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Aspirin, Nonsteroidal Anti-inflammatory Drug Use, and Risk for Crohn Disease Ulcerative Colitis:

A Cohort Study

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Abstract

Background—Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are anti-inflammatory but have been linked in some studies to Crohn disease (CD) and ulcerative colitis (UC).

Objective—To assess the association between aspirin and NSAID use and incident CD and UC.

Design—Prospective cohort study.

Setting—Nurses' Health Study I.

Patients—76 795 U.S. women who provided biennially updated data about aspirin and NSAID use.

Measurements—Incident CD and UC between 1990 and 2008 (outcome) and NSAID and aspirin use (exposure).

Results—123 incident cases of CD and 117 cases of UC occurred over 18 years and 1 295 317 person-years of follow-up. Compared with nonusers, women who used NSAIDs at least 15 days per month seemed to have increased risk for both CD (absolute difference in age-adjusted

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incidence, 6 cases per 100 000 person-years [95% CI, 0 to 13]; multivariate hazard ratio, 1.59 [CI, 0.99 to 2.56]) and UC (absolute difference, 7 cases per 100 000 person-years [CI, 1 to 12]; multivariate hazard ratio, 1.87 [CI, 1.16 to 2.99]). Less frequent NSAID use was not clearly associated with risk for CD or UC, and there was no clear association between aspirin use and disease.

Limitations—Cohort participants were exclusively women, most of whom were white. Aspirin and NSAID use were self-reported.

Conclusion—Frequent use of NSAIDs but not aspirin seemed to be associated with increased absolute incidence of CD and UC. The findings have more mechanistic than clinical implications, because the absolute incidence of CD or UC associated with NSAIDs was low and the increase in risk for CD or UC associated with NSAIDs is unlikely to alter the balance of more common and clinically significant risks and benefits associated with these agents.

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Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the risk for colorectal adenoma and cancer but are also associated with gastrointestinal mucosal injury (1, 2). These pleiotropic effects are probably mediated through inhibition of prostaglandin–endoperoxide synthase or cyclooxygenase (COX) enzymes, although other mechanisms may exist (3). Cyclooxygenase-mediated disruption of the intestinal epithelial barrier associated with aspirin or NSAID use can affect the interaction between the gut microbiome and immune cells in the intestine lining, thus affecting risk for inflammatory bowel disease (IBD) (Crohn disease [CD] or ulcerative colitis [UC]). In addition, NSAIDs and aspirin alter platelet aggregation, release of inflammatory mediators, and microvascular response to stress, which may mediate CD and UC pathogenesis.

Previous studies examining the association between aspirin or NSAID use and IBD have been primarily conducted among patients with established disease (4–9) and have yielded conflicting results (6–9). Data examining the role of aspirin or NSAID use in the initial development of IBD are scant (10–12) and limited by retrospective ascertainment of exposure, lack of physician confirmation of disease diagnosis (particularly to exclude misclassification of NSAID enteropathy), and inability to examine ranges of therapy frequency and duration.

We examined the association between aspirin and NSAID use and risk for physician-adjudicated CD and UC among women enrolled in the Nurses' Health Study I, a cohort with sufficiently detailed information about NSAID and aspirin use over 30 years that overcomes many of the limitations of previous research.

Methods

Study Population

The Nurses' Health Study I is a prospective cohort study that began in 1976 when 121 700 U.S. female registered nurses, aged 30 to 55 years, completed a mailed health questionnaire. With a follow-up rate of more than 90%, questionnaires have been mailed every 2 years to update health information. The observation period for this study began on the month of return of the 1990 questionnaire, from which time information about aspirin and NSAID use was collected with similar detail, and ended on the month of diagnosis of CD or UC, the date of death, or 1 June 2008—whichever came first. Among 76 795 women who returned the 1990 questionnaire and did not self-report a history of CD, UC, or cancer (with the exception of nonmelanoma skin cancer), 1809 subsequently reported a new diagnosis of CD

or UC between the 1990 and 2008 questionnaire cycles. We successfully contacted 1604 (89%) of these participants (or their next of kin) and, after exclusions detailed in Figure 1, ended with a total of 240 confirmed cases for this analysis. The baseline characteristics of participants for whom we were able to obtain complete medical records were similar to those of participants for whom we could not obtain sufficient records (Appendix Table 1, available at www.annals.org).

Ascertainment of CD and UC

Participants who reported a new diagnosis of UC or CD were identified from each biennial questionnaire. Beginning in 1995, we sent out a supplemental questionnaire to all participants who reported CD or UC, requesting more detailed information about symptoms, diagnostic testing, and treatments, as well as permission to review medical records. These records were reviewed independently by 2 gastroenterologists blinded to exposure information. Diagnosis of UC was based on a typical clinical presentation for 4 weeks or more and endoscopic, surgical, or radiologic changes consistent with UC based on accepted criteria (13–17). Diagnosis of CD was based on a typical clinical history of 4 weeks or more and endoscopy or radiologic evaluation demonstrating small-bowel findings or surgical findings consistent with CD combined with pathology suggesting that transmural inflammation or granuloma contributed to a diagnosis of CD (13–17). Disagreements were resolved through consensus.

Assessment of Aspirin and NSAID Use

We have previously detailed our assessment of aspirin and NSAID use in the Nurses' Health Study I cohort (1, 18, 19). In brief, in 1980, we asked participants to record the number of aspirin and/or NSAID pills or capsules taken each week and the number of years of use. For aspirin, this information was updated biennially, except in 1986; for NSAIDs, we assessed intake again in 1990, thereafter updating this information biennially (Figure 2). We estimated the amount of each drug consumed as the number of aspirin or NSAID tablets used each week. As previously described (1, 2, 18, 19), to reduce in-person variation and better estimate long-term intake, we used the cumulative average intake of aspirin and NSAIDs as reported on all available questionnaires up to the beginning of each 2-year follow-up interval. We estimated duration of use by using the starting duration in 1990 and updating this variable according to the duration of use on each subsequent biennial questionnaire. For example, if a participant reported 2 years of use in 1990, no use in 1992, and 2 years of use in 1994, she was considered to be a user for 4 years. On the basis of our previous analyses, women using at least 2 aspirin or NSAID tablets per week were considered regular users. Consistent with previous analyses (1, 2, 18–20), we categorized aspirin and NSAID use according to frequency, weekly dose, and duration. Because cases in the highest categories of our original questionnaires were limited, we combined the highest 2 categories for each analysis.

Information about the frequency of acetaminophen use (days per month) was also ascertained biennially, and duration and frequency were categorized into the same strata as for aspirin and NSAID use; information regarding weekly dose of acetaminophen use (tablets per week) was not collected. For all agents, women were asked about their regular use during the preceding 2 years. Because COX-2 inhibitors were introduced in the United States in 1999 and prevalence of their use was low (7% in 2000), there were insufficient regular users of these agents to examine associations with incident CD or UC in the present study.

Statistical Analysis

We calculated age-adjusted incidence rates by calculating age-specific incidence rates within 5-year age categories and used the Mantel–Haenszel method to adjust for differences in the distribution of age groups among the exposure categories. We used Cox proportional hazards modeling with time-dependent variables with the most updated information for aspirin, NSAIDs, and other covariates before each 2-year interval to calculate hazard ratios (HRs) and 95% CIs. Covariates were selected for inclusion in the multivariate model on the basis of previously published data demonstrating their role as risk factors for CD or UC (smoking status, oral contraceptive use, postmenopausal hormone therapy, and body mass index). In a final model, we used risk factors associated with CD or UC in univariate analyses (smoking status, oral contraceptive use, and postmenopausal hormone therapy) (21–24). Likelihood ratio tests that compared models with and without time-dependent variable-by-variable interaction terms demonstrated that the proportional hazards assumption was met. In sensitivity analyses, we assessed the association between drug use 4 years before diagnosis and CD or UC, a lead-time duration that made it less likely that NSAID intake was related to early IBD symptoms. Earlier and later follow-ups were compared to account for the transition from use of aspirin as an analgesic to its use for cardiovascular prevention. We also excluded women with rheumatoid arthritis or psoriatic arthritis to address the possibility that NSAIDs may be used more by women with rheumatologic conditions associated with IBD. Association in models that simultaneously adjusted for aspirin, NSAID, and acetaminophen use were also assessed. In addition, we performed an analysis to specify the amount of unmeasured confounding that would be necessary to annul statistically significant results (25). We used SAS, version 9.1 (SAS Institute, Cary, North Carolina), for all analyses, and all *P* values are 2-sided. The institutional review board at Brigham and Women's Hospital, Boston, Massachusetts, approved this study.

Role of the Funding Source

The American Gastroenterological Association, IBD Working Group, Broad Medical Research Program, and National Institutes of Health provided funding for the study. The funding sources had no role in the design and conduct of the study, analysis or interpretation of the data, or preparation or final approval of the manuscript. The research presented in this article is original. The contents of this article are solely the responsibility of the authors.

Results

Over 1 295 317 person-years of follow-up, 123 cases of CD and 117 cases of UC occurred. Mean cohort age in 1990 was 56.7 years (range, 43.5 to 76.7 years), and 44% of women reported regular aspirin use and 37% reported regular NSAID use. Compared with nonusers, women who used NSAIDs at least 15 days per month were less likely to be current smokers and more likely to be former smokers, and women who used aspirin at least 15 days per month were older and less likely to be premenopausal (Table 1 and Appendix Table 2, available at www.annals.org). We saw a higher risk for both CD and UC with the highest frequency of NSAID use (Table 2). Compared with nonusers, women who used NSAIDs at least 15 days per month seemed to have increased risk for both CD (absolute difference in age-adjusted incidence, 6 cases per 100 000 person-years [95% CI, 0 to 13]; multivariate HR, 1.59 [CI, 0.99 to 2.56]) and UC (absolute difference, 7 cases per 100 000 person-years [CI, 1 to 12]; multivariate HR, 1.87 [CI, 1.16 to 2.99]). Less frequent NSAID use was not clearly associated with incidence or hazard of either CD or UC. No clear association was observed between aspirin use and disease in any category of frequency. Findings were similar in analyses that examined weekly NSAID exposure (tablets per week) (Table 3). Compared with nonusers, women who used more than 5 NSAID tablets per week had an

increased risk for CD (absolute difference in age-adjusted incidence, 6 cases per 100 000 person-years [CI, 0 to 12]; multivariate HR, 1.71 [CI, 1.05 to 2.77]) and UC (absolute difference, 7 cases per 100 000 person-years [CI, 1 to 13]; multivariate HR, 1.78 [CI, 1.10 to 2.89]). In contrast, no clear association was found between weekly aspirin use and risk for either CD or UC.

Findings from analyses of duration of use supported those of frequency and weekly dose. Point estimates of hazard increased with longer NSAID use. Compared with nonusers, regular use of NSAIDs for more than 6 years was associated with an increased risk for CD (absolute difference in age-adjusted incidence, 7 cases per 100 000 person-years [CI, 1 to 13]; multivariate HR, 2.83 [CI, 1.65 to 4.85]) and UC (absolute difference, 5 cases per 100 000 person-years [CI, 0 to 10]; multivariate HR, 2.00 [CI, 1.15 to 3.49]) (Table 4), with no clear association for aspirin. There were also no clear associations between acetaminophen use and hazard of CD or UC, but there were so few cases of disease in exposure categories that nearly all hazard estimates were imprecise, with broad, inconclusive confidence bounds.

Findings of association with NSAIDs were also consistent in sensitivity analyses. Hazard estimates were qualitatively similar in analyses that attempted to address proto-pathic bias by using data on NSAID exposure 4 years before diagnosis, a lead-time duration that made it less likely that NSAID intake was related to early IBD symptoms (Appendix Tables 3 to 5, available at www.annals.org). They were also similar in comparisons of earlier and later follow-ups to account for the transition from use of aspirin as an analgesic to its use for cardiovascular prevention (HR for CD with aspirin use >5 tablets per week, 0.84 [CI, 0.41 to 1.74] from 1990 to 1998 and 1.13 [CI, 0.37 to 3.40] from 1998 to 2008; HR for UC with aspirin use >5 tablets per week, 1.10 [CI, 0.56 to 2.15] from 1990 to 1998 and 1.02 [CI, 0.34 to 3.08] from 1998 to 2008). Hazard estimates were also qualitatively similar in analyses that excluded women with rheumatoid arthritis or psoriatic arthritis (Appendix Tables 6 to 8, available at www.annals.org), in analyses that excluded women with a history of cardiovascular disease (to exclude those who may have been taking aspirin at low doses that are less likely to be associated with harm; data not shown), and in models simultaneously adjusted for aspirin, NSAID, and acetaminophen use. Finally, an analysis of the sensitivity of our results to an unmeasured confounder (25) found that the prevalence of a confounder with an effect size (HR) of 2.0 would need to be 80% among NSAID users for more than 6 years compared with 10% among nonusers to attenuate the association with CD to nonstatistical significance. The prevalence would need to be 30% among NSAID users for more than 6 years compared with 10% among nonusers to similarly attenuate the association with UC. The prevalence would need to be 20% among NSAID users who consume more than 5 tablets per week to attenuate the association between frequency of use and CD, and 30% to similarly attenuate the association with UC.

Discussion

In this large, prospective cohort study, we found that NSAIDs used at higher frequency, with greater weekly doses, and for longer duration were associated with an increased risk for and relative hazard of CD and UC. We did not observe any clear similar association between aspirin use and hazard of either CD or UC. However, the overall population incidence of CD or UC was low—as was the absolute risk difference—so for most women, the relative increase in hazard of CD or UC associated with NSAIDs is unlikely to alter the balance of more common and clinically significant risks and benefits associated with these agents.

Previous research has focused primarily on the effect of NSAIDs or aspirin on patients with established IBD (6–9). Although results have been conflicting, most studies demonstrated a slight increase in the rate of relapse among NSAID users (8–10). In contrast, only a few

previous studies have examined the relationship between aspirin or NSAID use and incident CD or UC. We searched the MEDLINE database using the terms *Crohn's disease*, *ulcerative colitis*, *inflammatory bowel disease*, and *IBD* in conjunction with *aspirin*, *NSAID*, *ibuprofen*, or *acetaminophen* to identify all studies published between 1966 and 1 June 2011. We found 3 relevant studies.

Evans and colleagues (10) found that current or recent NSAID use was associated with a 2-fold increase in the likelihood of emergency department visits for colitis identified by using International Classification of Diseases, Ninth Revision, codes. A second study by Gleeson and Davis (12) analyzed 105 new cases of colitis in patients presenting to a single gastroenterologist who were queried about recent aspirin or NSAID use. Seventy-eight patients (74%) had recently used NSAIDs compared with 20% of community control participants (12). Although interpretation of these study results are limited because of either reliance on diagnosis codes or a retrospective assessment of NSAID exposure, our findings of an association with NSAID use largely agree with these earlier results. However, our findings contrast with those of a nested case-control study within the General Practice Research Database in the United Kingdom (11). Among 444 case-patients with IBD and 10 000 control participants, duration of aspirin or NSAID use did not differ between them. These discrepant results may be due to the inability of the General Practice Research Database to account for frequency or dose of NSAID use. In our study, we did not observe a statistically significant elevation in risk for CD or UC among women who used NSAIDs infrequently or at low doses.

Our findings are biologically plausible. Key underlying mechanisms in IBD pathogenesis involve innate and adaptive immune responses and maintenance of intestinal barrier function. Nonsteroidal anti-inflammatory drugs inhibit COX, leading to decreased mucosal concentration of protective prostaglandins (3). In addition, NSAIDs undergo enterohepatic circulation and are secreted into the distal small intestine, where metabolism by gut bacteria (26) results in release of the active form, leading to uncoupling of mitochondrial oxidative phosphorylation, cyto-skeletal disruption, and increase in mucosal permeability (27). They may influence IBD pathogenesis through their effect in disrupting intestinal barrier function. Patients with IBD or their family members are known to have increased intestinal permeability compared with control participants (28, 29). Nonsteroidal anti-inflammatory drugs also alter the intestinal microvasculature and mediate endothelial dysfunction, which are potentially key events in IBD-associated pathogenesis.

Although aspirin and NSAIDs share the potential for gastrointestinal toxicity, aspirin was notably not associated with CD or UC in our study. There are a few potential explanations for this finding. There are established differences in the action of aspirin and NSAIDs on the COX isoenzymes. Nonsteroidal anti-inflammatory drugs at analgesic doses inhibit both the COX-1 and COX-2 enzymes (30, 31). At low and moderate doses, aspirin is relatively COX-1-selective, with only a weak inhibitory effect on COX-2 (5, 32). Animal models of colitis have shown that inhibition of COX-1 or COX-2 alone did not lead to colitis, and administration of nonselective NSAIDs inhibiting both COX isoenzymes resulted in early development of colitis (30, 33). The injurious effects of aspirin mediated through COX inhibition may also be counterbalanced by additional aspirin-specific effects that are anti-inflammatory or mucosally protective. For example, aspirin inhibition of platelet thromboxane attenuates release of sphingosine-1-phosphate, a bioactive immunomodulatory lipid that plays an important role in lymphocyte trafficking and monocyte chemotaxis (34). Pharmacologic inhibitors of sphingosine kinase have demonstrated therapeutic potential in mice models of colitis (35, 36). Aspirin may also promote the production of local anti-inflammatory lipoxins (37).

Our study had several strengths. First, we collected detailed, updated information on aspirin and NSAID use over 20 years of follow-up, permitting an evaluation of long-term use across a broad range of intake. Second, we were able to distinguish between aspirin and nonaspirin NSAID use and estimate several distinct measures of use, including frequency, dose, and duration of use. Thus, our findings are less prone to internal confounding due to correlations between these variables. Third, we obtained aspirin and NSAID data prospectively, before diagnosis. Fourth, because participants were all nurses, the accuracy of self-reported aspirin use is likely to be high and more likely to reflect actual consumption of these medications, which are largely sold over the counter. Fifth, we used physician-confirmed cases of CD and UC, thereby ensuring exclusion of cases that may represent acute gastrointestinal toxicity of these drugs (for example, NSAID enteropathy) rather than IBD. Finally, we collected detailed data on potential confounders and had a high follow-up response rate.

Study limitations also deserve consideration. First, our cohort consisted entirely of women, most of whom were white, and they were generally older, with a mean age of 57 years. Second, we lack information about which specific NSAIDs were used, although most women reported using ibuprofen. Third, we could not assess associations with dose categories of tablet strength (for example, milligram per tablet). However, most aspirin users in our study consumed standard 325-mg aspirin tablets and NSAID users consumed ibuprofen in 200-mg tablets. Fourth, we assessed regular aspirin use over a 2-year period on each biennial questionnaire and cannot assess the effect of more intermittent use (for example, over a few months) that may have occurred between biennial assessments. Fifth, although the outcomes were confirmed by chart review most exposure data were self-reported and not independently verified (38). However, because our cohort comprises nurses, reported medical information is probably accurate, as demonstrated by previous validation studies of anthropometric measurements and diet (39–41).

We also examined the sensitivity of our results to an unmeasured confounder through a formal sensitivity analysis (25) and found that the prevalence of an unmeasured confounder with an effect size (HR) of 2.0 would need to be 30% in NSAID users, compared with 10% in nonusers to attenuate the association with UC. Because we controlled for known risk factors for CD and UC, such strong confounding would probably not remain to explain the associations. Sixth, the limited number of cases of CD or UC in select strata affected the precision of some of our risk estimates. However, a younger population that may have more incident IBD diagnoses may also tend to use lower amounts of NSAIDs and aspirin, adversely affecting our ability to detect meaningful associations.

Finally, NSAIDs may have been used to treat IBD symptoms before physician diagnosis. However, we believe that is unlikely. First, we assessed the indication for NSAID use in a subset of the cohort, and no participant reported use for gastrointestinal symptoms. Although NSAIDs may be used for extraintestinal manifestations of IBD, the prevalence of these symptoms is low and rarely precedes the onset of bowel symptoms. Second, the risk for incident disease was highest in women who used NSAID for more than 6 years, a prolonged duration over which symptoms would not likely persist without a formal diagnosis. Third, a sensitivity analysis using a lag time of 4 years between exposure assessment and outcome did not affect our risk estimates. Finally, we did not find any association with other agents used for analgesia (aspirin and acetaminophen), suggesting specificity of the relationship with NSAIDs.

For now, our results have more mechanistic than clinical implications. They support the importance of pathways related to NSAIDs (but not aspirin) in the pathogenesis of IBD. Such insights could eventually lead to the development of novel lines of therapy as well as interventions that may modulate the risk for incident disease. Whether the association we

observed between NSAIDs and incident disease (and the lack of association between aspirin and disease) means anything about the safety of these common drugs in patients with existing IBD is unclear and merits further study. In addition, although the highest stratum of NSAID dose, frequency, or duration increases the risk for CD or UC, the absolute incidence of these diseases is low. Thus, the small increase in absolute risk associated with these therapies probably does not influence the balance between much more prevalent benefits and complications of these agents.

In conclusion, we observed an association between NSAID use, but not aspirin use, and incident CD and UC in middle-aged women. This risk is highest in those with greater frequency, higher dose, and longer duration of use. Further research into the association—and prospective studies of the safety of these agents in women with established CD and UC—are warranted.

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Appendix

Table 1
Comparison of Characteristics of Persons Who Responded and Those Who Did Not Respond to the Supplemental Questionnaire*

Characteristic	Able to Obtain Records	Unable to Obtain Records	P Value
Median age, y	57.1	57.1	0.41
Median body mass index, kg/m^2	25.1	24.9	0.53
Race, %			
White	95.0	95.0	0.99
Nonwhite	5.0	5.0	
Smoking status, %			0.27
Never	35.7	40.8	
Former	42.1	39.8	
Current	22.2	19.4	
Oral contraceptive use, %			0.20
Never	46.3	44.2	
Former	47.1	49.9	
Current	6.6	5.9	
Premenopausal, %	26.1	24.8	
Postmenopausal hormone use, %	17.7	15.8	0.85
Never	34.3	32.1	
Former	22.5	22.8	
Current	43.6	45.2	

Characteristic	Able to Obtain Records	Unable to Obtain Records	P Value
Regular aspirin use, % [†]	26.3	27.2	0.73
Regular NSAID use, % [†]	26.7	23.0	0.16
Regular acetaminophen use, % [†]	20.4	19.1	0.59
Coronary artery disease, %	1.0	1.4	0.53
Rheumatoid arthritis, %	0.3	0.8	0.21

NSAID = nonsteroidal anti-inflammatory drug.

* Percentages may not sum to 100% due to rounding.

[†] Regular use was defined as intake ≥ 2 times/wk.

Appendix Table 2

Baseline Characteristics of the Study Population, by Weekly Dose of NSAID and Aspirin Use in 1990*

Characteristic	0 tablets/wk	0.5–1.5 tablets/wk	2–5 tablets/wk	>5 tablets/wk
NSAIDs				
Patients, <i>n</i>	48 719	13 679	5836	8561
Median age (IQR), <i>y</i>	57.8 (51.8–63.7)	53.2 (48.3–59.4)	53.7 (48.8–60.0)	57.9 (52.3–63.7)
Median body mass index (IQR), <i>kg/m</i> ²	24.3 (21.9–27.5)	24.5 (22.1–27.9)	25.0 (22.5–28.3)	26.0 (23.0–30.0)
Race, %				
White	94.0	95.0	94.4	94.3
Nonwhite	6.0	5.0	5.6	5.7
Smoking status, %				
Never	44.8	43.6	41.4	42.1
Former	37.7	39.8	41.6	42.4
Current	17.5	16.6	17.0	15.6
Oral contraceptive use, %				
Never	55.3	41.1	41.0	49.5
Former	39.3	50.1	51.2	44.5
Current	5.4	8.8	7.8	5.9
Premenopausal, %	18.2	32.8	29.9	14.6
Postmenopausal hormone use, % [†]				
Never	43.2	35.5	33.8	30.3
Former	21.7	19.2	21.1	22.9
Current	35.1	45.3	44.9	46.7
Regular aspirin use, % [‡]	25.8	17.6	25.1	17.3
Regular acetaminophen use, % [‡]	13.9	12.1	24.2	21.6
Coronary artery disease, %	3.7	2.1	2.7	5.0
Rheumatoid arthritis, %	0.5	0.5	0.5	2.8
Psoriatic arthritis, %	0.5	0.5	1.0	1.6

Characteristic	0 tablets/wk	0.5–1.5 tablets/wk	2–5 tablets/wk	>5 tablets/wk
Aspirin				
Patients, <i>n</i>	41 655	16 717	9788	8635
Median age (IQR), <i>y</i>	56.2 (50.3–62.6)	55.5 (50.0–65.8)	57.0 (51.3–63.1)	60.5 (54.6–65.0)
Median body mass index (IQR), <i>kg/m²</i>	24.6 (22.1–28.2)	24.3 (22.0–27.5)	24.7 (22.1–28.2)	25.1 (22.3–28.7)
Race, %				
White	93.8	94.4	95.4	94.6
Nonwhite	6.2	5.6	4.6	5.4
Smoking status, %				
Never	43.8	46.6	44.0	40.2
Former	38.8	37.2	40.1	41.2
Current	17.4	16.2	15.9	18.5
Oral contraceptive use, %				
Never	50.2	48.7	51.9	58.7
Former	43.4	44.4	41.9	37.3
Current	6.5	7.0	6.2	4.0
Premenopausal, %	22.7	24.7	19.5	10.0
Postmenopausal hormone use, % [†]				
Never	40.1	41.0	38.5	37.3
Former	21.5	19.3	21.8	24.4
Current	38.3	39.7	39.8	38.3
Regular NSAID use, % [‡]	23.2	10.7	16.9	15.1
Regular acetaminophen use, % [‡]	18.7	8.5	16.1	13.1
Coronary artery disease, %	2.8	2.3	3.0	9.7
Rheumatoid arthritis, %	0.9	0.4	0.5	1.0
Psoriatic arthritis, %	0.7	0.4	0.5	0.9

IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug.

* Univariate comparisons were performed with an analysis of variance for categorical variables and the Wilcoxon signed-rank test for continuous variables. *P* < 0.001 for all comparisons due to the large size of the population. Percentages may not sum to 100% due to rounding.

[†] Percentages are among postmenopausal hormone users only.

[‡] Regular use was defined as intake ≥ 2 times/wk.

Appendix Table 3

Risk for CD and UC, by Frequency of NSAID, Aspirin, and Acetaminophen Use With a 2-Cycle Lag Between Exposure and Outcome*

Variable	0 d/mo	1–4 d/mo	5–14 d/mo	15 d/mo
NSAIDs				
Person-years of follow-up	936 252	127 086	87 410	144 570

Variable	0 d/mo	1–4 d/mo	5–14 d/mo	15 d/mo
CD				
Cases, <i>n</i>	75	16	12	20
Age-adjusted incidence, <i>n</i> [†]	8	13	14	14
Age-adjusted HR (95% CI)	1.0	1.57 (0.87–2.70)	1.76 (0.95–3.28)	1.63 (0.99–2.68)
Multivariate HR (95% CI) [‡]	1.0	1.48 (0.84–2.61)	1.76 (0.94–3.27)	1.58 (0.96–2.61)
UC				
Cases, <i>n</i>	76	11	6	24
Age-adjusted incidence, <i>n</i> [†]	8	9	7	17
Age-adjusted HR (95% CI)	1.00 (reference)	1.09 (0.57–2.10)	0.88 (0.38–2.03)	1.94 (1.22–3.09)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.06 (0.55–2.04)	0.85 (0.37–1.97)	1.84 (1.15–2.95)
Aspirin				
Person-years of follow-up	707 913	211 526	128 909	246 969
CD				
Cases, <i>n</i>	73	15	8	27
Age-adjusted incidence, <i>n</i> [†]	10	7	6	11
Age-adjusted HR (95% CI)	1.00 (reference)	0.76 (0.42–1.37)	0.73 (0.34–1.54)	1.02 (0.65–1.60)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.71 (0.37–1.34)	0.43 (0.18–1.00)	0.95 (0.60–1.50)
UC				
Cases, <i>n</i>	69	16	10	22
Age-adjusted incidence, <i>n</i> [†]	10	8	8	
Age-adjusted HR (95% CI)	1.00 (reference)	0.94 (0.53–1.68)	1.02 (0.51–2.04)	0.90 (0.55–1.47)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.96 (0.53–1.71)	1.03 (0.52–2.07)	0.89 (0.54–1.45)
Acetaminophen				
Person-years of follow-up	848 113	170 267	91 706	102 119
CD				
Cases, <i>n</i>	87	12	12	12
Age-adjusted incidence, <i>n</i> [†]	10	7	13	12
Age-adjusted HR (95% CI)	1.00 (reference)	0.63 (0.34–1.18)	1.34 (0.73–2.47)	1.17 (0.64–2.15)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.64 (0.34–1.20)	1.31 (0.71–2.41)	1.14 (0.62–2.10)
UC				
Cases, <i>n</i>	90	11	8	6
Age-adjusted incidence, <i>n</i> [†]	11	6	9	
Age-adjusted HR (95% CI)	1.00 (reference)	0.59 (0.31–1.13)	0.84 (0.41–1.75)	0.56 (0.25–1.29)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.58 (0.30–1.12)	0.82 (0.39–1.69)	0.55 (0.24–1.26)

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Exposure to aspirin, NSAIDs, or acetaminophen, according to the biennial questionnaire administered 2 cycles (4 y) before diagnosis.

[†] Age-adjusted incidence per 100 000 person-years.

[‡] Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

Appendix table 4

Risk for CD and UC, by Weekly Dose of NSAID and Aspirin Use With a 2-Cycle Lag Between Exposure and Outcome*

Variable	0 tablets/wk	0.5–1.5 tablets/wk	2–5 tablets/wk	>5 tablets/wk
NSAIDs				
Person-years of follow-up	641 520	293 384	180 286	180 127
CD				
Cases, <i>n</i>	52	22	21	28
Age-adjusted incidence, <i>n</i> [†]	8	8	12	16
Age-adjusted HR (95% CI)	1.00 (reference)	1.06 (0.64–1.76)	1.71 (1.01–2.87)	1.98 (1.24–3.15)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.02 (0.61–1.70)	1.67 (0.99–2.82)	1.90 (1.19–3.03)
UC				
Cases, <i>n</i>	52	22	15	28
Age-adjusted incidence, <i>n</i> [†]	8	8	8	16
Age-adjusted HR (95% CI)	1.00 (reference)	1.02 (0.61–1.70)	1.11 (0.62–1.99)	1.92 (1.20–3.05)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.99 (0.60–1.65)	1.05 (0.58–1.88)	1.79 (1.12–2.86)
Aspirin				
Person-years of follow-up	462 721	435 671	243 798	153 128
CD				
Cases, <i>n</i>	52	35	19	17
Age-adjusted incidence, <i>n</i> [†]	11	8	8	11
Age-adjusted HR (95% CI)	1.00 (reference)	0.79 (0.51–1.23)	0.73 (0.43–1.25)	1.02 (0.59–1.79)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.79 (0.51–1.24)	0.74 (0.43–1.26)	1.00 (0.57–1.74)
UC				
Cases, <i>n</i>	45	35	21	16
Age-adjusted incidence, <i>n</i> [†]	10	8	9	10
Age-adjusted HR (95% CI)	1.00 (reference)	0.86 (0.54–1.35)	0.88 (0.52–1.50)	1.07 (0.59–1.91)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.86 (0.55–1.36)	0.88 (0.51–1.49)	1.05 (0.59–1.89)

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Dose was assessed on each biennial questionnaire as the number of tablets used per week. Information on the number of tablets per week of acetaminophen was not collected. Exposure to aspirin, NSAIDs, or acetaminophen, according to the biennial questionnaire administered 2 cycles (4 y) before diagnosis.

[†] Age-adjusted incidence per 100 000 person-years.

[‡] Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

Appendix Table 5

Risk for CD and UC, by Duration of NSAID, Aspirin, and Acetaminophen Use With a 2-Cycle Lag Between Exposure and Outcome*

Variable	0 y	1–3 y	4–6 y	>6 y
NSAIDs				
Person-years of follow-up	590 074	298 000	262 848	144 395
CD				
Cases, <i>n</i>	50	22	33	18
Age-adjusted incidence, <i>n</i> [†]	8	7	13	12
Age-adjusted HR (95% CI)	1.00 (reference)	0.87 (0.53–1.45)	1.95 (1.20–3.18)	2.60 (1.39–4.83)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.85 (0.51–1.41)	1.88 (1.15–3.07)	2.53 (1.35–4.74)
UC				
Cases, <i>n</i>	49	22	35	11
Age-adjusted incidence, <i>n</i> [†]	8	7	13	
Age-adjusted HR (95% CI)	1.00 (reference)	0.93 (0.56–1.54)	1.70 (1.07–2.72)	1.31 (0.65–2.66)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.89 (0.54–1.48)	1.60 (1.00–2.56)	1.22 (0.60–2.49)
Aspirin				
Person-years of follow-up	387 946	161 670	219 410	526 291
CD				
Cases, <i>n</i>	38	15	19	51
Age-adjusted incidence, <i>n</i> [†]	10	9	9	10
Age-adjusted HR (95% CI)	1.00 (reference)	0.95 (0.52–1.72)	0.92 (0.53–1.60)	1.05 (0.68–1.60)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.95 (0.52–1.73)	0.92 (0.53–1.59)	1.02 (0.67–1.57)
UC				
Cases, <i>n</i>	32	11	22	52
Age-adjusted incidence, <i>n</i> [†]	8	7	10	1
Age-adjusted HR (95% CI)	1.00 (reference)	0.83 (0.42–1.65)	1.21 (0.70–2.10)	1.22 (0.78–1.91)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.81 (0.41–1.61)	1.18 (0.68–2.04)	1.20 (0.76–1.87)
Acetaminophen[§]				
Person-years of follow-up	1 018 363	52 081	50 627	41 725
CD				
Cases, <i>n</i>	103	6	8	2
Age-adjusted incidence, <i>n</i> [†]	10	12	16	5
UC Cases, <i>n</i>				
Age-adjusted incidence, <i>n</i> [†]	103	3	5	1
Age-adjusted incidence, <i>n</i> [†]	10	6	10	2

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Duration of use was calculated on the basis of cumulative duration of regular aspirin, NSAID, or acetaminophen use (2 tablets/wk). Exposure to aspirin, NSAIDs, or acetaminophen, according to the biennial questionnaire administered 2 cycles (4 y) before diagnosis.

[†] Age-adjusted incidence per 100 000 person-years.

[‡]Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

[§]Cox models were not fit for acetaminophen use because of the small number of cases reporting 1 y of use.

Appendix Table 6

Risk for CD and UC, by Frequency of NSAID, Aspirin, and Acetaminophen Use Among Women Without Rheumatoid or Psoriatic Arthritis*

Variable	0 d/mo	1–4 d/mo	5–14 d/mo	>15 d/mo
NSAIDs				
Person-years of follow-up	946 575	107 480	86 786	140 030
CD				
Cases, <i>n</i>	85	9	7	22
Age-adjusted incidence, <i>n</i> [‡]	9	8	8	16
Age-adjusted HR (95% CI)	1.00 (reference)	0.96 (0.47–1.94)	0.92 (0.42–2.00)	1.68 (1.05–2.70)
Multivariate HR (95% CI) ^{‡§}	1.00 (reference)	0.93 (0.46–1.90)	0.89 (0.40–1.94)	1.63 (1.01–2.63)
UC				
Cases, <i>n</i>	81	5	7	23
Age-adjusted incidence, <i>n</i> [‡]	9	5	8	16
Age-adjusted HR (95% CI)	1.00 (reference)	0.60 (0.24–1.50)	1.04 (0.48–2.27)	2.02 (1.26–3.23)
Multivariate HR (95% CI) ^{‡§}	1.00 (reference)	0.58 (0.23–1.46)	1.01 (0.46–2.20)	1.93 (1.20–3.09)
Aspirin				
Person-years of follow-up	638 630	245 973	162 415	233 855
CD				
Cases, <i>n</i>	73	17	7	26
Age-adjusted incidence, <i>n</i> [‡]	11	7	4	11
Age-adjusted HR (95% CI)	1.00 (reference)	0.69 (0.37–1.32)	0.43 (0.18–1.00)	0.96 (0.60–1.52)
Multivariate HR (95% CI) ^{‡§}	1.00 (reference)	0.71 (0.37–1.34)	0.43 (0.18–1.00)	0.94 (0.59–1.50)
UC				
Cases, <i>n</i>	63	20	10	23
Age-adjusted incidence, <i>n</i> [‡]	10	8	6	10
Age-adjusted HR (95% CI)	1.00 (reference)	1.12 (0.61–2.05)	0.80 (0.38–1.69)	1.06 (0.65–1.74)
Multivariate HR (95% CI) ^{‡§}	1.00 (reference)	1.14 (0.62–2.07)	0.82 (0.39–1.72)	1.04 (0.64–1.71)
Acetaminophen				
Person-years of follow-up	844 888	135 479	88 609	108 484
CD				
Cases, <i>n</i>	82	9	15	13
Age-adjusted incidence, <i>n</i> [‡]	10	7	17	12
Age-adjusted HR (95% CI)	1.00 (reference)	0.66 (0.32–1.3)	1.80 (1.03–3.16)	1.27 (0.70–2.30)
Multivariate HR (95% CI) ^{‡§}	1.00 (reference)	0.67 (0.33–1.37)	1.75 (0.99–3.09)	1.25 (0.69–2.25)
UC				
Cases, <i>n</i>	86	12	8	8

Variable	0 d/mo	1–4 d/mo	5–14 d/mo	>15 d/mo
Age-adjusted incidence, $n^{\dagger}$	10	9	9	7
Age-adjusted HR (95% CI)	1.00 (reference)	0.95 (0.50–1.79)	0.97 (0.46–2.01)	0.75 (0.36–1.56)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.92 (0.49–1.74)	0.95 (0.46–1.97)	0.73 (0.35–1.51)

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Total study population was 75 870 women after excluding 570 women with rheumatoid arthritis and 355 women with psoriatic arthritis.

[†] Age-adjusted incidence per 100 000 person-years.

[‡] Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

Appendix Table 7

Risk for CD and UC, by Weekly Dose of NSAID and Aspirin Use Among Women Without Rheumatoid or Psoriatic Arthritis*

Variable	0 tablets/wk	0.5–1.5 tablets/wk	2–5 tablets/wk	>5 tablets/wk
NSAIDs				
Person-years of follow-up	596 196	311 653	195 976	177 046
CD				
Cases, n	48	25	24	26
Age-adjusted incidence, $n^{\dagger}$	8	8	12	15
Age-adjusted HR (95% CI)	1.00 (reference)	1.13 (0.69–1.87)	1.73 (1.05–2.85)	1.83 (1.13–2.95)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.09 (0.66–1.79)	1.69 (1.02–2.79)	1.75 (1.08–2.84)
UC				
Cases, n	46	23	20	27
Age-adjusted incidence, $n^{\dagger}$	8	7	10	15
Age-adjusted HR (95% CI)	1.00 (reference)	1.05 (0.63–1.75)	1.43 (0.84–2.44)	1.99 (1.23–3.21)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.02 (0.61–1.71)	1.34 (0.78–2.30)	1.87 (1.15–3.04)
Aspirin				
Person-years of follow-up	401 366	468 127	258 351	153 028
CD				
Cases, n	44	42	22	15
Age-adjusted incidence, $n^{\dagger}$	11	9	9	10
Age-adjusted HR (95% CI)	1.00 (reference)	0.87 (0.57–1.35)	0.80 (0.47–1.34)	0.91 (0.50–1.66)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.87 (0.56–1.35)	0.80 (0.48–1.35)	0.88 (0.49–1.61)
UC				
Cases, n	41	37	21	17
Age-adjusted incidence, $n^{\dagger}$	10	8	8	11
Age-adjusted HR (95% CI)	1.00 (reference)	0.79 (0.50–1.25)	0.79 (0.46–1.35)	1.04 (0.58–1.85)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.80 (0.50–1.26)	0.78 (0.46–1.34)	1.03 (0.58–1.84)

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Total study population was 75 870 women after excluding 570 women with rheumatoid arthritis and 355 women with psoriatic arthritis. Dose was assessed on each biennial questionnaire as the number of tablets used per week. Information on the number of tablets per week of acetaminophen was not collected.

[†] Age-adjusted incidence per 100 000 person-years.

[‡] Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

Appendix Table 8

Risk for CD and UC, by Duration of NSAID, Aspirin, and Acetaminophen Use Among Women Without Rheumatoid or Psoriatic Arthritis*

Variable	0 y	1–3 y	4–6 y	>6 y
NSAIDs				
Person-years of follow-up	540 301	262 673	293 301	184 588
CD				
Cases, <i>n</i>	46	16	32	29
Age-adjusted incidence, <i>n</i> [†]	9	6	11	16
Age-adjusted HR (95% CI)	1.00 (reference)	0.74 (0.42–1.32)	1.43 (0.89–2.29)	2.96 (1.74–5.04)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.73 (0.41–1.29)	1.38 (0.86–2.22)	2.87 (1.67–4.92)
UC				
Cases <i>n</i>				
Age-adjusted incidence, <i>n</i> [†]	8	8	10	13
Age-adjusted HR (95% CI)	1.00 (reference)	0.97 (0.57–1.64)	1.34 (0.82–2.17)	2.14 (1.23–3.70)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.00 (0.58–1.70)	1.39 (0.85–2.56)	2.24 (1.29–3.90)
Aspirin				
Person-years of follow-up	505 008	183 475	188 857	403 532
CD				
Cases, <i>n</i>	50	25	13	35
Age-adjusted incidence, <i>n</i> [†]	10	14	7	
Age-adjusted HR (95% CI)	1.00 (reference)	1.34 (0.84–2.22)	0.72 (0.39–1.33)	0.94 (0.61–1.47)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.37 (0.84–2.21)	0.71 (0.38–1.31)	0.92 (0.59–1.43)
UC				
Cases, <i>n</i>	42	18	19	38
Age-adjusted incidence, <i>n</i> [†]	8	10	10	9
Age-adjusted HR (95% CI)	1.00 (reference)	1.23 (0.70–2.15)	1.24 (0.71–2.17)	1.22 (0.78–1.92)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.21 (0.69–2.11)	1.21 (0.69–2.11)	1.20 (0.76–1.89)
Acetaminophen[§]				
Person-years of follow-up	888 232	44 428	53 951	44 472
CD				
Cases, <i>n</i>	89	7	9	5
Age-adjusted incidence, <i>n</i> [†]	10	16	17	11
UC				
Cases, <i>n</i>	91	4	6	1

Variable	0 y	1–3 y	4–6 y	>6 y
Age-adjusted incidence, $n^{\dagger}$	10	9	11	2

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Total study population was 75 870 women after excluding 570 women with rheumatoid arthritis and 355 women with psoriatic arthritis. Duration of use was calculated on the basis of cumulative duration of regular aspirin, NSAID, or acetaminophen use (2 tablets/wk).

[†] Age-adjusted incidence per 100 000 person-years.

[‡] Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

[§] Cox models were not fit for acetaminophen use because of the small number of cases reporting 1 y of use.

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Context

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit inflammation but have been linked in some studies to inflammatory bowel disease.

Contribution

This observational study in nurses found an increase in incidence of Crohn disease and ulcerative colitis with frequent NSAID but not aspirin use.

Caution

The findings apply exclusively to women.

Implication

Use of NSAIDs but not aspirin is associated with higher incidence of Crohn disease and ulcerative colitis. Absolute incidence of both conditions was low, so any increase in risk is unlikely to alter the balance of more common and clinically significant risks and benefits associated with NSAIDs.

The Editors

Figure 1. Study flow diagram

CD = Crohn disease; IBD = inflammatory bowel disease; UC = ulcerative colitis.

Figure 2. Timing of ascertainment of exposures and outcome

CD = Crohn disease; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

Table 1
Baseline Characteristics of the Study Population, by Frequency of NSAID or Aspirin Use in 1990*

Characteristic	0 d/mo	1–4 d/mo	5–14 d/mo	15 d/mo
NSAIDs				
Patients, <i>n</i>	48 719	13 679	5836	8561
Median age (IQR), <i>y</i>	57.8 (51.8–63.7)	53.2 (48.3–59.4)	53.7 (48.8–60.0)	57.9 (52.3–63.7)
Median body mass index (IQR), <i>kg/m</i> ²	24.3 (21.9–27.5)	24.5 (22.1–27.9)	24.9 (22.5–28.3)	26.0 (23.0–30.0)
Race, %				
White	94.0	95.0	94.4	94.3
Nonwhite	6.0	5.0	5.6	5.7
Smoking status, %				
Never	45.0	43.8	41.5	42.3
Former	37.7	39.8	41.6	42.4
Current	17.3	16.4	16.9	15.3
Oral contraceptive use, %				
Never	55.3	41.1	41.0	49.5
Former	39.3	50.1	51.2	44.5
Current	5.4	8.8	7.8	5.9
Premenopausal, %	18.2	32.8	29.9	14.6
Postmenopausal hormone use, % [†]				
Never	43.2	35.5	33.9	30.3
Former	21.7	19.2	21.1	22.9
Current	35.1	45.3	45.0	46.7
Regular aspirin use, % [‡]	26.8	17.6	25.2	17.3
Regular acetaminophen use, % [‡]	13.9	11.4	24.2	21.7
Coronary artery disease, %	3.7	2.1	2.7	5.0
Rheumatoid arthritis, %	0.2	0.2	0.2	2.4
Psoriatic arthritis, %	0.5	0.5	1.0	1.6
Aspirin				
Patients, <i>n</i>	41 655	16 717	6852	11 571
Median age (IQR), <i>y</i>	56.2 (50.3–62.6)	55.5 (50.0–62.0)	56.5 (50.8–62.8)	59.9 (54.1–64.8)
Median body mass index (IQR), <i>kg/m</i> ²	24.6 (22.1–28.2)	24.3 (22.0–27.5)	24.5 (22.1–28.0)	25.0 (22.3–28.5)
Race, %				
White	93.8	94.4	95.7	94.6
Nonwhite	6.2	5.6	4.3	5.4
Smoking status, %				
Never	44.0	46.8	44.7	41.1
Former	38.8	37.2	39.9	41.0

Characteristic	0 d/mo	1–4 d/mo	5–14 d/mo	15 d/mo
Current	17.2	16.0	15.4	17.9
Oral contraceptive use, %				
Never	50.2	48.7	50.4	57.9
Former	43.4	44.4	43.1	37.7
Current	6.5	7.0	6.5	4.4
Premenopausal, %	22.7	24.7	21.1	11.5
Postmenopausal hormone use, % [†]				
Never	40.1	41.0	38.7	37.5
Former	21.5	19.3	21.2	24.0
Current	38.3	39.7	40.1	38.6
Regular NSAID use, % [‡]	23.2	10.7	17.0	15.4
Regular acetaminophen use, % [‡]	18.7	8.5	15.7	13.2
Coronary artery disease, %	2.8	2.3	2.8	8.1
Rheumatoid arthritis, %	0.9	0.4	0.5	0.9
Psoriatic arthritis, %	0.7	0.4	0.5	0.8

IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug.

* Univariate comparisons were performed with an analysis of variance for categorical variables and the Wilcoxon signed-rank test for continuous variables. $P < 0.001$ for all comparisons due to the large size of the study population. Percentages may not sum to 100% due to rounding.

[†] Percentages are among postmenopausal hormone users only.

[‡] Regular use was defined as intake >2 times/wk.

Table 2
Risk for CD and UC, by Frequency of NSAID, Aspirin, and Acetaminophen Use

Variable	0 d/mo	1–4 d/mo	5–14 d/mo	15 d/mo
NSAIDs				
Person-years of follow-up	955 735	108 368	87 611	143 603
CD				
Cases, <i>n</i>	85	9	7	22
Age-adjusted incidence, <i>n</i> [*]	9	8	8	15 [†]
Age-adjusted HR (95% CI)	1.00 (reference)	0.96 (0.46–1.94)	0.92 (0.42–2.00)	1.70 (1.02–2.65)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.94 (0.46–1.90)	0.89 (0.41–1.94)	1.60 (0.99–2.58)
UC				
Cases, <i>n</i>	82	5	7	23
Age-adjusted incidence, <i>n</i> [*]	9	5	8	16 [†]
Age-adjusted HR (95% CI)	1.00 (reference)	0.59 (0.24–1.48)	1.03 (0.47–2.25)	1.95 (1.22–3.12)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.57 (0.23–1.43)	0.99 (0.45–2.17)	1.87 (1.16–2.99)
Aspirin				
Person-years of follow-up	646 824	248 357	163 906	236 230
CD				
Cases, <i>n</i>	73	17	7	26
Age-adjusted incidence, <i>n</i> [*]	11	7	4	11
Age-adjusted HR (95% CI)	1.00 (reference)	0.70 (0.37–1.32)	0.43 (0.18–1.00)	0.96 (0.60–1.52)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.71 (0.37–1.35)	0.43 (0.18–1.00)	0.95 (0.60–1.50)
UC				
Cases, <i>n</i>	64	20	10	23
Age-adjusted incidence, <i>n</i> [*]	10	8	6	10
Age-adjusted HR (95% CI)	1.00 (reference)	1.11 (0.61–2.02)	0.80 (0.38–1.67)	1.03 (0.63–1.69)
Multivariate HR (95% CI) [‡]	1.00 (reference)	1.12 (0.62–2.04)	0.81 (0.38–1.70)	1.02 (0.62–1.67)
Acetaminophen				
Person-years of follow-up	853 938	136 881	89 746	110 462
CD				
Cases, <i>n</i>	82	9	15	13
Age-adjusted incidence, <i>n</i> [*]	10	7	17	12
Age-adjusted HR (95% CI)	1.00 (reference)	0.66 (0.32–1.34)	1.80 (1.02–3.16)	1.27 (0.70–2.29)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.67 (0.33–1.37)	1.75 (0.99–3.09)	1.24 (0.69–2.25)
UC Cases, <i>n</i>				
	87	12	8	8
Age-adjusted incidence, <i>n</i> [*]	10	9	9	
Age-adjusted HR (95% CI)	1.00 (reference)	0.94 (0.50–1.78)	0.94 (0.45–1.96)	0.73 (0.35–1.51)
Multivariate HR (95% CI) [‡]	1.00 (reference)	0.92 (0.48–1.73)	0.92 (0.44–1.92)	0.70 (0.34–1.46)

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Age-adjusted incidence per 100 000 person-years.

[†] Difference in incidence between women using NSAIDs for 15 d/mo and nonusers: 6 cases of CD per 100 000 person-years (95% CI, 0–13) and 7 cases of UC per 100 000 person-years (CI, 1–12).

[‡] Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

Table 3
Risk for CD and UC, by Weekly Dose of NSAID and Aspirin Use*

Variable	0 tablets/wk	0.5–1.5 tablets/wk	2–5 tablets/wk	>5 tablets/wk
NSAIDs				
Person-years of follow-up	600 068	314 140	198 903	182 207
CD				
Cases, <i>n</i>	48	25	24	26
Age-adjusted incidence, <i>n</i> [†]	8	8	12	14 [‡]
Age-adjusted HR (95% CI)	1.00 (reference)	1.13 (0.69–1.86)	1.72 (1.04–2.84)	1.78 (1.10–2.89)
Multivariate HR (95% CI) [§]	1.00 (reference)	1.09 (0.66–1.80)	1.68 (1.02–2.78)	1.71 (1.05–2.77)
UC				
Cases, <i>n</i>	47	23	20	27
Age-adjusted incidence, <i>n</i> [†]	8	7	10	15 [‡]
Age-adjusted HR (95% CI)	1.00 (reference)	1.03 (0.62–1.71)	1.38 (0.81–2.36)	1.90 (1.18–3.07)
Multivariate HR (95% CI) [§]	1.00 (reference)	1.00 (0.60–1.66)	1.30 (0.76–2.21)	1.78 (1.10–2.89)
Aspirin				
Person-years of follow-up	407 201	472 282	260 915	154 920
CD				
Cases, <i>n</i>	44	42	22	15
Age-adjusted incidence, <i>n</i> [†]	11	9	8	10
Age-adjusted HR (95% CI)	1.00 (reference)	0.88 (0.57–1.36)	0.80 (0.47–1.35)	0.91 (0.50–1.66)
Multivariate HR (95% CI) [§]	1.00 (reference)	0.88 (0.57–1.36)	0.80 (0.48–1.35)	0.89 (0.49–1.61)
UC				
Cases, <i>n</i>	42	37	21	17
Age-adjusted incidence, <i>n</i> [†]	10	8	8	11
Age-adjusted HR (95% CI)	1.00 (reference)	0.77 (0.49–1.22)	0.77 (0.45–1.31)	1.01 (0.57–1.79)
Multivariate HR (95% CI) [§]	1.00 (reference)	0.78 (0.50–1.23)	0.76 (0.45–1.30)	1.00 (0.56–1.78)

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Dose was assessed on each biennial questionnaire as the number of tablets used per week. Information on the number of tablets per week of acetaminophen was not collected.

[†] Age-adjusted incidence per 100 000 person-years.

[‡] Difference in incidence between women using ≥ 5 NSAID tablets/wk and nonusers: 6 cases of CD per 100 000 person-years (95% CI, 0–12) and 7 cases of UC per 100 000 person-years (CI, 1–13).

[§] Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

Table 4
Incidence and Relative Risk for CD and UC, by Duration of NSAID, Aspirin, and Acetaminophen Use*

Variable	0 y	1–3 y	4–6 y	>6 y
NSAIDs				
Person-years of follow-up	543 285	265 962	297 723	188 347
CD				
Cases, <i>n</i>	46	16	32	29
Age-adjusted incidence, <i>n</i> [†]	8	6	11	15 [‡]
Age-adjusted HR (95% CI)	1.00 (reference)	0.74 (0.42–1.31)	1.42 (0.88–2.27)	2.91 (1.71–4.95)
Multivariate HR (95% CI) [§]	1.00 (reference)	0.72 (0.41–1.28)	1.37 (0.85–2.20)	2.83 (1.65–4.85)
UC				
Cases, <i>n</i>	43	20	30	24
Age-adjusted incidence, <i>n</i> [†]	8	8	10	13 [‡]
Age-adjusted HR (95% CI)	1.00 (reference)	0.97 (0.57–1.64)	1.34 (0.82–2.17)	2.14 (1.23–3.70)
Multivariate HR (95% CI) [§]	1.00 (reference)	0.93 (0.54–1.58)	1.26 (0.77–2.05)	2.00 (1.15–3.49)
Aspirin				
Person-years of follow-up	358 129	158 077	222 631	556 481
CD				
Cases, <i>n</i>	33	20	19	51
Age-adjusted incidence, <i>n</i> [†]	9	13	9	
Age-adjusted HR (95% CI)	1.00 (reference)	1.34 (0.77–2.34)	0.96 (0.54–1.69)	1.04 (0.67–1.63)
Multivariate HR (95% CI) [§]	1.00 (reference)	1.35 (0.77–2.36)	0.95 (0.53–1.67)	1.02 (0.65–1.60)
UC				
Cases, <i>n</i>	31	8	22	56
Age-adjusted incidence, <i>n</i> [†]	9	5	10	10
Age-adjusted HR (95% CI)	1.00 (reference)	0.58 (0.27–1.27)	1.13 (0.65–1.96)	1.18 (0.77–1.84)
Multivariate HR (95% CI) [§]	1.00 (reference)	0.57 (0.26–1.23)	1.09 (0.63–1.89)	1.16 (0.74–1.81)
Acetaminophen //				
Person-years of follow-up	887 792	45 005	54 723	45 161
CD				
Cases, <i>n</i>	89	7	9	5
Age-adjusted incidence, <i>n</i> [†]	10	16	17	11
UC				
Cases, <i>n</i>	91	4	6	1
Age-adjusted incidence, <i>n</i> [†]	10	9	11	2

CD = Crohn disease; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; UC = ulcerative colitis.

* Duration of use was calculated on the basis of cumulative duration of regular aspirin, NSAID, or acetaminophen use (>2 tablets/wk).

[†]Age-adjusted incidence per 100 000 person-years.

[‡]Difference in incidence between women using NSAIDs for >6 y and nonusers: 7 cases of CD per 100 000 person-years (95% CI, 1–13) and 5 cases of UC per 100 000 person-years (CI, 0–10).

[§]Adjusted for age, smoking (never, former, or current), oral contraceptive use (never, former, or current), and postmenopausal hormone therapy use (premenopausal or never, former, or current).

// Cox models were not fit for acetaminophen use because of the small number of cases reporting >1 y of use.