkinson's disease (3, 6, 8) and support the hypothesis that postmeno-

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TABLE 4. Relative risk of Parkinson's disease mortality by estrogen use and other reproductive variables, Cancer Prevention Study II, 1982–1998

Variables	No. of person-years	No. of cases	Age- and smoking-adjusted relative risk	95% confidence interval	Multivariate relative risk*	95% confidence interval
Estrogen use						
Never user	1,117,528	169	1.0	Referent	1.0	Referent
Ever user	997,746	171	1.40	1.13, 1.73	1.33	1.07, 1.67
Duration of estrogen use†						
Never user	1,117,528	169	1.0	Referent	1.0	Referent
<5 years	439,113	60	1.25	0.93, 1.68	1.20	0.89, 1.62
≥5 years	382,011	70	1.41	1.07, 1.87	1.32	0.99, 1.78
Duration of oral contraception use†						
Never user	1,632,569	314	1.0	Referent	1.0	Referent
<5 years	233,531	4	0.50	0.19, 1.30	0.45	0.16, 1.22
≥5 years	188,213	10	1.48	0.78, 2.81	1.43	0.74, 2.76
Type of menopause						
Natural	1,342,478	233	1.0	Referent	1.0	Referent
Surgical	652,903	80	1.18	0.91, 1.52	1.13	0.81, 1.58
Unknown	119,893	27	1.64	1.10, 2.45	1.82	1.16, 2.86
Age (years) at natural menopause†						
<45	171,630	30	1.0	Referent	1.0	Referent
45–49	461,329	68	0.91	0.59, 1.40	0.92	0.60, 1.41
50–54	570,057	103	1.02	0.68, 1.53	1.02	0.68, 1.54
≥55	139,461	32	0.93	0.57, 1.53	0.91	0.55, 1.51
Parity†						
≤1	471,176	107	1.0	Referent	1.0	Referent
2–3	1,053,602	172	1.08	0.85, 1.38	1.07	0.83, 1.36
≥4	541,093	55	0.85	0.61, 1.19	0.84	0.60, 1.16

* Adjusted for age (5-year groups), smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day), alcohol (0, <5, 5–<15, 15–<30, ≥30 g), cups of coffee, estrogen use (ever/never), oral contraceptive use (ever/never), age at menopause, type of menopause, and parity.

† Number of cases does not add up to total because of missing values. Age at natural menopause was coded as missing for women who underwent hysterectomy.

pausal estrogens modify the effects of caffeine on risk of Parkinson's disease. Interestingly, in both men and in women not using postmenopausal estrogens, a significant reduction in risk of Parkinson's disease was already present at low levels of coffee consumption (3–6 cups per week), and little further reduction was apparent with increasing amounts of coffee. In our previous study, we also found a markedly reduced risk of Parkinson's disease among men who consumed small amounts of caffeine and no convincing evidence of further reductions above levels corresponding to 1 cup (150 ml) of coffee per day (3). On the other hand, in the Honolulu cohort, there was a clear progressive reduction in risk of Parkinson's disease with increasing levels of coffee consumption up to several cups per day (6). The inconsistency may be due to the moderate power of each study and the errors in measuring caffeine consumption that may originate from changes in coffee consumption during the follow-up, lack of information on caffeine intake from other sources, and, most importantly, differences in coffee strength. Because of severalfold variations in the amount of caffeine per cup of coffee (16), individuals who drink small amounts of strong coffee may ingest as much caffeine as those who drink large amounts of diluted coffee. On the other hand, if real, the lack of dose response would suggest that low doses of caffeine already provide the full biologic benefits (threshold effect). An alternative explanation is that the inverse relation between caffeine consumption and Parkinson's disease risk does not reflect a causal effect of caffeine but, rather, a shared cause between aversion to caffeine (as well as smoking and other addicting behaviors) and Parkinson's disease (4).

The main limitations of the present study include the absence of information on Parkinson's disease diagnoses among surviving participants and on changes in coffee consumption or estrogen use during the follow-up. Because cases of Parkinson's disease were detected only after death,

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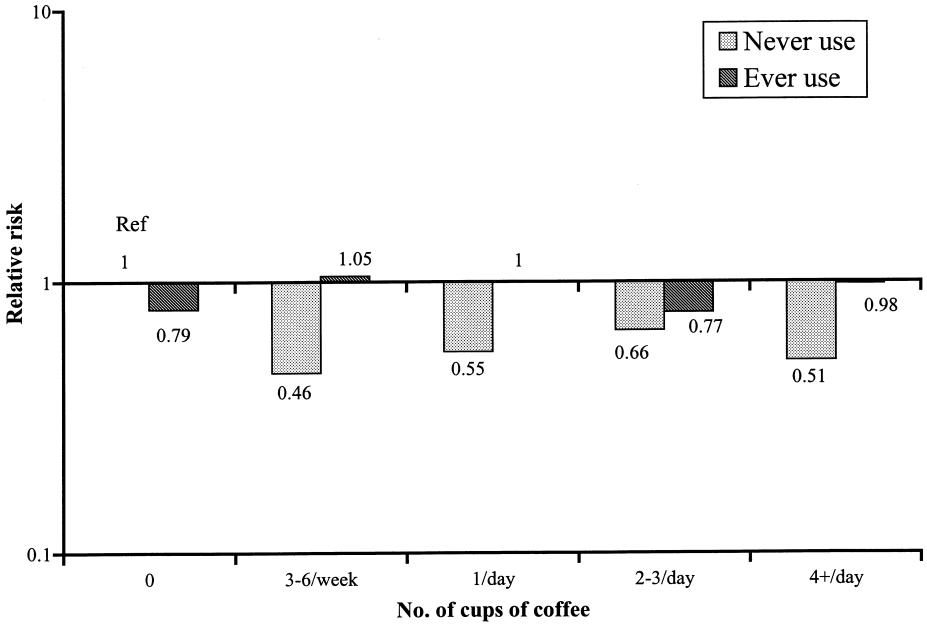

FIGURE 2. Age- and smoking-adjusted relative risk of Parkinson's disease mortality by coffee intake and estrogen use, Cancer Prevention Study II, 1982–1998. The number of cases of Parkinson's disease by coffee intake in cups (0, 3–6/week, 1/day, 2–3/day, and ≥4/day) and estrogen use is as follows: never use (39, 11, 30, 66, and 23 cases); ever use (23, 18, 39, 60, and 31 cases). One cup = 150 ml. Ref, referent.

the estimated relative risks reflect the effects of coffee or postmenopausal estrogens on both the incidence of Parkinson's disease and the survival time after the diagnosis, rather than on incidence alone. Reporting of Parkinson's disease in death certificates is known to be incomplete, approximately 70–75 percent according to previous studies (17, 18). Underreporting of Parkinson's disease, however, would bias the relative risk estimates only if the probability that Parkinson's disease is diagnosed and reported in the death certificate was related to the exposure of interest. For example, an artifactually reduced risk of Parkinson's disease death among men who drink coffee would occur if coffee drinkers with Parkinson's disease were less likely to have this diagnosis in their death certificates than were nondrinkers. This possibility seems unlikely, because factors that could affect the accuracy of death certificates were either included in the regression models (age and smoking) or were independent from coffee consumption (education and marital status). A hypothetical bias due to underreporting of Parkinson's disease is even less likely to explain the presence of an inverse association between coffee drinking and Parkinson's disease mortality among men and women who never used estrogens but not among estrogen users. The lack of updated information on coffee consumption and hormone use during the follow-up is likely to cause some attenuation of the estimated relative risks. For coffee consumption, this is likely to be modest as, in previous prospective studies, strong inverse associations were found in men between baseline coffee consumption and risk of Parkinson's disease over periods of 10 (3) or 30 years (6). An additional potential source of error is that information on caffeine from sources other than coffee was not available. However, since coffee in the United States typically contributes over 80 percent of total caffeine intake, this error is likely to be modest (3). The effect of misclassification of estrogen use, on the other hand, could be more substantial, because many women classified as estrogen users may in fact have suspended use soon after enrollment. Errors in reporting age at menopause and type of menopause may also have attenuated possible associations with these factors. It should also be noted that, because of the smaller number of Parkinson's disease deaths, the study had less power to detect significant associations in women than in men. Thus, overall Parkinson's disease mortality was lower among women who consumed coffee than among noncoffee drinkers, but this association was not significant because of the moderate sample size. Finally, there is no explanation for the elevated risk of Parkinson's disease among women whose menopause was not identified as either natural or surgical, which may be due to chance.

The potential connection between estrogen and Parkinson's disease has recently been reviewed (9). Experimental data indicate that estrogen modulates the nigrostriatal dopaminergic system and has neuroprotective, antioxidant, or neurotrophic effects, but the results are often conflicting (9). Interestingly, in recent experiments in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, pretreatment with caffeine significantly attenuated striatal dopamine depletion in placebo-treated, but not estrogen-treated, ovariectomized female mice (19). Although the mechanisms of this interaction remain unknown, this result suggests that estrogen modifies the effects of caffeine in a

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manner consistent with our epidemiologic results. Whether use of estrogen may be clinically useful in women with Parkinson's disease (9, 20) or in Parkinson's disease prevention also remains uncertain. A nonsignificant inverse association with Parkinson's disease risk has been found in a case-control study (21), but no association was found in two others (22, 23) or in the only previous prospective study (8).

In summary, in this large prospective investigation, we found that consumption of caffeinated coffee is inversely associated with Parkinson's disease mortality in men and in women who do not use postmenopausal estrogens, but not among estrogen users. As discussed previously (8), this result indirectly supports a neuroprotective effect of caffeine and suggests that it may be important to investigate the mechanisms of a possible interaction between estrogen and caffeine in the etiology of Parkinson's disease. Meanwhile, this potential interaction should be considered in the design of randomized trials assessing the effects of caffeine or estrogen in the progression of Parkinson's disease.

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