Anti-inflammatory drugs and risk of Parkinson disease

A meta-analysis

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ABSTRACT

Background/Objective: Anti-inflammatory drugs may prevent Parkinson disease (PD) by inhibiting a putative underlying neuroinflammatory process. We tested the hypothesis that anti-inflammatory drugs reduce PD incidence and that there are differential effects by type of anti-inflammatory, duration of use, or intensity of use.

Methods: MEDLINE and EMBASE were searched for studies that reported risk of PD associated with anti-inflammatory medications. Random-effects meta-analyses were used to pool results across studies for each type of anti-inflammatory drug. Stratified meta-analyses were used to assess duration- and intensity-response.

Results: Seven studies were identified that met the inclusion criteria, all of which reported associations between nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and PD, 6 of which reported on aspirin, and 2 of which reported on acetaminophen. Overall, a 15% reduction in PD incidence was observed among users of nonaspirin NSAIDS (relative risk [RR] 0.85, 95% confidence interval [CI] 0.77–0.94), with a similar effect observed for ibuprofen use. The protective effect of nonaspirin NSAIDs was more pronounced among regular users (RR 0.71, 95% CI 0.58–0.89) and long-term users (RR 0.79, 95% CI 0.59–1.07). No protective effect was observed for aspirin (RR 1.08, 95% CI 0.92–1.27) or acetaminophen (RR 1.06, 95% CI 0.87–1.30). Sensitivity analyses found results to be robust.

Conclusions: There may be a protective effect of nonaspirin nonsteroidal anti-inflammatory drug use on risk of Parkinson disease (PD) consistent with a possible neuroinflammatory pathway in PD pathogenesis. *Neurology*® 2010;74:995–1002

GLOSSARY

CI = confidence interval; **COX** = cyclooxygenase; **NOS** = Newcastle-Ottawa Scale; **NSAID** = nonsteroidal anti-inflammatory drug; **OTC** = over-the-counter; **PD** = Parkinson disease; **RR** = relative risk.

Parkinson disease (PD) is a common neurodegenerative movement disorder associated with substantial morbidity and mortality,[1] and the number of persons affected is expected to increase dramatically in coming years.[2] Although its pathogenesis is not fully understood, neuroinflammatory mechanisms may be involved.[3,4] If so, anti-inflammatory medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), may confer protection against PD. While studies of animal models of PD support this hypothesis,[5] the epidemiologic literature regarding the effect of anti-inflammatory drug use on PD is mixed. Several studies suggest a protective effect of anti-inflammatory medications on PD in humans,[6,7] whereas others do not corroborate these findings.[8,9]

The purpose of this study was to quantify the effect of anti-inflammatory drug use on PD incidence by meta-analyzing existing studies and to examine the effect by type of anti-inflammatory (e.g., nonaspirin NSAIDs, aspirin, acetaminophen), duration of use, and intensity of use.

METHODS **Search strategy.** Our systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines.[10] Each author independently conducted a systematic search of MEDLINE and EMBASE from their

Supplemental data at www.neurology.org

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commencement to April 2009. Separate search filters were constructed for each database and are provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org. Initial searches were restricted to English-language publications and studies conducted in humans. A secondary search with no language restriction did not identify any additional relevant articles. Reference lists of articles identified for inclusion in the meta-analysis were examined to identify additional potentially relevant studies.

Eligibility criteria. Abstracts of identified articles were screened to exclude studies that clearly did not meet the eligibility criteria. The full text of those selected for further review was obtained and evaluated. Studies were included if they met the following criteria: 1) presented original data from an epidemiologic study; 2) defined the outcome of interest as incident PD, based on clearly stated diagnostic criteria or identified through diagnostic codes with additional confirmation; 3) defined exposure as use of nonaspirin NSAIDs, aspirin, or acetaminophen; 4) ascertained exposure status during a period including time at least 1 year or more before PD diagnosis[11]; 5) described adjustment for potential confounding; 6) reported effect estimates with confidence intervals (CIs), standard errors, or sufficient information to calculate these; and 7) met at least 5 Newcastle-Ottawa Scale (NOS) criteria,[12] a standard set in other studies.[13,14] The NOS is an 8-item instrument, with up to 9 possible points, and is intended to assess the quality of observational studies to be included in systematic reviews and meta-analyses. It has been used in several recently published meta-analyses of observational studies.[13-16]

Data extraction. Both authors independently extracted data from each study. Discrepancies were discussed and resolved by agreement. The following data were extracted from each study: study name, year of publication, setting, study design, number of participants, mean age, outcome definition, exposure definitions, methods for confounding adjustment and variables adjusted for, effect estimates and CIs or standard errors (or information required to compute these), and information required to complete the NOS questionnaire.

When multiple effect estimates were reported, maximally adjusted estimates were extracted. When results were presented with and without lag periods, with multiple lag periods, or with multiple periods of exposure ascertainment, the estimates based on the longest time between exposure and disease onset were used, given the insidious nature of PD.[11]

Data analysis. For all analyses, we used random-effects models.[17] Primary analyses compared exposed vs unexposed for each of the 3 anti-inflammatory exposures of interest: nonaspirin NSAIDs, aspirin, and acetaminophen. For studies that reported only stratified results (e.g., by sex), fixed-effect methods with Mantel-Haenszel weighting were used to summarize the stratified estimates into a single parameter for each study.

When possible, stratified analyses were conducted to examine differences by sex, duration of use, and intensity of use. To investigate differential effects by duration of use, results were stratified on short- vs long-term use. Short-term use was defined as the first duration stratum for each study that reported results stratified by exposure duration over several years. Long-term use was defined as exposure duration beyond the first stratum. When studies reported more than 1 stratum that qualified for long-term use, we combined the estimates with fixed-effects methods. To investigate differential effects by intensity of use, results were stratified by whether exposure definitions required demonstration of regular use.

Furthermore, we hypothesized that, in the case of a true effect of anti-inflammatory agents on PD, reliance on prescription drug data alone would lead to nondifferential misclassification of exposure status due to widespread use of over-the-counter (OTC) anti-inflammatory drugs. If present, such misclassification would, in expectation, result in a biased estimate of association that would be closer to unity than an estimate that considered both prescription and OTC drug use to define exposure. To assess the potential for and impact of this exposure misclassification, we conducted analyses stratified by whether exposure status was defined on the basis of prescription data alone or whether it also captured possible OTC use.

Sensitivity analyses were conducted to assess the robustness of the primary analyses for each exposure type. Studies excluded from the analysis because they did not meet our eligibility criteria were included in sensitivity analyses. We also conducted sensitivity analyses by repeating the original analyses while separately omitting 1 study at a time to assess whether single studies had undue influence on the results.

Measures of association were combined under the assumption that odds ratios were accurate approximations of relative risks (RRs). Presence of heterogeneity in effects was assessed using the Cochrane Q test and quantified using the I^2 test.[18] Publication bias was assessed via visual inspection of the Begg funnel plot.

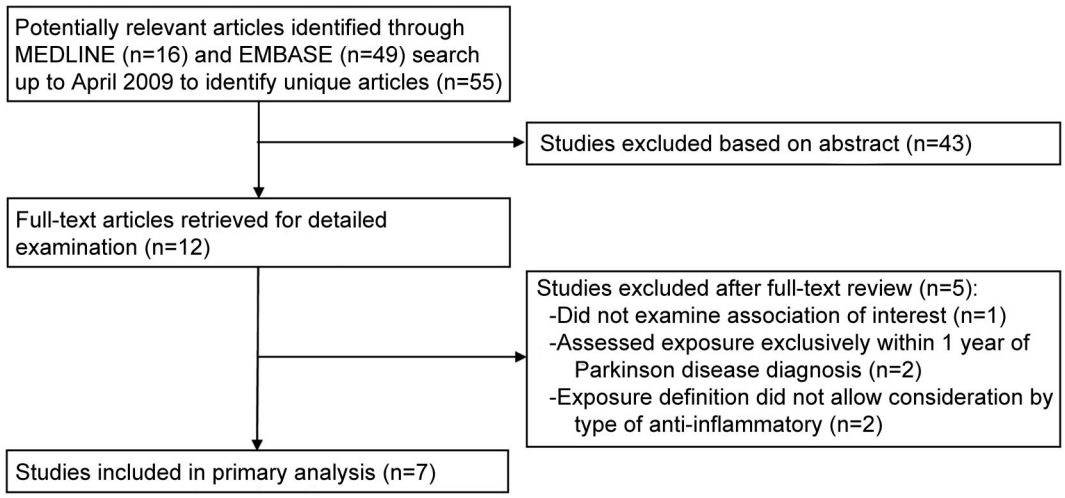
RESULTS

Literature search. The MEDLINE search yielded 16 potentially relevant articles and the EMBASE search yielded 49 articles, for a total of 55 unique citations (figure 1). Forty-three of these articles were excluded based on the abstract review because they were clearly irrelevant to the objectives of this meta-analysis. Thus, a total of 12 articles were obtained for full-text review. One of the 12 articles did not report on the association of interest and was excluded.[19] Two studies were excluded from primary analyses because exposures were ascertained exclusively within 1 year of PD diagnosis,[20,21] and 2 studies were excluded because exposure was defined as any anti-inflammatory drug without reporting of separate results for each drug type.[22,23] Thus, 7 studies met our inclusion criteria and were included in the primary analyses. The 4 studies that were excluded on the basis of exposure definitions were included in sensitivity analyses.

Study characteristics. Five of the 7 studies included in the analysis were case-control studies,[8,9,24-26] and 2 were cohort studies (table).[6,7] All 7 of the studies met at least 5 NOS criteria. All 7 studies reported on the association between nonaspirin NSAIDs and PD, with 3 additionally reporting specifically on the association between ibuprofen and PD,[6,8,9] 6 reporting on the association between aspirin and PD,[6-9,24,25] and 2 reporting on the association between acetaminophen and PD.[6,9]

Nonaspirin NSAID use and PD risk. The pooled estimate for the 7 studies that reported on the association between nonaspirin NSAIDs and PD was 0.85

Figure 1 Flow diagram of study selection



(95% CI 0.77–0.94; figure 2). No heterogeneity was observed in these results (I^2 = 0%, 95% CI 0%–71%). Analyses stratified by duration of use (short-term vs long-term) and intensity of use (nonregular use vs regular use) yielded results consistent with a dose-response relation (figure 3, A and B). Analyses stratified by type of exposure (prescription only vs both prescription and OTC) yielded results consistent with expected greater nondifferential exposure misclassification among studies considering only prescription nonaspirin NSAID exposure (figure 3C).

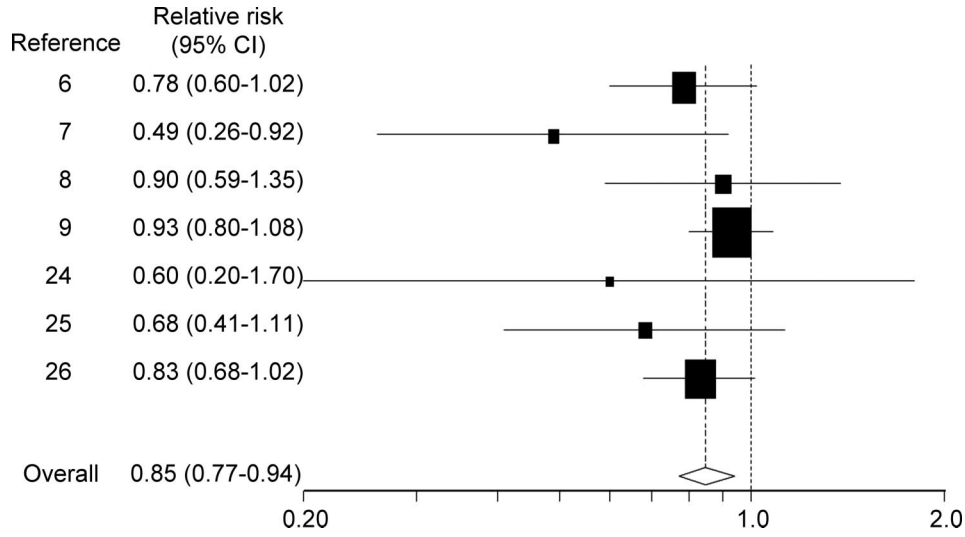
Adding the 2 studies that were excluded from the analysis because exposure status was ascertained within a year of PD diagnosis[20,21] slightly increased the primary estimate of effect (RR 0.87, 95% CI 0.77–0.97) and introduced some heterogeneity

Table Characteristics of studies evaluating the association between anti-inflammatory drugs and Parkinson disease

Reference	Setting (country)	n (cases/controls for case-control studies)	Study design	Parkinson diagnosis	Exposure assessment (exposure type)	Potential confounders considered
6	Cancer Prevention Study II Nutrition Cohort (US)	146,948	Cohort	Self-report followed by confirmation by treating physician or confirmatory chart review	Self-report mailed questionnaire (Rx, OTC)	Age, arthritis, coffee, multivitamin, other analgesics, sex, smoking, vitamin C, vitamin E
7	Nurses' Health Study and Health Professionals Follow-up Study (US)	142,902	Cohort	Self-report followed by confirmation by treating physician or confirmatory chart review	Self-report mailed questionnaire (Rx, OTC)	Age, alcohol, caffeine, sex, smoking
8	Group Health Cooperative (US)	589 (206/383)	Case-control	Clinical diagnosis with confirmatory chart review by neurologist	Automated pharmacy database (Rx, OTC[a])	Age, arthritis, clinic, diabetes, duration of health plan enrollment, education, heart disease, high blood pressure, sex, smoking, stroke
9	General Practice Research Database (UK)	7,896 (1,258/6,638)	Case-control	Computerized diagnosis and at least 2 prescriptions used to treat PD during follow-up with validation in random sample	Automated prescription data (Rx)	Age, arthritis, history of myocardial infarction, practice, sex, smoking, start date
24	Rochester Epidemiology Project (US)	392 (196/196)	Case-control	Medical record abstraction based on H-ICDA codes followed by confirmatory chart review by neurologist with validation studies	Medical chart review (Rx, OTC)	Age, sex
25	Three rural California counties: Fresno, Tulare, Kern (US)	579 (293/286)	Case-control	Clinical evaluation with defined diagnostic criteria	Self-report questionnaire (Rx, OTC)	Age, education, race, sex, smoking
26	NeuroGenetics Research Consortium (US)	2,114 (1,186/928)	Case-control	Evaluation by movement disorder neurologist using standard clinical criteria	Self-report questionnaire (Rx, OTC)	Age, coffee, ethnicity, sex, smoking, state

Abbreviations: H-ICDA = International Classification of Diseases, Adapted Code for Hospitals; OTC = exposure definition included over-the-counter drug use; PD = Parkinson disease; Rx = exposure definition included prescription drug use; UK = United Kingdom.
[a]This included data on over-the-counter drugs purchased at Group Health Cooperative pharmacies. However, according to a validation study completed in 1994, these data capture only 85% of OTC ibuprofen and 30% of OTC aspirin medications. The authors also suggest that greater underreporting is likely in later years.[8]

Figure 2 Relative risks (95% confidence intervals [CI]) from studies of nonaspirin nonsteroidal anti-inflammatory drug use and effect of Parkinson disease

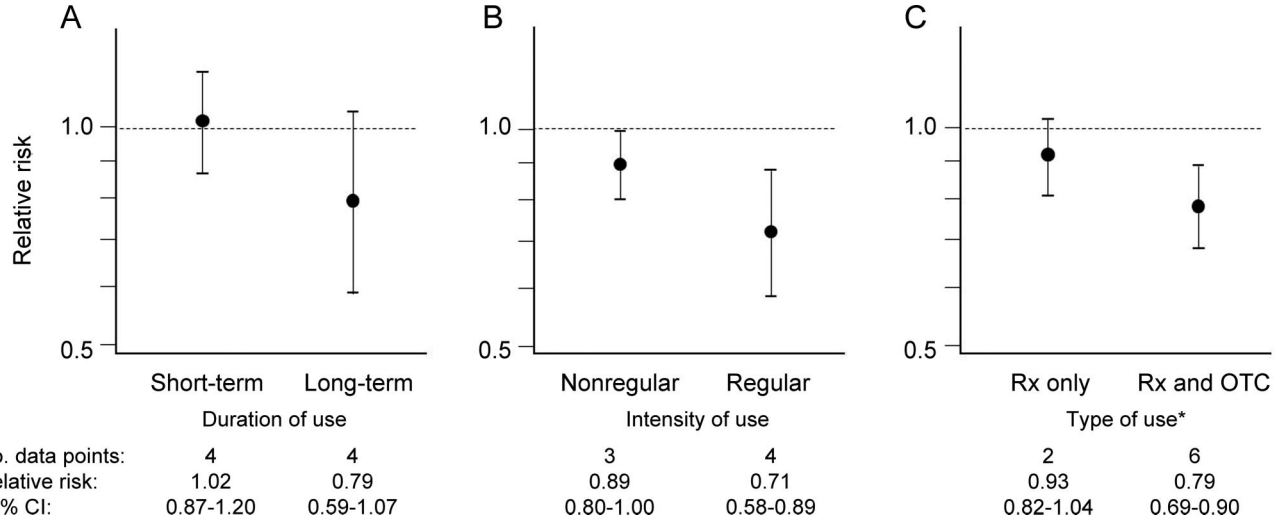


(I^2 = 25%, 95% CI 0%–65%). In a separate sensitivity analysis, including the 2 studies that defined NSAID exposure as combination of aspirin or nonaspirin NSAIDs[22,23] also slightly increased the effect estimate (RR 0.87, 95% CI 0.75–1.00) and introduced some heterogeneity (I^2 = 35%, 95% CI 0%–70%). A sensitivity analysis including all 4 excluded studies yielded a higher effect estimate (RR 0.90, 95% CI 0.79–1.01) and involved greater heterogeneity (I^2 = 39%, 95% CI 0%–70%). Sensitivity analyses omitting 1 study at a time from the original analysis found the main results to be robust.

Five studies reported results for nonaspirin NSAID use by sex.[6,7,9,25,26] Sex-stratified meta-analyses yielded similar results among men (RR 0.80, 95% CI 0.70–0.92) and women (RR 0.75, 95% CI 0.52–1.08). Three studies reported results specifically for ibuprofen.[6,8,9] The summary estimate for ibuprofen only was slightly stronger (RR 0.75, 95% CI 0.64–0.89) than the estimate for all nonaspirin NSAIDs. Given that data were available for only 3 studies, stratified and sensitivity analyses for ibuprofen use were not possible.

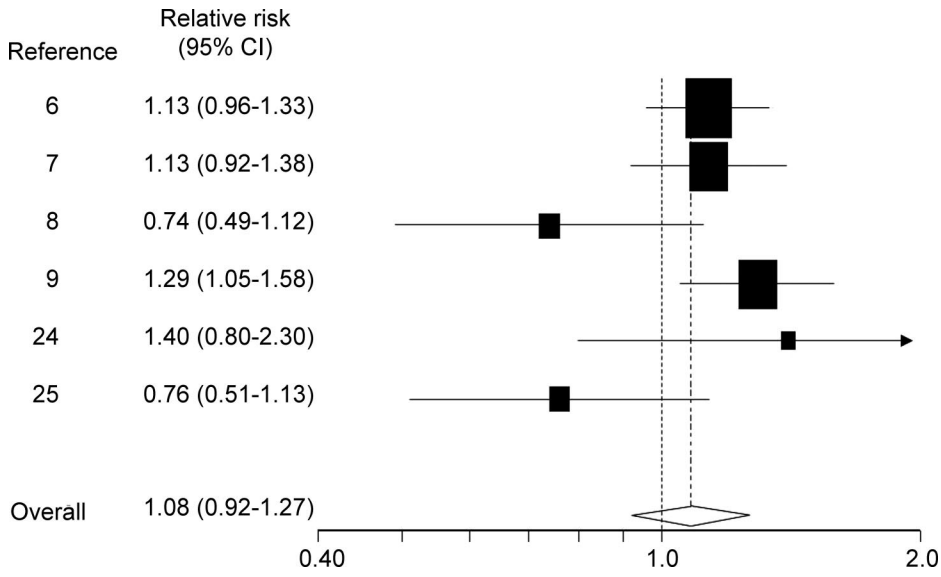
Aspirin use and PD risk. One of the 6 studies that examined the risk of PD in relation to aspirin use

Figure 3 Risk of Parkinson disease associated with nonaspirin nonsteroidal anti-inflammatory drug use stratified by duration, intensity, and type of use



*Rx only and Rx and OTC denote whether exposure definition included prescription (Rx) nonsteroidal anti-inflammatory drug (NSAID) use or both prescription and over-the-counter (OTC) NSAID use. CI = confidence interval.

Figure 4 Relative risks (95% confidence intervals [CI]) from studies of aspirin use and effect on Parkinson disease



reported only stratified results,[6] which we combined into a single summary estimate. Pooling this estimate with the other 5 studies[7-9,24,25] yielded an effect estimate of 1.08 (95% CI 0.92–1.27; figure 4). Some heterogeneity was observed in these results (I^2 = 50%, 95% CI 0%–80%). Duration-response analyses produced similar results for both short-term use (RR 1.13, 95% CI 0.66–1.94) and long-term use (RR 0.93, 95% CI 0.58–1.50) but were limited by the number of studies (n = 2)[9,25] that permitted such stratification. Intensity-response analyses also yielded similar results for nonregular use (RR 1.00, 95% CI 0.59–1.73) and regular use (RR 1.06, 95% CI 0.89–1.27). Analyses stratified by sex found an increased risk of PD associated with aspirin use among men (RR 1.22, 95% CI 1.03–1.44) but not women (RR 0.98, 95% CI 0.71–1.37). No substantial heterogeneity was observed in sex-stratified analyses.

Adding the results of the 2 studies that defined NSAID exposure as combination of aspirin or nonaspirin NSAIDs[22,23] did not substantially change the effect estimate (RR 1.10, 95% CI 0.96–1.27) or the amount of heterogeneity (I^2 = 43%, 95% CI 0%–75%). Sensitivity analyses omitting 1 study at a time from the original analysis found the primary results to be robust.

Acetaminophen use and PD risk. One study suggested a small potential protective effect of acetaminophen on PD,[6] whereas another reported a small adverse effect.[9] Combining these studies yielded an effect estimate of 1.06 (95% CI 0.87–1.30). Stratified, dose-response, and sensitivity analyses were not possible given the availability of data from only 2 studies.

Publication bias. Inspection of the Begg funnel plot did not suggest the presence of publication bias because the log RRs plotted against their standard errors yielded a rather symmetric distribution for studies that reported on nonaspirin NSAID use (figure e-1) and aspirin use (figure e-2). However, because these assessments are based on few studies, inference about publication bias should be made with caution. Assessment for publication bias for acetaminophen use or ibuprofen use was not meaningful because of the small number of studies that reported on these associations.

DISCUSSION

This analysis, which combined the results of several large epidemiologic studies, suggests that use of nonaspirin NSAIDs is associated with a 15% reduction in risk of PD. We also observed a greater reduction in risk with regular use (29% reduction) and long-term use (21% reduction), consistent with a dose-response relation. By contrast, no protective effect was observed with use of aspirin or acetaminophen.

The findings support a growing body of research that suggests the involvement of a neuroinflammatory process in PD pathogenesis. Postmortem and in vivo studies provide evidence of a neuroinflammatory response in patients with PD but do not differentiate whether such changes are a contributing cause or a result of the disorder.[3,4,27] Animal models of PD suggest that neuroinflammation is part of the pathologic process and precedes dopaminergic cell

death.[3,4] Genetic studies show increased PD risk associated with polymorphisms in inflammatory genes, including tumor necrosis factor α and interleukin 1β, and high plasma concentrations of interleukin 6 have also been associated with increased PD risk.[28,29]

Furthermore, NSAIDs have been shown to exhibit neuroprotective effects in animal models of PD.[30] However, the physiologic pathways on which these drugs act are many and varied,[31] and the exact mechanism by which they may act to prevent or minimize neurodegeneration has not been definitively determined.[3,30] Some theories postulate that inhibition of cyclooxygenase (COX)-2, COX-independent antioxidant effects, or modulation of the inflammatory response through impact on gene expression or cytokine production account for this neuroprotective effect.[3,30] Moreover, no association was observed between acetaminophen use and PD, further supporting the involvement of an underlying neuroinflammatory process in PD because acetaminophen lacks overall anti-inflammatory ability.[32]

The findings of this meta-analysis support the idea that nonaspirin NSAIDs confer protection against PD, because bias is unlikely to account for these findings. Reverse causation is an unlikely explanation, because we required all studies to include ascertainment of exposure at least 1 year before PD diagnosis and those studies incorporating longer lags also exhibit a protective effect of nonaspirin NSAIDs. Selection bias is unlikely to account for our results, because both cohort and case-control studies exhibit similar findings, controls were appropriately selected in case-control studies, and loss to follow-up in cohort studies was minimal. Nevertheless, selection effects due to differential mortality cannot be excluded[33]; however, the magnitude of such bias is likely small. Recall bias is unlikely to affect the majority of the studies included in these analyses because, for most studies, exposure was recorded or assessed before PD ascertainment. However, nondifferential misclassification of exposure status may be present and could have biased the results toward the null in the original studies as well as in this meta-analysis. Thus, the primary analyses may be underestimates of the true effect of anti-inflammatory drugs on PD. Indeed, analyses restricted to studies that relied on prescription drug data alone, which may be vulnerable to substantial exposure misclassification by failing to account for OTC use, found a smaller protective effect of nonaspirin NSAIDs than studies incorporating information on both prescription and OTC use.

Bias due to unmeasured or residual confounding cannot be excluded, and any confounding in the original studies would have persisted to this meta-analysis. However, confounding is unlikely to fully account for the observed protective association of nonaspirin NSAIDs. Most studies controlled for the most influential known risk factors of PD, age and smoking, and those that further adjusted for other known or suspected risk factors, such as caffeine intake, alcohol consumption, or gout, found that these further adjustments did not materially change the effect estimates. For example, one study reported an age- and smoking-adjusted RR of 0.58 (95% CI 0.30–1.12) and found the estimate to be substantially unchanged after further adjustment for caffeine intake and alcohol consumption (RR 0.60, 95% CI 0.31–1.17).[7] Additionally, adjustment for indications for nonaspirin NSAID use did not seem to substantially impact effect estimates.[22]

We observed a seemingly paradoxical harmful effect of aspirin use on PD risk among men. However, because men have historically been more likely to use aspirin for primary prevention of cardiovascular events,[34-36] we suspect that this finding may be due to confounding or selection bias. Unmeasured confounding would exist if cardiovascular indications for aspirin use were not adjusted for in the original analyses and these indications are also risk factors for PD. Alternatively, selection bias due to differential mortality may explain the results because, among older individuals, those who do not use aspirin are more likely to die of cardiovascular disease than those who do use aspirin, and death from cardiovascular disease precludes diagnosis of PD that would have developed later in life. Thus, the association between aspirin use and PD could be noncausal, and further research is needed determine whether the observed association is real or is an artifact of these potential sources of bias.

Our conclusion that use of certain types of anti-inflammatory drugs are associated with decreased PD risk conflicts with the conclusion drawn by the authors of another recently published meta-analysis on this topic.[37] Methodologic differences between the 2 meta-analyses account for the divergent findings and highlight the need to carefully consider the biology and pharmacology that govern the association of interest. First, whereas we considered nonaspirin NSAIDs and aspirin separately and observed a protective effect for nonaspirin NSAIDs but not for aspirin, the other authors considered these drugs as a single class and found no substantial overall effect (RR 0.95, 95% CI 0.80–1.12). Because these drugs act through different biologic pathways and exhibit different pharmacologic profiles,[31,38] it is reasonable to expect a different effect of aspirin and nonaspirin NSAIDs on PD risk. Second, whereas we excluded studies that assessed exposure entirely within 1 year of PD diagnosis, the other authors included these studies. Because PD initiation likely occurs long before symptom onset, it is

implausible that exposures ascertained within 1 year of PD diagnosis affect disease incidence.[11]

Additional well-designed and well-conducted epidemiologic studies can further our understanding of the relation between anti-inflammatory drugs and PD by investigating the relative effects of specific agents, doses, timing, and durations of use. In this analysis, we observed a stronger protective effect when examining ibuprofen alone vs all nonaspirin NSAIDs. Regular use and longer duration of use were also associated with stronger effects. However, optimal dose, timing, and duration of use are unknown. Moreover, the insult that initiates the hypothesized neuroinflammatory mechanism has not been conclusively identified.[39] Unraveling the biologic mechanism of neuroinflammation in PD, along with the mediators this process, may aid in the identification of its causes.[39] Although this meta-analysis suggests that use of nonaspirin NSAIDs may have a positive impact on PD risk, the prudent long-term public health strategy would focus on preventing exposure to the underlying causes of PD rather than relying on mitigating the consequences of such exposures through long-term NSAID administration.

AUTHOR CONTRIBUTIONS

Joshua J. Gagne (academic—Harvard School of Public Health) conducted the statistical analysis.

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DISCLOSURE

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