Nonsteroidal Anti-inflammatory Drugs and the Risk of Parkinson Disease

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce dopaminergic neuron degeneration in animal models of Parkinson disease (PD). However, no epidemiological data have been available on NSAID use and the risk of PD.

Objective: To investigate prospectively whether the use of nonaspirin NSAIDs or aspirin is associated with decreased PD risk.


Main Outcome Measure: Newly diagnosed PD.

Results: We documented 415 incident PD cases (236 men and 179 women). Participants who reported regular use of nonaspirin NSAIDs at the beginning of the study had a lower risk of PD than nonregular users during the follow-up; the pooled multivariate relative risk was 0.55 (95% confidence interval, 0.32-0.96, \( P = .04 \)). Compared with nonusers, a nonsignificantly lower risk of PD was also observed among men and women who took 2 or more tablets of aspirin per day (relative risk, 0.56; 95% confidence interval, 0.26-1.21).

Conclusion: These findings are consistent with the hypothesis that use of NSAIDs may delay or prevent the onset of PD.

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Nonaspirin NSAIDs was first collected in 1986 among men and in 1980 among women. The present investigation was restricted to men and women who provided baseline information on the use of aspirin or nonaspirin NSAIDs and who were free of PD, stroke, or cancer (other than nonmelanoma skin cancer) at that time. We followed up 4,057 eligible men and 98,845 women from baseline to the date when the first symptom of PD was reported, the date of death or stroke, or the end of the follow-up (January 31, 2000, for men and May 31, 1998, for women), whichever occurred first. These studies were approved by the human subjects research committees at the Harvard School of Public Health and the Brigham and Women’s Hospital.

CASE ASCERTAINMENT

Parkinson disease ascertainment in these cohorts has been previously described. Briefly, after obtaining permission from participants who reported a new diagnosis of PD, we asked the treating neurologist (or internist if the neurologist did not respond) to complete a questionnaire to confirm the PD diagnosis and the certainty of the diagnosis, or to send a copy of the medical record. A case was confirmed if the diagnosis was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of PD made by a neurologist, or evidence at a neurological examination of at least 2 of the 3 cardinal signs (rest tremor, rigidity, or bradykinesia) in the absence of features suggesting other diagnoses. The review of medical records was conducted by us, blinded to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in 82.3% of the cases, by review of the medical records in 3.1%, and by the treating internist in 14.6%.

NSAID USE

Participants in the Health Professionals Follow-up Study were asked whether they took nonaspirin NSAIDs (eg, Motrin [ibuprofen], Indocin [indomethacin], Naprosyn [naproxen], or Dolobid [diflunisal]) 2 or more times per week in 1986, 1988, 1990, 1992, and 1994. Although questions on the use of ibuprofen (eg, Motrin and Advil) were asked separately from other NSAID use in 1996 and 1998, we included users of ibuprofen as nonaspirin NSAID users for consistency with previous years. No information on the dosage of nonaspirin NSAID was collected in men. In the Nurses’ Health Study, participants were asked in 1980 whether they were currently taking nonsteroidal analgesics other than aspirin (Motrin, Indocin, Tolectin [tolmetin sodium], or Clinoril [sulindac]) in most weeks. Users were furthermore asked how many years they had taken the drugs and the numbers of tablets per week. Questions about nonaspirin NSAID use were not re-asked until 1990. In 1990 and 1992, participants were asked to report the frequency of nonaspirin NSAID use as 0, 1-4, 5-14, 15-21, or 22 or more days per month. In 1994 and 1996, questions on regular use (≥2 times per week) of nonaspirin NSAIDs were asked in the same way as in men.

Men were asked about regular use (≥2 times per week) of aspirin (eg, Anacin, Bufferin, or Alka-Seltzer) in 1986, 1988, 1990, 1992, and 1994. Questions were added in 1992 to collect information on the frequency and amount of use: “On average, how many days each month do you take aspirin (0, 1-4, 5-14, 15-21, or ≥22 days)?” and “On days that you take aspirin, how many do you usually take (0, <1 [eg, baby aspirin], 1, 2, 3-4, 5-6, or ≥7 tablets)?” Similar questions were included in the 1994, 1996, and 1998 questionnaires. Among women, questions on use of aspirin (including Bufferin, Anacin, etc, but not Tylenol [acetaminophen] or other aspirin-free products) were asked in 1980, 1982, 1984, 1988, 1990, 1992, 1994, and 1996. In 1980, women were asked to report current use of aspirin, the duration of use, and the number of tablets per week. In 1982, the participants were asked if they took aspirin at least once per week and, if so, the total amount of aspirin use per week (1-3, 4-6, 7-14, or ≥15 tablets), whereas in 1984, questions about the frequency and amount of aspirin use were separated in the same way as in men in 1992. Similar questions were used in the 1988, 1990, 1992, 1994, and 1996 questionnaires.

As with nonaspirin NSAIDs, information on regular acetaminophen use (eg, Tylenol) was collected among men in 1986 and thereafter every 2 years. In women, acetaminophen use was not asked about until 1990 and was re-asked thereafter in the following years along with questions about use of nonaspirin NSAIDs and aspirin.

A brief questionnaire was sent to 211 aspirin users in the Health Professionals Follow-up Study in 1993 to elicit their reasons for aspirin use. Eighty-eight percent of the participants returned the questionnaire and listed 1 or more of the following reasons for aspirin use: cardiovascular diseases (25.4%), to decrease the risk of cardiovascular diseases (58.4%), headaches (25.4%), joint or musculoskeletal pain (33.0%), and other reasons (7.0%). Similar reasons for aspirin use were reported in a survey in 1990 among 100 participants of the Nurses’ Health Study who reported taking 1 to 6 aspirins per week (90% response rate) and 100 women who reported taking 7 or more aspirins per week (92% response rate) on the 1980, 1982, and 1984 questionnaires. We did not ask the reasons for taking nonaspirin NSAIDs in either cohort. However, questions about the lifetime occurrences of rheumatoid arthritis, other arthritides, and gout were asked in men in 1986 and in women in 1982. Among men who took nonaspirin NSAIDs regularly in 1986, 12.9% reported having rheumatoid arthritis, 40.9% reported other arthritides, and 13.6% reported gout; in women, the corresponding proportions were 18.8%, 55.7%, and 4.7%.

STATISTICAL ANALYSIS

All statistical analyses were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC). Relative risks (RRs) and 95% confidence intervals (CIs) were calculated by dividing the incidence rate of PD in each exposure category by the corresponding rate in the reference category, adjusting for baseline age (3-year category) and smoking status (never, past, or current [1-14 or ≥15 cigarettes per day]) using the Mantel-Haenszel method. Multivariate RRs were calculated using Cox proportional hazards analysis, adjusting for age (in years), smoking status, caffeine intake (quintiles), and alcohol consumption (men, 0, 1-9, 10-19, 20-29, or ≥30 g/d; and women, 0, 1-4, 5-9, 10-14, or ≥15 g/d). Log RRs from the 2 cohorts were pooled by the inverse of their variances with the fixed-effects model, because none of the heterogeneity test results were statistically significant. All P values were 2-sided (α = 0.05).

For nonaspirin NSAIDs, regular use at baseline (defined as ≥2 times per week in men and as ≥2 tablets per week in women) was considered as the primary exposure, because this definition could be most consistently applied in both cohorts. Further analysis was conducted in men to relate the duration of regular use to PD risk. Duration of use was computed from the answers to the questions on nonaspirin NSAID use in each questionnaire and added as a time-dependent variable in the Cox proportional hazards model. This analysis could not be conducted in women because of the 10-year gap in the assessment of the use of nonaspirin NSAIDs between 1980 and 1990. For aspirin, men and women were defined as regular users or nonregular users at baseline, as was done for nonaspirin NSAIDs. We further estimated the association between the amount of aspirin use and the risk of PD. In men, information on dosage of aspirin was first collected in 1992; therefore, in this analysis...
the date of return of the 1992 questionnaire was used as the baseline. In women, we averaged the amount of aspirin use reported in 1980, 1982, and 1984 to get a stable estimate of the dosage of aspirin, and 1984 was used as the baseline. Nonaspirin NSAID users were excluded from the analyses for aspirin dosage. Finally, we calculated the updated duration of aspirin use in men and women and included it in the Cox proportional hazards models as a time-dependent variable. In men, duration was defined as years of regular use after 1986, because information before enrollment was not collected; in women, it was calculated as duration before enrollment in the study plus years of regular use after 1980.

To address the possibility that use of NSAIDs was caused by the early symptoms of PD, we also analyzed the data by excluding the first 4 years of follow-up. Similar analyses were conducted for dosage of aspirin, but excluding only the first 2 years of follow-up, as aspirin dosage was not collected until 1992 in men. Duration was defined as years of regular use after 1986, because information before enrollment was not collected; in women, it was calculated as duration before enrollment in the study plus years of regular use after 1980.

To address the possibility that use of NSAIDs was caused by the early symptoms of PD, we also analyzed the data by excluding the first 4 years of follow-up. Similar analyses were conducted for dosage of aspirin, but excluding only the first 2 years of follow-up, as aspirin dosage was not collected until 1992 in men. Moreover, because NSAID use has been shown to be protective in Alzheimer disease, we repeated the main analyses by excluding participants with PD in whom dementia was reported during the follow-up.

### RESULTS

Regular use of nonaspirin NSAIDs was reported by 6.1% of men and 3.7% of women. Users and nonusers were similar in terms of smoking status, caffeine intake, and alcohol consumption, except for a slightly higher proportion of past smokers and higher caffeine intake among men taking nonaspirin NSAIDs (Table 1). Use of aspirin tended to be weakly positively related to cigarette smoking, caffeine intake, and alcohol consumption in men, and to caffeine intake in women.

During the follow-up, 415 incident PD cases (236 men and 179 women) were identified. In both cohorts, regular use of nonaspirin NSAIDs at baseline was associated with a lower risk of PD (men: RR, 0.60; and women: RR, 0.46) (Table 2) compared with nonregular users; the association was statistically significant when the results from men and women were pooled (RR, 0.55; 95% CI, 0.32-0.96; P = .04). Additional adjustments for self-reported rheumatoid arthritis, other arthritis, and gout made the results slightly stronger (pooled RR, 0.50; 95% CI, 0.29-0.89; P = .02). This inverse association remained even when we excluded the first 4 years of follow-up (pooled RR, 0.49; 95% CI, 0.26-0.92) or the 33 participants with PD and dementia (pooled RR, 0.61; 95% CI, 0.35-1.06). Also, the risk of developing PD tended to decrease with increasing duration of regular use of nonaspirin NSAIDs. Among men, compared with never users, the RRs for those who had taken nonaspirin NSAIDs for 1 to 2, 3 to 4, and 5 or more years were 1.10, 0.95, and 0.59, respectively (P = .40 for trend) (Table 2). According to the information collected in 1980 among women, the RRs associated with years of past use of nonaspirin NSAIDs were 1.00 (referent) for nonusers, 0.65 (95% CI, 0.21-2.04) for less than 1 year of use, and 0.25 (95% CI, 0.04-1.78) for more than 1 year of use (P = .10 for trend).

Unlike nonaspirin NSAIDs, baseline regular aspirin use was not related to PD risk (Table 3). In men and women, the RRs for regular aspirin use were 1.28 (95% CI, 0.79-2.09) for men and 0.88 (95% CI, 0.50-1.54) for women. The results remained similar when we excluded the first 4 years of follow-up (pooled RR, 1.24; 95% CI, 0.73-2.12) or the participants with PD and dementia (pooled RR, 1.18; 95% CI, 0.63-2.21).

*Table 1. Characteristics of Subjects*

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*Means and proportions were directly standardized to the age distribution of each cohort; numbers may not add up to total because of missing values.
† Regular use was defined as ≥2 times per week for men and ≥2 tablets per week for women.
‡ Dosage in 1992 was used for men, and the average dosage from 1980 to 1984 was used for women; caffeine intake reported in 1990 was used for men as dietary data were not available in 1992.

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women, compared with nonregular users, the multivariate RR for aspirin users was 1.13. Duration of aspirin use was not significantly associated with PD risk in men or women. However, in men and women, taking 2 or more tablets of aspirin per day was associated with a lower risk of PD (compared with nonusers, pooled RR.
0.56; \( P = .07 \) for trend). Adding self-reported rheumatoid arthritis, other arthritis, and gout in the Cox proportional hazards models had minimal effect on the results (pooled RR, 0.58; 95% CI, 0.26-1.28). The pooled RR was 0.52 (95% CI, 0.21-1.25) in the 2-year lag analyses and became more pronounced when 18 participants with dementia were excluded (pooled RR, 0.43; 95% CI, 0.18-1.03).

No significant association was found between acetaminophen use and the risk of PD in either cohort. Regular use (\( \geq 2 \) times per week) of acetaminophen in men was associated with a RR of 0.70 (95% CI, 0.36-1.37); compared with nonregular users, the RR was 1.22 (95% CI, 0.54-2.76; \( P > .99 \) for trend) for 5 or more years of use. The multivariate RRs associated with acetaminophen use reported in 1990 among women were 1.00 (reference) for nonusers, 1.07 for 1 to 4 days of use per month, 1.12 for 5 to 14, 0.83 for 15 to 21, and 0.48 for 22 or more (95% CI, 0.12-1.98; \( P = .40 \) for trend).

In these large prospective studies, we found a 45% lower risk of PD among regular users of nonaspirin NSAIDs compared with nonusers. A similar decrease in risk was observed among participants who took 2 or more tablets of aspirin per day compared with nonusers, but not among those taking smaller amounts of aspirin. These results did not change appreciably after excluding the first 2 or 4 years of follow-up or after excluding participants with PD and dementia.

Our results are similar between men and women and are unlikely to be explained by bias or confounding. Both cohorts were prospectively designed, with at least 14 years of follow-up and minimal losses; thus, selection bias should be minimal. Although for PD diagnosis we have relied on the judgment of the patients’ treating neurologists or internists, a recent clinicopathological study\(^\text{17}^\) suggests that the clinical Parkinson diagnosis (made by a neurologist in 86% of their case series) was accurate in 90% of the cases. The use of aspirin or nonaspirin NSAIDs assessed in these cohorts has been shown to predict the risk of colorectal cancer and cardiovascular diseases, consistent with their pharmacological effects.\(^\text{13,14,18}^\) Moreover, because of the prospective design, any misclassification of baseline exposures would most likely be nondifferential and would have attenuated the true associations. Age and smoking were adjusted for throughout the analyses, and further adjustment for other potential confounders had minimal effects, so the residual confounding due to these factors is probably modest. Inverse associations similar to what we observed in this study could occur if arthritis or other conditions that lead to NSAID use were independently associated with a lower PD risk. However, none of these conditions are known to decrease PD risk, and they were not significantly associated with PD risk in our cohorts; furthermore, adjusting for these conditions had no effects on the results. Finally, some over-the-counter NSAID tablets contain significant amounts of caffeine, and this could hypothetically contribute to their protective effect. The average daily dose of caffeine from these sources is, however, likely to be small. Furthermore, our results on NSAIDs were similar in men and women, whereas caffeine was inversely associated with PD risk only among men.\(^\text{12}^\)

The environmental factors that have been found to be strongly related to PD risk in our cohorts and others include smoking\(^\text{19,20}^\) (inverse association) and caffeine intake\(^\text{19,21}^\) (inverse association in men but not in women). It is unclear, however, whether these associations reflect a causal effect or are the manifestation of an underlying common etiological factor, such as a low basal ganglia dopamine level that may protect from addiction but predispose to PD.\(^\text{22}^\) However, a relationship between NSAID addiction and enhanced dopaminergic activity has not been reported. It seems, therefore, unlikely that the inverse association between NSAID use and PD risk reflects only preexisting levels of dopaminergic activity.

Nonsteroidal anti-inflammatory drugs are best known as inhibitors of cyclooxygenase enzymes, which are induced by cytokines or inflammatory stimuli and generate important mediators in inflammatory reactions.\(^\text{23}^\) Previous animal and postmortem studies suggest that inflammation is involved in PD pathogenesis.\(^\text{24}^\) Evidence includes glial activation and increased levels of nuclear factor–κB and proinflammatory cytokines in animal models of PD\(^\text{25,26}^\) and in brains of patients who died with PD.\(^\text{27-30}^\) Ongoing inflammatory reactions were observed in the brains of 3 men up to 16 years after developing parkinsonism following exposures to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine,\(^\text{30}^\) supporting a role of chronic self-perpetuating inflammation. Recent experimental investigations further suggest that NSAIDs may protect against PD. Aspirin and salicylate have been shown to reduce striatal dopamine depletion and dopaminergic neuron loss induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.\(^\text{2-5}^\) Furthermore, anti-inflammatory dosages of these drugs protected neurons from glutamate-induced toxicity by inhibiting the activation of nuclear factor–κB.\(^\text{31}^\) An attenuation of glutamate toxicity toward dopaminergic neurons was also reported for nonaspirin NSAIDs such as ibuprofen.\(^\text{32}^\) Finally, NSAIDs are effective scavengers for hydroxyl radicals and nitric oxide,\(^\text{3,4,33,34}^\) which may play critical roles in PD occurrence. At lower dosages, aspirin has minimal anti-inflammatory effects.\(^\text{30}^\) This may explain why regular use of aspirin (often taken at a low dosage to inhibit platelet aggregation) was not associated with PD risk, yet at higher dosages a lower risk was suggested.

Therefore, the results from our human investigations provide support for the neuroprotective effects of NSAIDs demonstrated by previous experimental findings. Moreover, our results are also consistent with the previous epidemiological support of a protective effect of NSAIDs on the risk of Alzheimer disease,\(^\text{8,9}^\) for which similar biological hypotheses have been proposed.\(^\text{6,7}^\) A protective role of NSAIDs in the central nervous system seems therefore likely and should be addressed in future investigations.

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**Author contributions:** Study concept and design (Drs Chen, Schwarzschild, Willett, and Ascherio); acquisition of data (Drs Chen, Harnain, Willett, Colditz, Speizer, and
Ascherio; analysis and interpretation of data (Drs Chen, Zhang, Hernán, Schwarzschild, Willett, Colditz, Speizer, and Ascherio); drafting of the manuscript (Drs Chen, Zhang, Willett, and Ascherio); critical revision of the manuscript for important intellectual content (Drs Chen, Zhang, Hernán, Schwarzschild, Willett, Colditz, Speizer, and Ascherio); statistical expertise (Drs Chen, Willett, and Ascherio); obtained funding (Drs Willett, Colditz, Speizer, and Ascherio); administrative, technical, and material support (Drs Willett, Colditz, Speizer, and Ascherio); study supervision (Drs Willett and Ascherio).

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