

Prospective Study of Acetaminophen Use and Newly Diagnosed Asthma among Women

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Acetaminophen decreases glutathione levels in the lung, which may predispose to oxidative injury and bronchospasm. Acetaminophen use has been associated with asthma in cross-sectional studies and a birth cohort. We hypothesized that acetaminophen use would be associated with newly diagnosed adult-onset asthma in the Nurses' Health Study, a prospective cohort study of 121,700 women. Participants were first asked about frequency of acetaminophen use in 1990. Cases with asthma were defined as those with a new physician diagnosis of asthma between 1990 and 1996 plus reiteration of the diagnosis and controller medication use. Proportional hazard models included age, race, socioeconomic status, body mass index, smoking, other analgesic use, and postmenopausal hormone use. During 352,719 person-years of follow-up, 346 participants reported a new physician diagnosis of asthma meeting diagnostic criteria. Increasing frequency of acetaminophen use was positively associated with newly diagnosed asthma (p for trend = 0.006). The multivariate rate ratio for asthma for participants who received acetaminophen for more than 14 days per month was 1.63 (95% confidence interval, 1.11–2.39) compared with nonusers. It would be premature to recommend acetaminophen avoidance for patients with asthma, but further research on pulmonary responses to acetaminophen is necessary to confirm or refute these findings and to identify subgroups whose asthma may be modified by acetaminophen.

Keywords: analgesics; paracetamol; aspirin; analgesic drugs, nonsteroidal

Asthma prevalence has increased dramatically since the 1970s and currently affects 5 to 8% of the population of the United States (1). Concurrent increases in asthma-related hospitalization and mortality suggest that the change in asthma prevalence did not result from greater diagnosis and detection alone (2), although asthma-related hospitalization and mortality appear to have declined since 1995 with the more widespread use of inhaled corticosteroids (3).

Various hypotheses have been proposed to explain the rise in asthma prevalence, including those relating to changes in early life antigen exposure (4) and to the obesity epidemic (5, 6). The rise in the prevalence and severity of asthma in the United States, however, also coincided with a large increase in the use of acet-

aminophen in the 1970s and 1980s. The switch from aspirin to acetaminophen was particularly pronounced among children following reports that linked aspirin to Reyes Syndrome in the early 1980s (7).

This substitution of acetaminophen for aspirin was not evaluated in randomized trials. By contrast, ibuprofen was recently compared with acetaminophen for pediatric febrile illness in a large randomized, double-blind, clinical trial (8). Among the subgroup of 1,879 children with asthma, asthma-related outpatient visits were significantly lower in the ibuprofen arm, and asthma hospitalizations were nonsignificantly reduced compared with the acetaminophen arm (9). The trial did not include a placebo arm, therefore it is uncertain whether ibuprofen decreased or acetaminophen increased asthma morbidity. Alternatively, the finding may have been due to chance.

An increase in asthma risk related to acetaminophen use was also suggested by a population-based case-control study (10). The study was limited, however, by the case-control design in which the diagnosis of asthma preceded ascertainment of acetaminophen use. We therefore analyzed data from a prospective study to examine if acetaminophen use was associated with a new physician diagnosis of asthma among participants not previously diagnosed with asthma. Some of the results have been previously reported in the form of an abstract (11).

METHODS

In 1976, the Nurses' Health Study enrolled 121,700 married female registered nurses, aged 30 to 55 years, who resided in one of 11 U.S. states and who completed a mailed questionnaire (12). We updated the information with biennial follow-up questionnaires and inquired about a physician diagnosis of asthma from 1988 onward. Follow-up of the original cohort was greater than 90%.

Ascertainment of Analgesic Use

In 1990, all participants were asked about acetaminophen use with the question, "On average, how many days each month do you take ... acetaminophen (e.g., Tylenol)?" Categories of response were: none, 1 to 4 days, 5 to 14 days, 15 to 21 days, and 22 or more days. Frequency of aspirin use and frequency of other nonsteroidal antiinflammatory drug (NSAID) use were assessed in the same way. Identical items were administered in 1992.

Definitions of Asthma

During follow-up through 1996, 10,496 women reported a physician diagnosis of asthma. In 1998, we sent supplemental questionnaires to all of these participants, excluding those who died ($n = 437$) or who either withdrew from the study or were lost to follow-up ($n = 223$). Of 9,836 recipients who were sent questionnaires, 163 died and 8,197 responded (85%).

Cases with asthma were defined as those with a report of a physician diagnosis of asthma on both the regular questionnaire (1990–1996) and the supplementary questionnaire (1998) plus use of an asthma-controller medication (inhaled or systemic corticosteroid, theophylline, leukotriene modifier, or cromolyn) in the preceding 12 months. Cases

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reporting comorbid pulmonary disease (e.g., sarcoidosis) were excluded. This asthma definition was validated in a parallel study (5) (*see* online supplement for details).

Study Sample

Follow-up for this analysis began in June 1990. Accordingly, women who reported asthma diagnosed before 1990 were excluded. Participants with a history of rheumatoid arthritis or chronic obstructive pulmonary disease before 1990 and participants reporting asthma that did not meet diagnostic criteria were also excluded. Because asthma must be diagnosed by a physician but acetaminophen is available over the counter, we restricted analyses to participants who reported at least one physician visit during the follow-up period (94% of eligible participants). Between 1990 and 1996, 73,321 women were included in the analysis.

Statistical Analysis

For each participant, person-months were allocated to categories of acetaminophen use in 1990. This allocation was updated for 1992 values

of acetaminophen use. Acetaminophen use was not ascertained in 1994; therefore, further updating of acetaminophen use was not performed. Follow-up ended when asthma was first diagnosed, when an exclusion diagnosis was reported, when the participant died, or when the last questionnaire was returned.

Incidence rates were calculated as the number of new cases divided by the person-time in each category of acetaminophen use, and rate ratios were defined as the incidence rate of asthma in each category of acetaminophen use divided by the corresponding incidence rate among nonusers. Age-adjusted rates were calculated, and Mantel-Haenszel ratios (13) and 95% confidence intervals were estimated (14).

Cox proportional hazards models (15) were used to adjust the rate ratio for newly diagnosed asthma for covariates (listed in Table 2). Specification of multivariate models is described in the online supplement. Secondary analyses included (1) restriction to participants who reported consistent analgesic use, defined as a change in reported analgesic use of no more than two categories of use between 1990 and 1992; (2) inclusion in multivariate models of indices of depressive symptomatology and role limitation due to emotional problems from the Medical

TABLE 1. AGE-STANDARDIZED DISTRIBUTION OF CHARACTERISTICS OF PARTICIPANTS IN THE NURSES' HEALTH STUDY IN 1990, ACCORDING TO FREQUENCY OF ACETAMINOPHEN USE IN 1990

	Frequency of Acetaminophen Use (<i>days per month</i>)				
	None	1–4	5–14	15–21	22+
No. of participants (n = 48,028)*	23,205	16,178	5,001	1,484	2,160
Mean age, yr $\pm$ SD	57 $\pm$ 7	55 $\pm$ 7	55 $\pm$ 7	56 $\pm$ 7	58 $\pm$ 7
White race/ethnicity, %	91	90	90	91	90
Spouse's educational attainment, %					
Graduate school	21	18	18	17	16
College	23	23	22	22	21
High school	34	36	37	38	38
Region, %					
New England	14	14	16	15	15
Mid-Atlantic	42	43	43	41	42
East North Central	19	19	20	21	20
South-Atlantic	6	6	6	6	6
West South Central	5	5	5	6	6
Pacific	14	13	10	10	10
Smoking status, %					
Never	46	46	45	42	43
Past	39	40	41	43	39
Current	15	14	14	15	18
Median pack-years [†] (interquartile range)	24 (11, 42)	22 (10, 39)	23 (11, 40)	25 (12, 41)	28 (14, 47)
Bilateral oophorectomy/postradiation, %	29	31	34	35	39
Mean age at menopause, yr $\pm$ SD	47 $\pm$ 6	46 $\pm$ 6	46 $\pm$ 7	46 $\pm$ 7	46 $\pm$ 7
Past use of oral contraceptives, %	51	50	49	48	50
Median body mass index, kg/m ² (interquartile range)	24 (22, 27)	25 (22, 28)	25 (22, 28)	25 (23, 29)	26 (23, 29)
Secondhand smoke exposure, %					
None	13	11	10	10	9
Work only	25	25	25	26	24
Home only	5	5	5	4	6
Home and work	26	28	28	25	30
Frequency of other NSAID use, d/mo, %					
None	68	47	36	32	36
1–4	15	23	18	14	10
5–14	6	6	14	14	7
15–21	2	1	3	7	4
22+	6	5	8	9	19
Frequency of aspirin use, d/mo, %					
None	51	45	37	39	41
1–4	25	23	16	9	7
5–14	9	5	12	8	5
15–21	4	2	3	7	3
22+	11	6	7	8	16

Definition of abbreviation: NSAID = nonsteroidal antiinflammatory drug.

* Total differs from text due to number of participants with missing data in 1990 but available data in 1992. Column totals may not sum to 100% due to rounding and/or missing data.

[†] Among current and past smokers.

Outcomes Study Short-Form 36 Health Survey (16, 17), which were available only for 1992; (3) use of date of first asthma symptoms rather than the date of diagnosis as the incidence date. All *p* values were two tailed, with *p* values less than 0.05 being considered statistically significant. Analyses were performed using SAS 6.12 (SAS Institute, Cary, NC).

RESULTS

During 352,719 person-years of follow-up from 1990 to 1996, 346 participants reported a new physician diagnosis of asthma that fulfilled diagnostic criteria. Participants who reported no acetaminophen use accounted for 39% of follow-up person-time. The distribution of follow-up person-time by average acetaminophen use was: 1 to 4 days per month, 28% of person-time; 5 to 14 days per month, 9%; 15 to 21 days per month, 3%; and 22 days per month or more, 5%. Information on acetaminophen use was missing for the remaining 16% of person-time.

Acetaminophen use remained fairly stable over time. Sixty-two percent of participants who reported no acetaminophen use in 1990 also reported no acetaminophen use in 1992. Similarly, 73% of participants who reported acetaminophen use in 1990 reported usage in 1992. Overall, less than 3% of participants reported a change in acetaminophen use of two or more categories between 1990 and 1992.

Women who used acetaminophen had generally similar demographics and health habits as women who did not use acetaminophen (Table 1). Women who frequently used acetaminophen were more likely to frequently use aspirin and other NSAIDs; conversely, women who did not use acetaminophen were less likely to use other analgesics (Table 1).

The age-adjusted rate ratio for new physician-diagnosed asthma rose with increasing frequency of acetaminophen use (Table 2, *p* for trend < 0.001). Adjustment for use of other analgesics attenuated the association only slightly, as did multivariate adjustment for age, time period of diagnosis, other analgesic use, race/ethnicity, socioeconomic status, region, smoking, secondhand smoke exposure, body mass index, postmenopausal hormone use, and type of menopause (Table 2). The multivariate rate ratio for newly diagnosed asthma for participants who received acetaminophen for more than 14 days per month was 1.63 (95% confidence interval, 1.11–2.39) compared with nonusers of acetaminophen.

Because analgesic use was assessed at only two time intervals and some participants altered their acetaminophen use over time, we restricted the analysis to consistent acetaminophen users, excluding the 3% of participants who reported a change in acetaminophen use of more than two categories between 1990 and 1992. The results of this better-classified analysis showed a monotonic relationship between frequency of acetaminophen

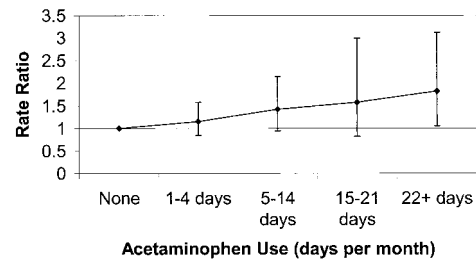


Figure 1. Multivariate rate ratios for newly diagnosed asthma according to frequency of acetaminophen use among participants with consistent analgesic use. The reference group did not use acetaminophen. Points represent rate ratios and bars represent 95% confidence intervals (*p* value for trend = 0.008).

use and asthma (Figure 1, *p* for trend = 0.008). Further restriction to participants who reported exactly the same acetaminophen use in 1990 and 1992 produced a similar relationship. Defining exposure by 1990 values of analgesic use (i.e., analyzing the data without updating the exposure) yielded similar results (*p* for trend = 0.002) as did defining exposure by 1992 values of analgesic use (*p* for trend = 0.04).

The positive association of acetaminophen use and asthma did not differ significantly between participants who did and did not receive aspirin (*p* for interaction = 0.52). There was therefore no statistical evidence for a difference in the association of acetaminophen and asthma by subgroups of aspirin use. The rate ratio for asthma increased with increasing acetaminophen use in the subgroup that received aspirin, although the smaller sample size increased the variability in the estimates (Table 3). A similar pattern was observed in the subgroup that did not receive aspirin, although this did not attain statistical significance in the multivariate analysis.

Further analyses restricting the asthma case definition to never smokers excluding participants with heart disease and including those without physician visits produced qualitatively similar results, as did adjustment for depression, role limitation due to emotional problems, and nutritional factors such as vitamin E intake and defining the index date by onset of asthma symptoms rather than by asthma diagnosis (data not shown).

Many participants also received aspirin and other NSAIDs, as described in Table 1. Frequency of use of other NSAIDs was significantly associated with newly diagnosed asthma in analgesic-adjusted analyses but was not significantly associated with newly diagnosed asthma in multivariate analyses (*p* for trend = 0.12; Table 4). Restricting the analysis to consistent users of other NSAIDs produced a similar result (*p* for trend = 0.10).

TABLE 2. RATE RATIO FOR NEWLY DIAGNOSED ASTHMA IN THE NURSES' HEALTH STUDY FROM 1990 TO 1996, ACCORDING TO FREQUENCY OF ACETAMINOPHEN USE

	Frequency of Acetaminophen Use (days per month)					<i>p</i> Value for Trend
	None	1–4	5–14	15–21	22+	
No. of cases	108	112	41	16	22	
Person-years	137,568	99,922	32,077	10,656	17,059	
Age-adjusted RR (95% CI)	1 (Reference)	1.37 (1.05–1.78)	1.54 (1.07–2.21)	1.92 (1.14–3.25)	1.72 (1.09–2.72)	< 0.001
Analgesic-adjusted RR* (95% CI)	1 (Reference)	1.30 (0.99–1.71)	1.49 (1.03–2.16)	1.91 (1.12–3.25)	1.63 (1.02–2.62)	0.001
Multivariate RR† (95% CI)	1 (Reference)	1.27 (0.96–1.66)	1.43 (0.99–2.07)	1.78 (1.04–3.04)	1.53 (0.95–2.46)	0.006

Definition of abbreviations: CI = confidence interval; NSAID = nonsteroidal antiinflammatory drug; RR = rate ratio.

* Analgesic-adjusted RRs were adjusted for age, time period of diagnosis, frequency of aspirin use, and frequency of other NSAID use.

† Multivariate RRs were adjusted for age, time period of diagnosis, frequency of aspirin use, frequency of other NSAID use, race/ethnicity, husband's educational attainment, region, smoking status, secondhand smoke exposure, body mass index, postmenopausal hormone use, and type of menopause.

TABLE 3. RATE RATIO FOR NEWLY DIAGNOSED ASTHMA IN THE NURSES' HEALTH STUDY FROM 1990 TO 1996, ACCORDING TO FREQUENCY OF ACETAMINOPHEN USE BY SUBGROUPS OF ASPIRIN USE*

	Frequency of Acetaminophen Use (<i>days per month</i>)					
	None	1–4	5–14	15–21	22+	p Value for Trend
Aspirin users						
No. of cases	47	50	12	4	10	
Person-years	68,270	40,458	13,068	3,979	5,850	
Age-adjusted RR (95% CI)	1 (Reference)	1.69 (1.14–2.51)	1.22 (0.64–2.31)	1.50 (0.54–4.16)	2.60 (1.31–5.17)	0.01
Multivariate RR† (95% CI)	1 (Reference)	1.55 (1.03–2.34)	1.10 (0.57–2.09)	1.47 (0.52–4.12)	2.56 (1.26–5.21)	0.04
Aspirin nonusers						
No. of cases	57	56	23	8	8	
Person-years	67,690	45,697	12,531	4,268	7,267	
Age-adjusted RR (95% CI)	1 (Reference)	1.39 (0.95–2.01)	2.10 (1.29–3.41)	2.19 (1.04–4.59)	1.35 (0.65–2.80)	0.03
Multivariate RR† (95% CI)	1 (Reference)	1.31 (0.90–1.91)	1.92 (1.17–3.14)	1.82 (0.86–3.85)	1.04 (0.49–2.19)	0.15

Definition of abbreviations: CI = confidence interval; NSAID = nonsteroidal antiinflammatory drug; RR = rate ratio.

* The p value of the interaction term by aspirin use was not significant ($p = 0.52$); therefore, there was no statistical evidence of a difference in the association of acetaminophen use and asthma by subgroup of aspirin use.

[†] Multivariate RRs were adjusted for age, time period of diagnosis, frequency of other NSAID use, race/ethnicity, husband's educational attainment, region, smoking status, secondhand smoke exposure, body mass index, postmenopausal hormone use, and type of menopause.

Frequency of aspirin use was not associated with newly diagnosed asthma in analgesic-adjusted analyses but was inversely associated with newly diagnosed asthma in multivariate analyses (p for trend = 0.03; Table 5). The exclusion of participants who reported a change in aspirin use of more than two categories produced a similar result (p for trend = 0.01), as did the exclusion of participants with heart disease (p for trend = 0.04).

DISCUSSION

During 352,719 person-years of follow-up of participants in the Nurses' Health Study, greater use of acetaminophen was prospectively associated with increased rate of new physician diagnosis of adult-onset asthma.

Our findings confirm and extend the findings of prior cross-sectional studies of asthma and acetaminophen use. Across countries in Europe, per capita consumption of acetaminophen was ecologically associated with the prevalence of wheeze, diagnosed asthma, and bronchial hyperresponsiveness (18). In addition to the ecologic findings, a population-based, case-control study from the United Kingdom showed a dose-dependent relationship between acetaminophen use and asthma, with a multivariate odds ratio for asthma of 2.4 (95% confidence interval, 1.2–4.6) comparing daily users with never users (10). The association was much stronger for severe asthma (odds ratio 8.2; 95% confidence interval, 2.8–23). Aspirin use was equally common among cases and control subjects (odds ratio 1.05; 95% confidence interval, 0.47–2.35). Although aspirin avoidance was slightly more com-

mon among cases than among control subjects, the magnitude of the difference in that study was not large enough to explain the association of acetaminophen and asthma. Our findings are also consistent with a recently published study of acetaminophen use in pregnancy, which showed that acetaminophen use in late pregnancy was associated with an increased risk of wheeze among offspring (19).

Acetaminophen-related bronchospasm has been reported for at least 35 years in a subset of patients with asthma (20, 21). Acetaminophen provokes bronchospasm in up to 32% of patients with stable, aspirin-sensitive asthma (22, 23). Reactions generally are milder than seen after aspirin challenge and occur with a high, but clinically relevant, dose of acetaminophen (e.g., 1,000 mg). Acetaminophen-related bronchospasm also has been demonstrated in some patients with no history of aspirin-sensitive asthma (24).

The mechanism for this phenomenon is unclear, but may involve glutathione, an antioxidant (in its reduced state) that mitigates lung oxidative stress (25, 26). Acetaminophen decreases levels of glutathione in the liver, kidneys, and lungs (27, 28). These decreases are dose dependant: overdose levels of acetaminophen are cytotoxic to pneumocytes and cause acute lung injury (29), whereas nontoxic, therapeutic doses produce smaller, but significant, reductions in glutathione levels in type II pneumocytes and alveolar macrophages (30). Oxidative stress in asthma occurs from the production of reactive oxygen species in the lung by inflammatory cells (31). Reactive oxygen species

TABLE 4. RATE RATIO FOR NEWLY DIAGNOSED ASTHMA IN THE NURSES' HEALTH STUDY FROM 1990 TO 1996, ACCORDING TO FREQUENCY OF OTHER NONSTEROIDAL ANTIINFLAMMATORY DRUG USE

	Frequency of Other NSAID Use (<i>days per month</i>)					p Value for Trend
	None	1–4	5–14	15–21	22+	
No. of cases	135	79	39	11	44	
Person-years	162,046	65,715	29,804	9,967	30,843	
Age-adjusted RR (95% CI)	1 (Reference)	1.31 (0.98–1.75)	1.47 (1.02–2.11)	1.28 (0.69–2.38)	1.76 (1.25–2.47)	0.0008
Analgesic-adjusted RR* (95% CI)	1 (Reference)	1.23 (0.92–1.65)	1.37 (0.94–1.99)	1.22 (0.65–2.29)	1.66 (1.16–2.39)	0.008
Multivariate RR [†] (95% CI)	1 (Reference)	1.19 (0.89–1.59)	1.27 (0.88–1.85)	1.07 (0.57–2.01)	1.39 (0.96–2.00)	0.12

For definition of abbreviations see Table 3.

* Analgesic-adjusted RRs were adjusted for age, time period of diagnosis, frequency of acetaminophen use, and frequency of aspirin use.

[†] Multivariate RRs were adjusted for age, time period of diagnosis, frequency of acetaminophen use, frequency of aspirin use, race/ethnicity, husband's educational attainment, region, smoking status, secondhand smoke exposure, body mass index, postmenopausal hormone use, and type of menopause.

TABLE 5. RATE RATIO FOR NEWLY DIAGNOSED ASTHMA IN THE NURSES' HEALTH STUDY FROM 1990 TO 1996, ACCORDING TO FREQUENCY OF ASPIRIN USE

	Frequency of Aspirin Use (<i>days per month</i>)					p Value for Trend
	None	1–4	5–14	15–21	22+	
No. of cases	152	73	32	7	31	
Person-years	138,006	70,719	32,971	15,858	45,503	
Age-adjusted RR (95% CI)	1 (Reference)	0.94 (0.71–1.24)	0.92 (0.62–1.34)	0.43 (0.20–0.92)	0.70 (0.48–1.04)	0.02
Analgesic-adjusted RR* (95% CI)	1 (Reference)	0.98 (0.73–1.30)	0.92 (0.62–1.37)	0.43 (0.20–0.93)	0.74 (0.49–1.11)	0.07
Multivariate RR† (95% CI)	1 (Reference)	0.97 (0.73–1.29)	0.89 (0.60–1.32)	0.41 (0.19–0.89)	0.70 (0.47–1.05)	0.03

For definition of abbreviations see Table 3.

* Analgesic-adjusted RRs were adjusted for age, time period of diagnosis, frequency of acetaminophen use, and frequency of other NSAID use.

† Multivariate RRs were adjusted for age, time period of diagnosis, frequency of acetaminophen use, frequency of other NSAID use, race/ethnicity, husband's educational attainment, region, smoking status, secondhand smoke exposure, body mass index, postmenopausal hormone use, and type of menopause.

cause contraction of airway smooth muscle and release of leukotrienes and other secondary inflammatory mediators, leading to bronchial hyperresponsiveness and bronchoconstriction (31). The importance of the glutathione pathway in asthma is reinforced by the finding that polymorphisms in glutathione-S-transferase are associated with increased susceptibility to pediatric asthma and with slowed lung function growth in childhood (32, 33).

Although we were interested primarily in the association of acetaminophen use and asthma, we also evaluated use of other over-the-counter analgesics. An unanticipated finding was that aspirin use was inversely associated with newly diagnosed, adult-onset asthma. This result may be a chance finding because, in contrast to the findings for acetaminophen, the association of aspirin use and asthma was not significant in analgesic-adjusted analyses and remained close to the standard threshold for statistical significance in multivariate analyses.

An alternative explanation for the aspirin finding is "depletion of susceptibles" before the start of the follow-up period. Asthma is a heterogeneous disease; aspirin provokes bronchospasm in the subgroup of patients with aspirin-sensitive asthma (34) but improves bronchospasm in other patients with asthma (35–37). Given secular trends in analgesic consumption in the United States, the study participants (mean age, 57 years) were likely to have been exposed to aspirin as children or young adults. Those prone to aspirin-sensitive asthma were likely to have been diagnosed with asthma in childhood or as young adults and consequently excluded from this analysis, leaving only those for whom aspirin had no effect or an ameliorative effect. Given that acetaminophen was not widely prescribed to children and young adults in the United States before the 1970s, no similar selective pressure for acetaminophen occurred in this older cohort.

A third possible explanation, given the observational design of the study, is a form of confounding by indication (38). The prospective design, however, ensured that, for confounding by indication to occur, persons with asthma symptoms or at a high risk of asthma must have preferentially avoided aspirin and used acetaminophen—before they were diagnosed with asthma. We evaluated for the presence of such confounding by indication by repeating analyses on the basis of date of onset of asthma symptom rather than date of diagnosis. We also inquired about remission and relapse of early-onset asthma and excluded participants who reported a relapse, rather than a new diagnosis, of asthma. Although some participants may have forgotten and therefore not reported childhood asthma that had remitted, we believe it unlikely that many such participants avoided aspirin in adulthood—particularly in this cohort whose participants' first 2 decades of life (the 1930s and 1940s, on average) preceded most, although not all, of the literature on aspirin-sensitive asthma. Finally, a large randomized, double-blind, clinical trial

that compared acetaminophen and ibuprofen showed a higher rate of asthma morbidity among children randomized to acetaminophen (9). Because the trial did not include a placebo group, the direction of causal effects could not be determined; the trial does, however, suggest that observed differences in asthma may not be due to confounding by indication.

Other potential known confounders such as body mass index were measured with validated instruments. Participants with depression, anxiety, feelings of limitation due to emotional problems, or headaches/migraine may be more likely to receive analgesics and be diagnosed with asthma. Psychosocial measures were available from 1992, and adjustment for these measures did not appreciably alter the findings. Bias from unknown and unmeasured confounders is always a possibility, given the observational nature of the study.

Frequency of analgesic use was assessed at two time intervals. More frequent measures of analgesic use and more quantitative information, such as doses of analgesics would have been desirable. Most participants in the study, however, were fairly consistent in their analgesic use over 2 years. When analyses were restricted to participants who reported consistent analgesic use, the association of acetaminophen use and asthma became monotonic.

The Nurses' Health Study sample is not representative of the general U.S. female population and not all participants in the Nurses' Health Study provided information of analgesic use. Given the prospective design of this study, the nonrepresentative nature of this sample should not bias the study's findings but may affect its generalizability. We do not believe, however, that the putative mechanism of acetaminophen and asthma differs by race/ethnicity or socioeconomic class; therefore, we expect findings of this study to be generalizable. Furthermore, the above-mentioned case-control study (10) and randomized trial (9) were population based and practitioner based, respectively.

In summary, we found that acetaminophen use was associated with an increased rate of newly diagnosed, adult-onset asthma. This finding suggests that the population-level increases in asthma in the United States might be attributable, in part, to historical trends in analgesic use. Asthma is a heterogeneous disorder. Clearly, many patients with asthma tolerate acetaminophen without problems, and a small subgroup of patients with asthma react severely to aspirin and, less frequently, with other NSAIDs. The U.S. National Asthma Education and Prevention Program recommends counseling patients with severe persistent asthma or a history of aspirin sensitivity about aspirin avoidance (39). It would be premature, on the basis of the current report, to recommend the avoidance of acetaminophen for all adults with asthma. Children were not included in our study. Further epidemiologic and biologic research on the pulmonary responses to over-the-counter analgesics is indicated to better understand

these phenomena and to examine if patient subgroups exist that might benefit from a more deliberate selection of analgesic medications for regular use.

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