CLINICAL REPORT

Use of Aspirin, Non-steroidal Anti-inflammatory Drugs, and Acetaminophen (Paracetamol), and Risk of Psoriasis and Psoriatic Arthritis: A Cohort Study

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Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to induce or exacerbate psoriasis. We aimed to evaluate the association between several widely used analgesics, including aspirin, non-aspirin NSAIDs, and acetaminophen (paracetamol), and risk of psoriasis and psoriatic arthritis (PsA) in a large cohort of US women, the Nurses' Health Study II (1991–2005). Information on regular use of aspirin, NSAIDs, and acetaminophen was collected for 95,540 participants during the follow-up. During 1,321,280 person-years of follow-up, we documented 646 incident psoriasis cases and 165 concomitant PsA cases. Compared to women who reported no use, regular acetaminophen and NSAIDs users with more than 10 years of use had multivariate hazard ratios of 3.60 [95% confidence interval (CI): 2.02–6.41] and 2.10 (95% CI: 1.11–3.96) for PsA, respectively. There was no clear association between aspirin and risk of psoriasis or PsA. In conclusion, long-term acetaminophen and NSAIDs use may be associated with an increased risk of PsA. Special attention on psoriasis and PsA screening may be needed for those who are prescribed for acetaminophen and NSAIDs for long-term periods. *Key words: acetaminophen; aspirin; inflammation; non-steroidal anti-inflammatory drugs; psoriasis; psoriatic arthritis.*

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Psoriasis is an immune-mediated chronic systemic disease that affects about 1.5–3% of the population in Western countries (1, 2). Psoriasis is associated with an inflammatory psoriatic arthritis (PsA) that can be disabling and develop into a deforming erosive arthropathy in some patients (3). PsA occurs in 6–39% of psoriasis cases and affects an estimated number of 520,000 individuals in the US population (4, 5). Both psoriasis and PsA have been associated with substantial morbidity and economic costs (4, 6). Prevention and management of psoriasis and PsA require a better understanding of the disease pathogenesis, whereas prospective evidence on the pathogenesis of these two conditions, especially PsA, is still limited.

Aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen (paracetamol), are widely used over-the-counter analgesics and antipyretics. Aspirin and NSAIDs also have anti-inflammatory properties at higher doses whereas acetaminophen only exhibits weak anti-inflammatory activity. The mechanism of action of aspirin and other NSAIDs is probably mediated through inhibition of prostaglandin–endoperoxide synthase or cyclooxygenase (COX) enzymes, though other mechanisms may also exist (7). The mechanism of action of acetaminophen is not completely understood, whereas the main mechanism proposed is also the inhibition of COX (8, 9). Along with the medical uses, these medications may also cause a series of adverse effects, such as gastrointestinal ulceration and bleeding, hepato-renal dysfunction and organ failure, and serious cutaneous reactions (7, 10). Specifically, a number of previous reports have documented worsening of psoriasis with initiation of NSAIDs therapy (11–17). In a recent prospective study, regular use of NSAIDs but not aspirin is found to be associated with an increased risk of inflammatory bowel disease (Crohn disease or ulcerative colitis) (18). Increased occurrence of psoriasis among patients with established inflammatory bowel disease has been reported (19, 20), and our previous study also found an increased risk of Crohn's disease associated with psoriasis and PsA (21). A close examination reveals genetic and pathologic connections between psoriasis and Crohn's disease (22). Based on the aforementioned evidence, we infer a potential link between use of these medications and risk of psoriasis and PsA. To address the hypothesis, we investigated the association between use of aspirin, NSAIDs, and acetaminophen, and risk of incident psoriasis and PsA using data from a large cohort of US women, the Nurses' Health Study II (NHS II).

MATERIAL AND METHODS

Study population

The NHS II was established in 1989 when 116,430 registered female nurses aged 25–42 years were enrolled using a mailed

baseline questionnaire which inquired about medical history and lifestyle practices. Biennially, cohort members receive a questionnaire enquiring about diseases and health-related factors. The follow-up rate exceeds 90% for each cycle. The institutional review board of Partners Health Care System approved this study. The completion and return of the self-administered questionnaire was considered as informed consent.

Ascertainment of psoriasis and psoriatric arthritis cases

In 2005, women in the NHS II were asked if they had personal history of clinician-diagnosed psoriasis and the date of diagnosis (before 1991, 1991–1994, 1995–1998, 1999–2002, or 2003–2005) on the biannual questionnaire. During 2008–2011, we confirmed self-reported psoriasis using Psoriasis Screening Tool (PST) questionnaire, which inquired about the type of clinicians making the diagnosis and phenotypes (23). A pilot study using the PST showed 99% sensitivity and 94% specificity for psoriasis screening (23). Diagnosis of psoriasis with concomitant PsA was confirmed using psoriatic arthritis screening and evaluation (PASE) questionnaire, which includes a symptom scale with 7 items and a function scale with 8 items (24). Women chose one of 5 categories relating to agreement (strongly agree to strongly disagree) for each item. A total score of 47 or greater has been shown to identify PsA with a high sensitivity and specificity in our pilot study (24, 25). PASE has good test–retest reliability (25), and has been shown to be an effective tool in identifying PsA cases with 77% sensitivity and 79% specificity in the present cohort (26).

Assessment of medication use

Cohort participants were asked about regular use (defined as ≥2 times/week) of aspirin, other NSAIDs, and acetaminophen (paracetamol) on baseline questionnaire in 1989. Since 1993, regular use of these medications during the past two years was assessed biennially. Information on average weekly dose (0, 1–2 tablets/week, 3–5 tablets/week, 6–14 tablets/week, and ≥15 tablets/week) of these medications during the past two years was first collected in 1999, and updated biennially thereafter. In 2001 and 2003, we also asked women about weekly dose of low-dose (baby) aspirin. Intake of 4 baby aspirin was converted to 1 adult standard-dose tablet (325 mg) as previously documented (27). We estimated duration of use by using the starting duration in 1989 and updating this variable according to the duration of use on each subsequent biennial questionnaire (18). We categorized medication use according to regular use status, duration, and weekly dose (27–29).

Statistical analysis

Among the women who responded to psoriasis questions, we excluded those who self-reported psoriasis but did not respond to the PST or PASE questionnaire or were not confirmed ($n = 1,007$), had prevalent psoriasis/PsA at baseline ($n = 895$), and self-reported psoriasis but with missing diagnosis date $n = 34$. In the present analysis, 95,540 women were included, and they contributed person-years of follow-up from the return date of the baseline questionnaire to the diagnosis date of psoriasis/PsA or the end of follow-up, whichever came first.

We used Cox proportional hazards analyses to estimate the age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between medication use and risk of psoriasis and PsA. Multivariate-adjusted HRs were calculated after adjusting for age, follow-up interval, race (White or others), body mass index (BMI) (<25.0, 25–29.9, 30–34.9, and ≥35 kg/m²), alcohol intake (0, <5, 5–9.9, or ≥10 g/day), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, and ≥27

metabolic equivalent h/week), smoking status (never, past, current smoking with 1–14, 15–24, or ≥25 cigarettes/day), oral contraceptives use (never, past, or current use), postmenopausal hormones use (premenopausal, never, past, or current use), multi-vitamins use (never, past, or current use), cardiovascular disease (yes or no), type 2 diabetes (yes or no), hypertension (yes or no), and hypercholesterolemia (yes or no). We used the most updated information for time-varying variables (e.g. BMI) prior to each follow-up interval to take into account potential changes over the follow-up. We also performed secondary analyses with a 4-year (2-cycle) interval between drug exposure and diagnosis of disease. The 4-year lag made it less likely that medication use was related to early disease symptoms.

All statistical analyses were performed using Statistical Analysis System software (SAS, version 9.2; SAS Institute Inc, Cary, NC). All statistical tests were 2-tailed, and the significance level was set at $p < 0.05$.

RESULTS

During 1,321,280 person-years of follow-up from 1991 to 2005, we documented a total of 646 incident psoriasis cases and 165 concomitant PsA cases. Table I shows the baseline characteristics of the study participants. Compared to non-regular users, regular users of acetaminophen, NSAIDs, and aspirin all tended to have higher BMIs and higher prevalence rates of other medications, and personal histories of chronic diseases.

Regular acetaminophen users were at a higher risk of developing psoriasis (age-adjusted HR 1.29, 95% CI: 1.08–1.54) or psoriasis with concomitant PsA (age-adjusted HR 2.23, 95% CI: 1.63–3.07) when compared to non-regular users (Table II). These associations persisted in multivariate-adjusted models. However, only the HR of PsA associated with regular acetaminophen use remained significant in fully-adjusted models accounting for aspirin and other NSAIDs (HR 1.78, 95% CI: 1.28–4.46). Regular NSAIDs users were also more likely to develop psoriasis (age-adjusted HR 1.26, 95% CI: 1.06–1.49) or PsA (age-adjusted HR 1.74, 95% CI: 1.26–2.40) when compared to non-regular users. However, these associations did not persist in multivariate models with or without acetaminophen and aspirin. Only HR of PsA associated with regular NSAIDs use was of marginal significance in fully-adjusted models (multivariate HR 1.35, 95% CI: 0.98–1.88). In contrast, there was no clear association between regular aspirin use and disease risk. These findings were consistent in secondary analyses with 4-year lag between exposure and outcome (Table SI[1]). Interestingly, regular NSAIDs users had a fully-adjusted HR of 1.71 (95% CI: 1.16–2.52) for PsA after 4 years.

Analyses by duration of regular use suggest a trend towards higher disease risk after long-term acetaminophen or NSAIDs use, especially for PsA (Table II). Compared to women who reported no use, regular ace-

Table I. *Age-adjusted baseline characteristics of the study participants by status of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and aspirin use*[a]

	Acetaminophen (Paracetamol)		NSAIDs		Aspirin	
	Non-regular users ($n=74,996$)	Regular users ($n=20,544$)	Non-regular users ($n=77,300$)	Regular users ($n=18,240$)	Non-regular users ($n=84,866$)	Regular users ($n=10,674$)
Age, years, mean (SD)	36.2 (4.6)	36.1 (4.7)	36.0 (4.6)	36.9 (4.6)	36.0 (4.7)	37.5 (4.4)
White race, %	95.1	95.9	94.9	96.7	95.0	97.2
Body mass index, kg/m², mean (SD)	24.4 (5.2)	25.2 (5.6)	24.3 (5.1)	25.6 (5.9)	24.5 (5.2)	24.9 (5.5)
Alcohol intake, g/day, mean (SD)	3.2 (6.1)	3.0 (6.1)	3.1 (5.9)	3.5 (6.7)	3.0 (5.9)	4.0 (7.1)
Physical activity, met-h/week, mean (SD)	21.0 (26.9)	19.9 (26.2)	20.7 (26.7)	21.1 (27.4)	20.7 (26.7)	21.3 (27.4)
Current smoking, %	11.1	12.9	10.9	14.2	11.1	15.3
Medications						
Acetaminophen use, %	–	–	19.2	31.4	20.8	27.9
NSAIDs use, %	16.8	27.6	–	–	18.5	24.4
Aspirin use, %	10.3	14.2	10.5	14.1	–	–
Oral contraceptives use, %	10.3	10.7	10.1	11.9	10.3	11.9
Postmenopausal hormones use, %	82.5	84.6	81.4	87.5	82.5	85.9
Multi-vitamins use, %	43.4	46.7	43.2	47.8	43.5	49.0
History of chronic diseases						
Cardiovascular disease, %	0.02	0.06	0.03	0.03	0.03	0.02
Type 2 diabetes, %	0.1	0.2	0.1	0.2	0.1	0.2
Hypertension, %	5.7	8.4	5.6	8.9	6.0	8.5
Hypercholesterolemia, %	13.6	17.3	13.6	17.8	14.0	17.1

[a]All values other than for age have been directly standardized according to the age distribution of the study population.

Table II. *Risk of psoriasis and psoriatic arthritis (PsA) according to regular use and duration of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and aspirin in the Nurses' Health Study II (1991–2005)*

	Non-regular users	Regular users	Duration			
			0	1–6 years	7–10 years	≥11 years
Acetaminophen						
Psoriasis						
No. of cases/person-years	411/904,444	183/280,671	303/688,413	154/268,733	49/80,609	33/32,300
Age-adjusted HR (95% CI)	1.00	1.29 (1.08, 1.54)	1.00	1.26 (1.03, 1.53)	1.26 (0.92, 1.71)	1.54 (1.06, 2.23)
Multivariate HR (95% CI)[a]	1.00	1.19 (1.00, 1.42)	1.00	1.16 (0.96, 1.42)	1.12 (0.82, 1.53)	1.33 (0.91, 1.94)
Multivariate HR (95% CI)[b]	1.00	1.17 (0.97, 1.39)	1.00	1.14 (0.94, 1.39)	1.09 (0.80, 1.50)	1.29 (0.89, 1.89)
PsA						
No. of cases/person-years	89/904,444	68/280,671	57/688,413	48/268,733	15/80,609	19/32,300
Age-adjusted HR (95% CI)	1.00	2.23 (1.63, 3.07)	1.00	2.16 (1.47, 3.19)	2.23 (1.23, 4.04)	5.22 (2.96, 9.21)
Multivariate HR (95% CI)[a]	1.00	1.86 (1.35, 2.56)	1.00	1.83 (1.24, 2.70)	1.75 (0.97, 3.18)	3.79 (2.13, 3.18)
Multivariate HR (95% CI)[b]	1.00	1.78 (1.28, 2.46)	1.00	1.77 (1.19, 2.62)	1.66 (0.91, 3.02)	3.60 (2.02, 6.41)
NSAIDs						
Psoriasis						
No. of cases/person-years	343/765,167	254/420,137	245/582,384	168/315,423	73/121,158	51/47,416
Age-adjusted HR (95% CI)	1.00	1.26 (1.06, 1.49)	1.00	1.24 (1.01, 1.52)	1.27 (0.96, 1.68)	1.62 (1.16, 2.25)
Multivariate HR (95% CI)[a]	1.00	1.15 (0.97, 1.36)	1.00	1.11 (0.91, 1.37)	1.07 (0.80, 1.42)	1.30 (0.93, 1.82)
Multivariate HR (95% CI)[b]	1.00	1.12 (0.94, 1.33)	1.00	1.09 (0.88, 1.34)	1.04 (0.78, 1.38)	1.26 (0.90, 1.76)
PsA						
No. of cases/person-years	78/765,167	79/420,137	45/582,384	46/315,423	29/121,158	18/47,416
Age-adjusted HR (95% CI)	1.00	1.74 (1.26, 2.40)	1.00	2.04 (1.33, 3.14)	3.26 (1.92, 5.54)	3.61 (1.93, 6.76)
Multivariate HR (95% CI)[a]	1.00	1.47 (1.06, 2.03)	1.00	1.63 (1.06, 2.51)	2.30 (1.35, 3.91)	2.32 (1.23, 4.36)
Multivariate HR (95% CI)[b]	1.00	1.35 (0.98, 1.88)	1.00	1.51 (0.98, 2.33)	2.09 (1.22, 3.58)	2.10 (1.11, 3.96)
Aspirin						
Psoriasis						
No. of cases/person-years	474/1,003,279	119/182,107	385/825,789	114/191,386	25/43,366	18/16,365
Age-adjusted HR (95% CI)	1.00	1.13 (0.92, 1.39)	1.00	1.14 (0.92, 1.41)	0.99 (0.66, 1.50)	1.38 (0.84, 2.24)
Multivariate HR (95% CI)[a]	1.00	0.99 (0.80, 1.22)	1.00	1.01 (0.81, 1.26)	0.85 (0.56, 1.29)	1.17 (0.72, 1.92)
Multivariate HR (95% CI)[b]	1.00	0.97 (0.79, 1.20)	1.00	0.99 (0.79, 1.23)	0.83 (0.55, 1.26)	1.14 (0.70, 1.86)
PsA						
No. of cases/person-years	119/1,003,279	37/182,107	96/825,789	32/191,386	9/43,366	4/16,365
Age-adjusted HR (95% CI)	1.00	1.28 (0.88, 1.88)	1.00	1.18 (0.78, 1.78)	1.29 (0.64, 2.61)	1.04 (0.37, 2.91)
Multivariate HR (95% CI)[a]	1.00	0.99 (0.67, 1.46)	1.00	0.94 (0.62, 1.43)	0.97 (0.47, 1.96)	0.78 (0.28, 2.19)
Multivariate HR (95% CI)[b]	1.00	0.94 (0.64, 1.39)	1.00	0.88 (0.58, 1.33)	0.90 (0.44, 1.84)	0.72 (0.26, 2.02)

[a]Multivariate hazard ratios (HRs) were adjusted for age, follow-up interval, race, BMI, physical activity, smoking status, oral contraceptive use, postmenopausal hormones use, multi-vitamins use, cardiovascular disease, type 2 diabetes, hypertension, and hypercholesterolemia.
[b]HRs were further adjusted for the other drugs (depending on the model) listed in the Table.

taminophen users with use duration of 1–6 years, 7–10 years, and >10 years had fully-adjusted HRs of 1.77 (95% CI: 1.19–2.62), 1.66 (95% CI: 0.91–3.02), and 3.60 (95% CI: 2.02–6.41), respectively, for PsA, and regular NSAIDs users with use duration of 1–6 years, 7–10 years, and >10 years had fully-adjusted HRs of 1.51 (95% CI: 0.98–2.33), 2.09 (95% CI: 1.22–3.58), and 2.10 (95% CI: 1.11–3.96), respectively, for PsA. Secondary analyses with 4-year lag between exposure and outcome yielded similar results (Table SI[1]).

Analyses by weekly dosage of medications were limited to follow-up period between 1999 and 2005 when dosage information was available. Acetaminophen dosage showed the most robust associations with psoriasis and PsA among the 3 drugs (Table III). Compared to women who reported no use, regular acetaminophen users with weekly dosage of 1–5 tablets/week and ≥6 tablets/week had fully-adjusted HRs of 1.37 (95% CI: 1.01–1.84) and 1.62 (95% CI: 1.11–2.37), respectively, for psoriasis, and fully-adjusted HRs of 2.12 (95% CI: 1.20–3.77) and 3.05 (95% CI: 1.63–5.70), respectively,

for PsA. Regular NSAIDs users with weekly dosage of ≥6 tablets/week appeared to be more likely to develop PsA, but this risk became insignificant after accounting for the other medications (fully-adjusted HR=1.66, 95% CI: 0.91–3.02).

DISCUSSION

In this large, prospective cohort study, we found that regular acetaminophen (paracetamol) use may be associated with an increased risk of psoriasis with concomitant PsA in women, and women who used this medication more than 10 years were at a substantially increased risk of developing PsA. Although the association between regular NSAIDs use and risk of PsA was of marginal significance, analysis by duration suggested that women who used NSAIDs for long durations were also more likely to develop PsA. In addition, analysis by dosage also suggested an increased risk of psoriasis associated with acetaminophen use. However, we did not observe any clear association between aspirin use and risk of psoriasis or PsA. Secondary analyses with 4-year lag between exposure and outcome yielded very similar findings.

Psoriasis is characterized by T-cell-mediated hyperproliferation of keratinocytes and inflammatory processes, whereas PsA is an inflammatory arthritis that occurs in the presence of psoriasis (1). Initial studies have revealed that abundant T cells are accumulated at sites of inflammation (30). Aspirin and other NSAIDs reduce the inflammatory response by inhibiting COX, which is responsible for the formation of eicosanoids, a group of important inflammatory mediators (31). Of note, aspirin and NSAIDs have different inhibitory effects on the COX isoenzymes. NSAIDs inhibit both the COX-1 and COX-2 isoenzymes, whereas aspirin is relatively COX-1 selective and has only a weak inhibitory effect on COX-2 (31–33). The main mechanism proposed for acetaminophen action is also the inhibition of COX (8), and recent findings suggest that it is highly selective for COX-2 (9). However, acetaminophen has little anti-inflammatory activity (34). In the present study we found that acetaminophen (a COX-2 selective inhibitor) showed the most robust associations with risk of psoriasis and PsA, followed by NSAIDs (non-specific COX inhibitors), and aspirin (a COX-1 selective inhibitor) was not associated with risk of psoriasis and PsA. Therefore, it seems that the drug effects were closely related to the selectivity of COX inhibition.

In clinical practices, NSAIDs are commonly used as initial therapy for PsA which may provide well symptomatic control (35, 36). However, data

Table III. *Risk of psoriasis and psoriatic arthritis (PsA) according to weekly dosage of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and aspirin in the Nurses' Health Study II (1999–2005)*

	0	1–5 tablets/week	≥ 6 tablets/week
Acetaminophen			
Psoriasis			
No. of cases/person-years	149/262,051	65/75,291	35/29,465
Age-adjusted HR (95% CI)	1.00	1.44 (1.08, 1.93)	1.98 (1.37, 2.86)
Multivariate HR (95% CI)[a]	1.00	1.34 (1.00, 1.80)	1.59 (1.10, 2.32)
Multivariate HR (95% CI)[b]	1.00	1.37 (1.01, 1.84)	1.62 (1.11, 2.37)
PsA			
No. of cases/person-years	29/262,051	21/75,291	16/29,465
Age-adjusted HR (95% CI)	1.00	2.44 (1.39, 4.28)	4.48 (2.43, 8.26)
Multivariate HR (95% CI)[a]	1.00	2.14 (1.22, 3.76)	3.04 (1.63, 5.67)
Multivariate HR (95% CI)[b]	1.00	2.12 (1.20, 3.77)	3.05 (1.63, 5.70)
NSAIDs			
Psoriasis			
No. of cases/person-years	114/183,634	75/103,485	51/71,547
Age-adjusted HR (95% CI)	1.00	1.13 (0.84, 1.51)	1.13 (0.81, 1.58)
Multivariate HR (95% CI)[a]	1.00	1.06 (0.79, 1.42)	0.94 (0.67, 1.31)
Multivariate HR (95% CI)[b]	1.00	1.00 (0.74, 1.35)	0.91 (0.65, 1.28)
PsA			
No. of cases/person-years	22/183,634	13/103,485	23/71,547
Age-adjusted HR (95% CI)	1.00	1.03 (0.52, 2.04)	2.56 (1.43, 4.60)
Multivariate HR (95% CI)[a]	1.00	0.92 (0.46, 1.84)	1.83 (1.01, 3.32)
Multivariate HR (95% CI)[b]	1.00	0.79 (0.39, 1.59)	1.66 (0.91, 3.02)
Aspirin			
Psoriasis			
No. of cases/person-years	197/315,268	19/16,829	15/11,203
Age-adjusted HR (95% CI)	1.00	1.39 (0.85, 2.25)	1.56 (0.91, 2.68)
Multivariate HR (95% CI)[a]	1.00	1.27 (0.78, 2.06)	1.23 (0.71, 2.12)
Multivariate HR (95% CI)[b]	1.00	1.20 (0.74, 1.96)	1.20 (0.69, 2.07)
PsA			
No. of cases/person-years	50/315,268	6/16,829	4/11,203
Age-adjusted HR (95% CI)	1.00	1.68 (0.70, 4.04)	1.52 (0.53, 4.34)
Multivariate HR (95% CI)[a]	1.00	1.43 (0.59, 3.44)	1.02 (0.35, 2.93)
Multivariate HR (95% CI)[b]	1.00	1.23 (0.51, 2.98)	0.95 (0.33, 2.74)

[a]Multivariate hazard ratios (HRs) were adjusted for the covariates listed in Table II footnote[a]. [b]HRs were further adjusted for the other drugs (depending on the model) listed in the Table.

regarding the usefulness of NSAIDs in PsA treatment are limited and only a few controlled studies have assessed their efficacy (37). A previous controlled study confirmed an NSAID's (nimesulide) superiority to placebo on tender/swollen joint counts, and pain scores, but show no effect on rash (assessed by Psoriasis Area and Severity Index score) or on the erythrocyte sedimentation rate to suggest disease modification (38). An early double-blind controlled trial found limited efficacy of ibuprofen in the treatment of PsA (39), and another randomized controlled trial also confirmed that symptomatic therapy using NSAIDs and/or prednisone was less efficacious than cyclosporine (40). A more recent randomized, double-blind, placebo-controlled study found that celecoxib (a COX-2 selective inhibitor) was efficacious and well tolerated in treating the signs and symptoms of PsA in flare after 2 weeks of treatment, however, there were no differences relative to placebo treatment at week 12 (41). In contrast, worsening of psoriasis with initiation of NSAIDs therapy has been observed for both non-specific and COX-2 specific NSAIDs (11–17).

Arachidonic acid can be metabolized to form either prostaglandins (members of eicosanoids) via the COX pathway or leukotrienes via the 5-lipoxygenase pathway (42). Possible mechanisms for worsening of psoriasis associated with NSAIDs may include an increased migration of leukocytes associated with use of non-specific COX inhibitors (43). This migration of leukocytes may result from a diversion of arachidonic acid metabolism toward the 5-lipoxygenase pathway and thus lead to accumulation of leukotrienes. The increased migration of leukocytes could lead to their infiltration into the epidermis, thereby stimulating the psoriatic eruption (44). Furthermore, it has been reported that some NSAIDs (e.g., indomethacin and salicylates) do nothing to reverse the underlying causes of chronic inflammatory diseases (45). This may be due to use of the drugs at doses which give good symptomatic control but actually potentiate the accumulation of inflammatory cells.

A few points may help explain the effect difference between these medications. COX-2 is involved in the synthesis of proinflammatory eicosanoids, and it is likely that selective antagonism of this enzyme by COX-2 inhibitors (e.g., rofecoxib) would also lead to a compensatory increase in leukocyte migration as nonspecific NSAIDs (16). Acetaminophen has little anti-inflammatory activity (34), may inhibit the metabolism of arachidonic acid by the COX pathway like COX-2 selective inhibitors, and finally leads to an accumulation of leukotrienes associated with psoriasis development (42, 44). In contrast, the adverse effects of aspirin mediated through COX inhibition may be counterbalanced by aspirin-specific anti-inflammatory effects. For example, aspirin may promote the production of local anti-inflammatory lipoxins (46), and 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 (47).

Our study has several strengths. First, because we collected detailed, updated information on medication use during 14 years of follow-up, we were able to evaluate long-term use across a broad range of intake. Second, we were also able to examine the effects of 3 major analgesics and antipyretics (acetaminophen, NSAIDs, and aspirin) simultaneously. Third, we obtained medication data prospectively, prior to diagnosis, and thus our study avoided the potential recall bias of case-control studies that collect exposure data after diagnosis of disease. Any errors in recall would be likely to attenuate rather than exaggerate true associations. Fourth, we were able to estimate medication effects using several distinct measures of drug use, including status, duration, and dosage. Thus, our findings are less prone to internal confounding because of correlations between these parameters. Fifth, the results of secondary analyses with a 4-year lag between exposure and outcome are consistent with the primary analyses, suggesting that the associations between exposure and outcome were unlikely to be entirely explained by protopathic bias. Sixth, our participants were all registered nurses, and the accuracy of self-reported medication use is likely to be high and to reflect actual consumption of these largely over-the-counter medications. Finally, based on detailed and validated cohort follow-up information, we were able to control for a number of potential confounders (e.g., hypercholesterolemia) which may have affected the association of interest. Hypercholesterolemia has been associated with risk of psoriasis and PsA in our previous study (26). The associations between regular acetaminophen and NSAIDs use and risk of PsA were essentially unchanged before and after adjusting for hypercholesterolemia, whereas the associations between hypercholesterolemia and risk of psoriasis and PsA were also consistent before and after adjusting for acetaminophen and NSAIDs use (26). These results suggest that the potential biological linkages between cholesterol and psoriasis/PsA and between acetaminophen and NSAIDs use and psoriasis/PsA may be independent of each other.

Our study has several limitations. First, case ascertainment could be a concern due to misclassification. We ascertained PsA diagnosis using the PASE questionnaire among self-reported women with psoriasis. PASE picks up individuals with active disease who are potentially more likely to have inflamed joints and increased systemic inflammation, and therefore it probably underestimates the number of real cases (48). However, the psoriasis self-reports reached a confirmation rate of 92% (23), and our previous studies suggested that PASE questionnaire was a valid and reliable tool for PsA screening (24, 25). Our previous studies have established associations between PsA and several health risk factors (e.g., hypercholesterolemia, obesity, smoking) (26, 49, 50) and Crohn's disease (21) using data from the same

cohort. Therefore, we expect a high validity of PsA confirmation among the well educated nurses. Second, we lack information on which specific NSAIDs were used, although most women reported using ibuprofen. Third, our cohort consisted entirely of women, most of whom were Whites, and thus the generalizability of the results to other gender and ethnicities may be limited. Finally, our study was observational, although we were able to adjust a number of potential confounders, we cannot completely exclude residual confounding by unmeasured or imperfectly measured factors.

In conclusion, our findings suggest that regular acetaminophen use may be associated with an increased risk of psoriasis and concomitant PsA. In addition, long-term NSAIDs use also appeared to be associated with an increased risk of PsA. These associations were generally consistent in secondary analyses with a 4-year lag between exposure and outcome. However, the biological mechanism linking these drugs and development of psoriasis and concomitant PsA is plausible, and further work is warranted to replicate our findings and to explore the underlying biological evidence. Based on the previous evidence as well as our results, the efficacy of NSAIDs in treating PsA may need to be assessed more thoroughly, and special attention on psoriasis and PsA screening may be needed for those who are prescribed for acetaminophen and NSAIDs for long-term periods.

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