

Prescription-Acquired Acetaminophen Use and the Risk of Asthma in Adults: A Case-Control Study

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Acetaminophen is a widely used analgesic and antipyretic drug in the US, with annual sales of approximately \$1 billion.¹ Although it is considered relatively safe, concerns are being expressed over excessive acetaminophen consumption. The organs principally affected by acetaminophen overdose are the liver and kidneys, but dose-dependent lung toxicity may also occur.² Instances of acute lung injury in patients with acetaminophen-induced fulminant hepatic failure have been reported.³ Advanced liver disease is associated with hypoxemia and respiratory failure by various mechanisms,⁴ suggesting that the lung injury may be a result of physiologic changes related to hepatic dysfunction rather than the direct effect of acetaminophen. Although the cause of lung injury among acetaminophen-induced fulminant liver failure cases is not clear, possible reasons are excessive production or lack of clearance of an endogenous vasodilator associated with acute liver failure, increased intracranial pressure, or a direct cytotoxic effect of acetaminophen metabolites on the lung.³ It has also been suggested that acetaminophen-induced glutathione deple-

BACKGROUND: Studies have examined the association between acetaminophen use and asthma; however, their interpretation is limited by several methodologic issues.

OBJECTIVE: To investigate the association between recent and chronic prescription-acquired acetaminophen use and asthma.

METHODS: This retrospective case-control study used a 10% random sample of the IMS LifeLink commercial claims data from 1997 to 2009. Cases had to have at least 1 incident claim of asthma; 3:1 controls matched on age, sex, and region were randomly chosen. Acetaminophen exposure, dose, and duration were measured in the 7- and 30-day (recent) and the 1-year (chronic) look-back periods. Multivariable conditional logistic regression was used to estimate the risk of asthma associated with acetaminophen use adjusted for comorbidities, other drugs increasing asthma risk, and health system factors.

RESULTS: There were 28,892 cases and 86,676 controls, with mean age of 42.8 years; 37.7% were males, and 22.6% of cases and 18.2% of controls had acetaminophen exposure in the pre-index year, with mean cumulative doses of 78.7 g and 59.8 g, respectively. There was no significant association between recent prescription acetaminophen exposure and asthma (7 days: OR 1.02, $p = 0.74$; 30 days: OR 0.97, $p = 0.38$). Cumulative prescription acetaminophen dose in the year prior increased asthma risk compared to acetaminophen nonusers (≤ 1 kg: OR 1.09, $p < 0.001$ and > 1 kg: OR = 1.60, $p = 0.02$). Duration of prescription acetaminophen use greater than 30 days was associated with elevated asthma risk (OR 1.39, $p < 0.001$).

CONCLUSIONS: Chronic prescription-acquired acetaminophen use was associated with an increased risk of asthma, while recent use was not. However, over-the-counter acetaminophen use was not captured in this study and further epidemiologic research with complete acetaminophen exposure ascertainment and research on pathophysiologic mechanisms is needed to confirm these relationships.

KEY WORDS: acetaminophen, acetaminophen toxicity, asthma, pharmacoepidemiology.

Ann Pharmacother 2012;46:1598-608.

Published Online, 20 Nov 2012, *theannals.com*, doi: 10.1345/aph.1R430

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tion, independent of advanced liver disease, leads to lung damage, and regular acetaminophen users without liver manifestations may be at an increased risk of asthma.⁵ A review of publications on this topic² reported an association between acetaminophen use and the development of asthma symptoms, but mechanistic studies in humans to support these associations have not been performed. Alterations in lung glutathione levels⁶ and/or metabolic activation of acetaminophen,⁷ or cyclooxygenase-mediated effects² may represent important mechanisms in the pathogenesis of asthma based on data from experimental animal models.

The hypothesis of an association between acetaminophen use and asthma was first proposed about a decade ago.⁸ At the population level, associations between per capita acetaminophen consumption and the prevalence of asthma have been reported.⁸ The prevalence of asthma in the US has increased over the last 30 years for reasons not completely understood.² Because of a surge in asthma prevalence that occurred concurrently with increasing acetaminophen use, there is renewed interest in the role of acetaminophen in the development of asthma.^{2,8}

Several reviews on this topic suggested a positive link between acetaminophen use and the risk of asthma in adults and children,⁹⁻¹¹ but whether this association is causal remains debatable.¹² The interpretation of epidemiologic studies^{7,13-15} supporting the acetaminophen-asthma association in adults is limited by a number of issues, such as lack of rigorous case definitions and not controlling for key confounders.² Moreover, these studies have measured acetaminophen use in terms of frequency of use rather than the dose, which plays a major role in determining the degree of glutathione depletion. Finally, only 1 study¹³ used incident cases rather than prevalent asthma cases, and there is no way of knowing whether acetaminophen use preceded asthma or vice versa in these other studies. To our knowledge, there are no large-scale claims-based studies examining the association between acetaminophen use and asthma. One of the reasons could be incomplete acetaminophen exposure ascertainment because of incomplete recording of over-the-counter (OTC) acetaminophen use. Chronic prescription-acquired acetaminophen use has increased in the past few years, which parallels increases in the use of acetaminophen/opioid combination products.^{16,17} Our previous claims-based study of annual acetaminophen use reported approximately 30% of acetaminophen users with potential peak acetaminophen consumption more than the maximum recommended daily dose (4 g/day) based exclusively on prescription claims, indicating that administrative claims data capture high-risk acetaminophen use.¹⁶ Unlike retrospective interview-based studies, claims-based studies are not biased due to differential exposure recall of the cases compared to the controls. Pharmacy claims record the start and end dates of a prescription and the amount of drug prescribed and therefore are not bi-

ased by knowledge about the study outcome.¹⁸ Given these advantages and a lack of claims-based studies examining the acetaminophen-asthma link, we sought to investigate the association between recent and chronic prescription-acquired acetaminophen consumption and asthma using a large nationally representative commercial claims database.

Methods

STUDY DESIGN AND DATA SOURCE

This study was part of a larger project examining the association between recent and chronic acetaminophen use and hepatic (hepatotoxicity) and nonhepatic (renal disease and asthma) outcomes using a retrospective case-control design.¹⁹ The data source used was a 10% random sample of the IMS LifeLink Health Plans' commercial claims data from 1997 to 2009. This dataset consists of claims from over 98 managed care organizations in the US and is representative of the commercially insured population in the US with respect to age, sex, and region. The data include pharmacy claims, inpatient and outpatient claims, and enrollment information for about 6 million individuals. The data contain records for both OTC and prescription acetaminophen-containing products billed as a prescription claim. The acetaminophen records from this data source have been used in our previous study examining the trends in acetaminophen use and potential overuse.¹⁶

CASES

Eligible cases were individuals aged 18 years or older with at least 1 incident primary diagnosis of asthma (493.xx)²⁰ between January 1, 1998, and December 31, 2009. The date of an incident asthma diagnosis was designated as the index date and the cases were required to have continuous plan enrollment in the pre-index year. Since this study was part of a larger project with 3 outcomes, to keep the methods consistent, cases with diagnoses of hepatotoxicity, renal disease, or asthma in the pre-index year were excluded. The exclusion codes contained a broader set of related conditions in addition to the case definitions (Supplementary Material, Tables S1-S4, www.hwbooks.com/pdf/appendices/R430.pdf) to exclude persons with possible manifestations of the disease. We also excluded cases with previous liver, kidney, or lung transplant; those receiving immunosuppressant therapy; and those with liver, renal, respiratory tract cancer, or secondary malignancies.

CONTROLS

Three controls for every case matched on age, sex, and geographic location were randomly selected from a group of individuals without evidence of asthma, hepatotoxicity, and nephrotoxicity at the end of the follow-up period. Controls were assigned the same index date as the corresponding case

and were required to have continuous plan enrollment in the pre-index year. We excluded controls that had a previous diagnosis code of acetaminophen poisoning (965.4x).²¹ Other exclusion criteria were the same as those of the cases. Selection of cases and controls is depicted in Figure 1.

ACETAMINOPHEN EXPOSURE MEASURES

Acetaminophen-containing products were identified using unique generic product identifier codes in the data. We measured any acetaminophen exposure, doses, and use durations for recent (7 and 30 days pre-index) and chronic (365 days pre-index) look-back periods. Doses calculated were as follows:

1. Potential maximum daily dose (PMDD) in the 7 and 30 days pre-index: the highest potential acetaminophen dose calculated in the pre-index period using the days supplied, strength, and quantity fields in the data. Overlapping prescriptions were identified using fill dates and days supplied, and the daily doses were summed to obtain the potential maximum dose.
2. Potential average daily dose in the pre-index month: dose obtained by summing the acetaminophen doses

contained in all prescriptions in the 30 days pre-index, divided by the total days of acetaminophen use.

3. Cumulative dose in the pre-index year: the sum of acetaminophen doses from all acetaminophen-containing prescriptions during the pre-index year.

Table 1 describes the details of all of the acetaminophen use measures.

OTHER COVARIATES

We obtained data on the following potential confounders in the pre-index period:

1. Medical conditions: These were measured in the 365-day pre-index period for both recent and chronic analyses and included eczema,²² rhinitis,^{23,24} chronic obstructive pulmonary disease,²³ acute respiratory tract infections,^{25,26} gastrointestinal reflux disease,^{27,28} and cancer²⁹ (Table S5).
2. Drug variables: Drug exposure was measured in the 30 days pre-index for recent use analyses and in the 365 days pre-index for the chronic acetaminophen use models. Use of β -blockers,²⁵ antibiotics,³⁰ and nonsteroidal antiinflammatory drugs (NSAIDs)³¹ was

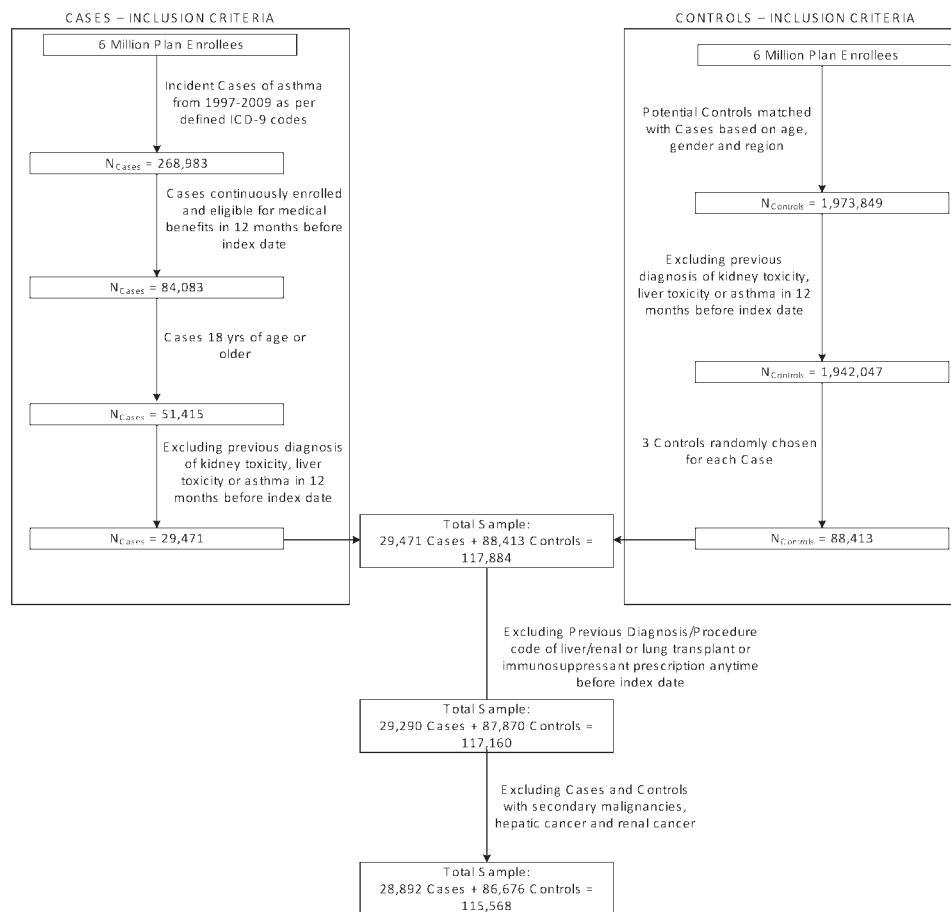


Figure 1. Flowchart of case and control selection.

measured. We also controlled for use of single-ingredient unmixed opioid analgesics, since their use is linked to respiratory depression.³²

3. Health system variables: Using the enrollment information, we obtained data on insurance payer/plan type (Table 2) for our sample.

In addition to the above covariates, we included a binary term for acetaminophen use in the 30 days pre-index to control for recent use of acetaminophen for the chronic acetaminophen use models. We could not adjust for race since it was not available in our data source.

ANALYSIS

We obtained the baseline descriptive characteristics of our sample in the recent and chronic pre-index periods. χ^2 Tests were used to conduct bivariate comparisons between the characteristics of cases and controls. Adjusted and un-

adjusted conditional logistic regression models were used to determine the effect of recent and chronic acetaminophen use on the risk of asthma. Odds ratios and 95% confidence interval estimates obtained from the regression are reported. Dose-response relationships were assessed using the Cochran-Armitage trend test. All analyses were carried out using SAS version 9.2 (SAS Institute). This study was approved by the institutional review board of the University of Arkansas for Medical Sciences.

Results

Included in the study were 28,892 incident asthma cases and 86,676 controls (Figure 1). The mean age of the sample was 42.8 years and 37.7% were males. Use of drugs and presence of comorbidities that increase asthma risk were significantly higher among the cases compared to the controls (Table 2). A total of 1415 cases (4.9%) and 3271

Table 1. Description of Recent and Chronic Acetaminophen Exposure Measures

Acetaminophen Use Measure	Definition/Description	Categories	Reference Group
Recent acetaminophen exposure measures (measured in the 7 days pre-index)			
Acetaminophen exposure in the 7-day pre-index period	Use of an acetaminophen-containing prescription for at least 1 day in the 7-day pre-index period	Yes/no	No acetaminophen exposure in the 7-day pre-index period
PMDD in the 7-day pre-index period	The highest potential acetaminophen dose on any day during the 7 days pre-index Calculated using the days supplied, strength, and quantity fields in the data Overlapping prescriptions were identified using fill dates and days supplied, and the daily doses were summed to obtain the PMDD	PMDD $\leq$ 4 g/day PMDD > 4 g/day	No acetaminophen use (PMDD = 0 g/day)
Recent acetaminophen exposure measures (measured in the 30 days pre-index)			
Acetaminophen exposure in the 30-day pre-index period	Use of an acetaminophen-containing prescription for at least 1 day in the 30-day pre-index period	Yes/no	No acetaminophen exposure in the 30-day pre-index period
PMDD in the 30-day pre-index	The highest potential acetaminophen dose on any day during the 30 days pre-index Calculated using the days supplied, strength, and quantity fields in the data Overlapping prescriptions were identified using fill dates and days supplied, and the daily doses were summed to obtain the PMDD	PMDD $\leq$ 4 g/day PMDD > 4 g/day	No acetaminophen use (PMDD = 0 g/day)
PADD in the pre-index month	Dose obtained by summing the acetaminophen doses contained in all prescriptions in the 30 days pre-index and dividing by the total days of acetaminophen use in the 30-day pre-index period	PADD $\leq$ 4 g/day PADD > 4 g/day	No acetaminophen use (PADD = 0 g/day)
Chronic acetaminophen exposure measures (measured in the pre-index year)			
CD for 1 year pre-index	Sum of acetaminophen doses in all acetaminophen-containing prescriptions in the pre-index year	CD $\leq$ 1 kg CD > 1 kg	No acetaminophen use (CD = 0 kg)
Duration of acetaminophen use	Total number of days of acetaminophen use in the pre-index year	1-30 days 31-365 days	No acetaminophen use
Combination of dose and duration of acetaminophen use	Joint effect of acetaminophen dose and duration of acetaminophen use in the pre-index year	PMDD $\leq$ 4 g/day and duration $\leq$ 30 days PMDD $\leq$ 4 g/day and duration > 30 days PMDD > 4 g/day and duration $\leq$ 30 days PMDD > 4 g/day and duration > 30 days	No acetaminophen use (PMDD = 0 and duration = 0)
CD = cumulative dose; PADD = potential average daily dose; PMDD = potential maximum daily dose.			

controls (3.8%) were exposed to acetaminophen for at least 1 day in the 30 days pre-index, with mean maximum daily doses of 3393.5 mg and 3346.4 mg, respectively (Table 3). In the pre-index year, 6537 cases (22.6%) and 15,809 controls (18.2%) had acetaminophen exposure, with mean cumulative doses of 78.7 g and 59.8 g, respectively. The mean number of total days of acetaminophen use was significantly greater among the cases (32.2 days) compared to the controls (24.7 days). More than 90% of the prescriptions used by both cases and controls were for opioid/acetaminophen combinations (Table 3).

There was no significant association between any of the adjusted recent acetaminophen exposure measures and asthma (Table 4). To determine whether our study was sufficiently powered to detect significant differences between cases and controls, we performed power analysis using the Epicalc package in R software.³³ Assuming a true odds ra-

tio of 1.5, the power of our study was >80% to detect significant differences with all of the recent acetaminophen variables (data not shown).

Cumulative acetaminophen dose in the pre-index year increased the risk of asthma by 10-60% compared to acetaminophen nonusers (≤ 1 kg: OR 1.09, 95% CI 1.05 to 1.13 and >1 kg: OR 1.60, 95% CI 1.09 to 2.37, respectively; Table 5). Doses greater than 1 kg conferred a significantly higher risk compared to lower cumulative doses (p for trend = 0.05). The risk of asthma with acetaminophen use 30 days or less in the pre-index year was 1.07 times that of nonusers and increased 1.39-fold when acetaminophen use duration was greater than 30 days (OR 1.07, 95% CI 1.03 to 1.11 and OR 1.39, 95% CI 1.27 to 1.53, respectively; $p < 0.001$ for trend; Table 5). Categories of PMDD and total acetaminophen use duration in the pre-index year indicate that irrespective of the dose, the risk of

Table 2. Demographic, Comorbidity, and Drug Exposure Variables for Asthma Cases and Matched Controls: IMS LifeLink Claims Data, 1997-2009^a

Variable	Cases (n = 28,892)	Controls (n = 86,676)
Demographic variables		
Age at index date, years, mean (SD)	42.77 (15.1)	42.77 (15.1)
Male, n (%)	10,878 (37.7)	32,634 (37.7)
Region, n (%)		
East	6,717 (23.3)	20,151 (23.3)
West	4,125 (14.3)	12,375 (14.3)
Midwest	11,207 (38.8)	33,621 (38.8)
South	6,843 (23.7)	20,529 (23.7)
Health system variables, n (%)		
Medicaid	927 (3.2)	1,598 (1.8)
Commercial HMO	7,791 (27.0)	24,280 (28.0)
Medicare	942 (3.3)	2,402 (2.8)
Non-HMO commercial and unknown type	19,232 (66.6)	58,396 (67.4)
Pre-index exposure to drugs that increase the risk of asthma, n (%)		
Antibiotic exposure, 30 days	4,327 (15.0)	6,091 (7.0)
Antibiotic exposure, 365 days	14,325 (49.6)	32,227 (37.2)
NSAID exposure, 30 days	942 (3.3)	1,920 (2.2)
NSAID exposure, 365 days	5,094 (17.6)	12,004 (13.9)
β -Blocker exposure, 30 days	1,432 (5.0)	3,992 (4.6)
β -Blocker exposure, 365 days	1,906 (6.6)	5,256 (6.1)
Use of unmixed opioids, 365 days	565 (1.9)	1,247 (1.4)
Comorbidity variables in the 365 days pre-index (n, %)		
Eczema	1,640 (5.7)	3,614 (4.2)
Respiratory tract infection	10,424 (36.1)	14,712 (17.0)
Rhinitis	5,307 (18.4)	5,091 (5.9)
COPD	1,546 (5.4)	1,042 (1.2)
GERD	1,674 (5.8)	3,151 (3.6)
Cancer	2,003 (6.9)	5,557 (6.4)
COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; HMO = health maintenance organization; NSAID = non-steroidal antiinflammatory drug.		
^a $p < 0.05$ for all variables.		

asthma with acetaminophen use for 30 days or less was significantly lower than the risk conferred by durations longer than 30 days (Table 5).

Discussion

In our sample, recent prescription-acquired acetaminophen use did not increase the risk of asthma. This is in agreement with studies reporting no significant asthma risk with infrequent (less than monthly) acetaminophen use or use for up

to 22 days in 1 month.^{13,14} Although there are no studies reporting an association between recent acetaminophen use and asthma, acute acetaminophen overdose may have a direct cytotoxic effect on pneumocytes and lead to lung injury.³ Whether or not this lung injury leads to the development of asthma requires further investigation. Chronic prescription-acquired acetaminophen use, however, increased the risk of asthma by 10-60% compared to acetaminophen nonuse. This is consistent with a recent meta-analysis that reported a 74% increased asthma risk (pooled OR 1.74)

Table 3. Prescription-Acquired Acetaminophen Exposure, Doses, and Durations of Use in the Pre-Index Period

Variable	Cases (n = 28,892)	Controls (n = 86,676)
Acetaminophen exposure for at least 1 day, n (%)		
Acetaminophen exposure; 7 days	798 (2.8)	1,721 (2.0)
Acetaminophen exposure; 30 days	1,415 (4.9)	3,271 (3.8)
Acetaminophen exposure; 365 days	6,537 (22.6)	15,809 (18.2)
MDD in the 7 days pre-index		
MDD, mg, mean (SD) ^a	3,004.4 (4871.3)	2,947.2 (7,533.1)
MDD ≤4 g/day, n (%)	690 (2.4)	1,486 (1.7)
MDD >4 g/day, n (%)	108 (0.4)	235 (0.3)
MDD in the 30 days pre-index		
MDD, mg, mean (SD) ^b	3,393.5 (5,219.0)	3,346.4 (6,279.2)
MDD ≤4 g/day, n (%)	1,148 (4.0)	2,632 (3.0)
MDD >4 g/day, n (%)	267 (0.9)	639 (0.7)
ADD in the 30 days pre-index		
ADD, mg, mean (SD) ^b	2,940 (4,133.0)	2,946.4 (4,374.0)
ADD ≤4 g/day, n (%)	1,240 (4.3)	2,819 (3.3)
ADD >4 g/day, n (%)	35 (0.1)	45 (0.05)
Cumulative dose in the pre-index year		
Cumulative dose, grams, in the pre-index year, mean (SD) ^c	78.7 (224.6)	59.8 (157.1)
Cumulative dose ≤1 kg, n (%)	6,488 (22.5)	15,734 (18.2)
Cumulative dose >1 kg, n (%)	49 (0.2)	75 (0.1)
Duration of acetaminophen use in the pre-index year		
Total days of acetaminophen use, mean (SD) ^c	32.2 (67.9)	24.7 (57.6)
Total days of acetaminophen use ≤30 days, n (%)	5,309 (18.4)	13,559 (15.6)
Total days of acetaminophen use >30 days, n (%)	1,228 (4.3)	2,250 (2.6)
PMDD and duration of acetaminophen use in the pre-index year		
PMDD ≤4 g and total days ≤30 days, n (%)	4,002 (13.9)	10,294 (11.9)
PMDD ≤4 g and total days >30 days, n (%)	654 (2.3)	1,161 (1.3)
PMDD >4 g and total days ≤30 days, n (%)	1,307 (4.5)	3,265 (3.8)
PMDD >4 g and total days >30 days, n (%)	574 (2.0)	1,089 (1.3)
Types of acetaminophen prescriptions for 22,346 acetaminophen users^d		
Opioid/acetaminophen combinations	19,740 (93.5)	39,480 (92.5)
Cough/cold products	10 (0.1)	72 (0.2)
Nonopioid combination analgesics	1,260 (6.0)	2,924 (6.9)
Acetaminophen only ^e	97 (0.5)	226 (0.5)

ADD = average daily dose; MDD = maximum daily dose.

^aMean values calculated for 798 cases and 1721 controls.

^bMean values calculated for 1415 cases and 3271 controls.

^c||,¶ Mean values calculated for 6537 cases and 15,809 controls.

^dTotal acetaminophen prescriptions among cases, 21,107; total acetaminophen prescriptions among controls, 42,702.

^eNot significant at $\alpha = 0.05$

among adult acetaminophen users compared to nonusers.³⁴ The risk conferred by cumulative dose in the pre-index year increased in a dose-dependent fashion. This is in keeping with the theory that acetaminophen-induced glutathione depletion in the lungs is dose-dependent.² Consistent with the existing epidemiologic literature,^{13,14} asthma risk also increased with acetaminophen use duration.

Our results are biologically plausible based on pathophysiologic mechanisms describing acetaminophen-induced lung toxicity. The primary organs affected by acetaminophen overdose are the liver and the kidneys. However, acetaminophen also depletes glutathione in the lung tissue, which leads to contraction of the airway smooth muscles by reactive oxygen species, resulting in inflammation and bronchoconstriction.^{2,13,14} This could lead to symptoms of asthma in individuals who otherwise have subclinical disease.¹⁴ Other mechanisms of acetaminophen-induced lung injury are through the lack of inhibition of the cyclooxygenase enzyme and through increased immunoglobulin E antibody levels as a result of antigenic activity of acetaminophen.³⁴ To our knowledge, there is a paucity of research on the detailed mechanisms of acetaminophen-induced lung injury, particularly concerning the time of onset of lung injury after acetaminophen consumption in humans. If it is true that acetaminophen first affects the liver and kidneys before affecting the lungs, the process of lung injury might be slower and could require prolonged consumption of acetaminophen. It has been reported that cross-sensitivity to acetaminophen may go un-

recognized in aspirin-sensitive asthmatics since the effect of acetaminophen on the lungs is smaller and of slower onset than that of aspirin.¹⁴ Although this finding is in individuals with asthma, it provides some evidence of the slow onset of lung injury with acetaminophen. While an association between chronic acetaminophen consumption and asthma is consistent with other studies and biologically plausible based on the theory of glutathione depletion, further pathophysiological research is warranted to confirm the slower onset of acetaminophen-induced lung toxicity.

Our results should be interpreted in light of exposure misclassification bias. We calculated maximum daily doses based on days' supply and quantity in our dataset and assumed that overlapping prescriptions were consumed concurrently, which could overstate the PMDD in some instances and bias the results toward the null. This is why we refer to "potential" maximum daily doses and average daily doses; however, PMDD was not significantly related to asthma in our study and this calculation does not affect our other acetaminophen dose measures. A larger concern is not accounting for unrecorded OTC acetaminophen use that could bias our results. The acetaminophen product market consists of 48% prescription and 52% OTC products³⁵; thus, we may have accounted for approximately half of all acetaminophen use with our data and our calculated acetaminophen use measures may be understated substantially. If the misclassification is nondifferential (ie, an equal proportion of cases and controls are misclassified), our results would most likely be biased toward the null. If a

Table 4. Adjusted and Unadjusted Odds Ratios of Acute Acetaminophen Exposure^a

Variable	Cases, n	Controls, n	Unadjusted OR (95% CI)	Adjusted OR ^b (95% CI)	p Value
Acetaminophen exposure for at least 1 day in the 7 days pre-index	798	1721	1.40 (1.29 to 1.53)	1.02 (0.93 to 1.11)	0.74
Acetaminophen exposure for at least 1 day in the 30 days pre-index	1415	3271	1.31 (1.23 to 1.40)	0.97 (0.90 to 1.04)	0.38
MDD, 7 days pre-index					
MDD (≤4 g)	690	1486	1.40 (1.28 to 1.54)	1.03 (0.93 to 1.13)	0.62
MDD (>4 g)	108	235	1.39 (1.11 to 1.74)	0.96 (0.75 to 1.23)	0.74
MDD, 30 days pre-index					
MDD (≤4 g)	1148	2632	1.32 (1.24 to 1.42)	0.98 (0.90 to 1.05)	0.53
MDD (>4 g)	267	639	1.27 (1.10 to 1.46)	0.94 (0.81 to 1.10)	0.45
ADD, 30 days pre-index					
ADD (≤4 g)	1240	2819	1.33 (1.25 to 1.43)	0.98 (0.91 to 1.06)	0.66
ADD (> 4 g)	175	452	1.17 (0.99 to 1.40)	0.88 (0.73 to 1.06)	0.18

ADD = average daily dose; MDD = maximum daily dose.

^aReference group: no acetaminophen exposure.

^bAnalyses adjusted for (1) drug exposure variables such as antibiotics, nonsteroidal antiinflammatory drugs, and β-blockers (30 days pre-index); (2) diagnosis variables such as eczema, rhinitis, chronic obstructive pulmonary disease, respiratory tract infections, gastrointestinal reflux disease, and cancer (365 days pre-index); (3) unimixed opioid use in pre-index year; and (4) health system variables such as Medicare, Medicaid, and commercial health maintenance organization.

greater proportion of cases that exhibited higher comorbidity levels than controls used unrecorded acetaminophen, they could be differentially misclassified as nonexposed and the results would also bias our results toward the null. Although this could be a reason for the lack of an association between recent acetaminophen use and asthma, the same consideration makes our observed association between chronic acetaminophen use and asthma more plausible; perhaps the strength of association was understated. The role of confounding by indication (in this case, reverse causality bias) should be considered to explain the positive association observed in our study.³⁶ This could arise if a greater proportion of cases than controls used acetaminophen products in the pre-index period to manage early manifestations of asthma. However, 93.5% of all acetaminophen prescriptions of cases were opioid/acetaminophen combinations primarily used for pain, while cough-cold prescriptions, which would generally be used to treat asthma-like symptoms, accounted for less than 1% of acetaminophen use and cough-cold acetaminophen product use was slightly higher in controls compared to cases. Hence, bias due to reverse causality is unlikely to be of significant concern.

Opioid analgesics have been linked to respiratory depression.³² Since an overwhelming majority of the acetaminophen prescriptions in our sample were for opioid/ac-

etaminophen combinations, the possibility of opioids contributing to the development of asthma should be considered. Respiratory depression is a greater problem with the use of single-ingredient unmixed opioids compared to opioid combinations,³⁷ which is likely due to a higher narcotic dose in unmixed opioids. A total of 1.9% of the cases and 1.4% of controls used unmixed opioids in the pre-index year and, in spite of controlling for this, we observed a positive association between chronic acetaminophen use and asthma. The models without this adjustment provided similar results. Respiratory depression is kept to a minimum in patients with chronic pain who are maintained on regularly monitored opioid doses,³² suggesting that respiratory depression may not be a significant concern with regular long-term opioid use. A consensus statement from the American Academy of Pain Medicine and the American Pain Society states that opioid-induced respiratory depression is a short-lived phenomenon and generally occurs in patients who are opioid-naïve rather than in those on chronic opioid therapy.³⁸ This could be because patients develop tolerance to the opioid respiratory depressant effect over time.³⁹ Therefore, respiratory depression is rare among patients on chronic opioid therapy.³⁹ This would support the notion that it is acetaminophen and not the opioids in these combination products that is associated with asthma in our chronic use models.

Table 5. Adjusted and Unadjusted Odds Ratios of Chronic Acetaminophen Exposure^a

Variable	Cases, n	Controls, n	Unadjusted OR (95% CI)	Adjusted OR ^b (95% CI)	p Value
Cumulative dose in the pre-index year					
≤1 kg ^c	6,488	15,734	1.31 (1.26 to 1.35)	1.09 (1.05 to 1.13)	<0.001
>1 kg ^c	49	75	2.08 (1.45 to 2.98)	1.60 (1.09 to 2.37)	0.02
Acetaminophen use 30 days pre-index	1,415	3,271		0.96 (0.89 to 1.03)	0.24
Total acetaminophen use duration in the pre-index year					
≤30 days ^d	5,309	13,559	1.24 (1.20 to 1.28)	1.07 (1.03 to 1.11)	0.01
>30 days ^d	1,228	2,250	1.74 (1.62 to 1.87)	1.39 (1.27 to 1.53)	<0.001
Acetaminophen use 30 days pre-index	1,415	3,271		0.87 (0.80 to 0.95)	0.01
Categories of PMDD in the pre-index year and the total days of acetaminophen use					
PMDD ≤4 g and total days ≤30 days ^e	4,002	10,294	1.23 (1.18 to 1.28)	1.06 (1.02 to 1.11)	0.01
PMDD ≤4 g and total days >30 days ^e	654	1,161	1.79 (1.63 to 1.98)	1.44 (1.29 to 1.61)	<0.001
PMDD >4 g and total days ≤30 days ^e	1,307	3,265	1.27 (1.19 to 1.36)	1.09 (1.01 to 1.17)	0.01
PMDD >4 g and total days >30 days ^e	574	1,089	1.68 (1.51 to 1.86)	1.34 (1.19 to 1.52)	<0.001
Acetaminophen use 30 days pre-index	1,415	3,271		0.87 (0.80 to 0.95)	0.01

PMDD = potential maximum daily dose.

^aReference group: no acetaminophen exposure.

^bAnalyses adjusted for the following: (1) acute acetaminophen exposure in the 30 days pre-index; (2) drug exposure variables such as antibiotics, nonsteroidal antiinflammatory drugs, and β -blockers (365 days pre-index); (3) diagnosis variables such as eczema, rhinitis, chronic obstructive pulmonary disease, respiratory tract infections, gastrointestinal reflux disease, and cancer (365 days pre-index); (4) health system variables such as Medicare, Medicaid, and commercial health maintenance organization (365 days pre-index); and (5) use of unmixed opioids in the pre-index year.

^cCoefficients of the 2 categories were marginally different ($p = 0.0521$).

^d $p < 0.001$ for trend.

^eCoefficients on categories I & II and categories III & IV were significantly different ($p < 0.0001$ and $p = 0.0020$, respectively).

Given the increased odds of asthma with chronic acetaminophen consumption, clinical decisions guiding acetaminophen use should be based on a thorough risk-benefit assessment of acetaminophen. A clinical trial reported the use of 4 g/day of acetaminophen for 12 months to be safe and effective in 287 patients with osteoarthritis.⁴⁰ However, this trial did not measure lung disorders as one of its outcomes and there is no way of knowing whether lung function was affected by acetaminophen use for a year. Adequately powered clinical trials measuring lung function with chronic acetaminophen use are needed to more clearly elucidate the asthma risks of chronic acetaminophen to aid its risk-benefit assessment. Common alternatives to acetaminophen may be NSAIDs and opioid analgesics. However, these are associated with a number of adverse events⁴¹⁻⁴³ and a thorough comparison of risk-benefit profile of acetaminophen and other analgesic alternatives should be used to guide clinical and policy recommendations about acetaminophen use.

Our results should be interpreted in light of some other limitations in addition to exposure misclassification. First, since our data source did not include clinical measures to detect asthma, we used ICD-9-CM codes exclusively to define asthma cases. The ICD-9-CM codes for asthma have a low sensitivity and we may not have captured all true cases, which increases the possibility that some controls may indeed have had asthma.⁴⁴ Since we selected controls from among the asthma-free individuals at the end of the follow-up period, the ORs calculated in the study represent the odds ratios in the base population and not the risk/rate ratio.⁴⁵ Second, in the absence of a well-established definition of chronicity of acetaminophen use, we used a somewhat arbitrary time window of 1 year. Third, our study included only subjects who were aged 18 years or older. The incidence of asthma is greater in pediatric patients compared to adults, and if acetaminophen was the preferred analgesic in individuals with a history of asthma (since other analgesics like NSAIDs exacerbate asthma) the results could be biased away from the null due to confounding by indication. Finally, since this was an insurance database, we did not have data on factors like body mass index, environmental exposure to allergens, and anthropometric measures. Therefore, the possibility of omitted variable bias cannot be excluded.

Consistent with the results of other studies, chronic prescription-acquired acetaminophen use was significantly associated with asthma in a dose-dependent manner, while recent use was not. Based on our study, it does not appear that occasional short-term use of prescription acetaminophen confers additional asthma risk, but long-term chronic use should be more carefully considered, particularly in asthma-prone individuals. It would be premature to recommend avoidance of acetaminophen, particularly in those with symptoms of asthma, because the most common sub-

stitute analgesic class, NSAIDs, has been linked to asthma. Epidemiologic studies with more complete acetaminophen use measures, including OTC and prescription-acquired use, are warranted to confirm our findings. More basic research to determine the time of onset of lung injury and the causal pathways of asthma associated with acetaminophen use is also needed.

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Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1R430

Conflict of interest: Authors reported none

The use of LifeLink Health Plans data was supported by the University of Arkansas Translational Research Institute (NIH grant UL1 TR000039).

We thank Gary Moore MS for his help with SAS techniques to obtain the study sample from a large number of records.

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EXTRACTO

Uso de Acetaminofeno Obtenido por Receta y el Riesgo de Asma en Adultos: Un Estudio Caso-Control

M Kelkar, MA Cleves, HR Foster, WR Hogan, LP James, y BC Martin

Ann Pharmacother 2012;46:1598-608.

TRASFONDO: Varios estudios han examinado la asociación entre el uso de acetaminofeno (APAP) y asma. Sin embargo, su interpretación es limitada por razones metodológicas.

OBJETIVO: Investigamos la asociación entre el uso reciente y crónico de APAP obtenido mediante receta médica y asma.

MÉTODOS: Estudio retrospectivo de caso-control usando una muestra aleatoria de 10% de la reclamaciones comerciales en IMS LifeLink entre 1997 y 2009. Los casos tenían que tener por lo menos una reclamación de incidencia de asma. Se seleccionaron aleatoriamente controles a razón de 3:1 pareados de acuerdo a edad, género y región. La exposición, dosis y duración del uso de APAP se midió en el período de referencia de 7 a 30 días (para uso reciente) y un año (para uso crónico). Para estimar el riesgo de asma asociado con el uso de APAP ajustado por co-morbilidades, uso de otros medicamentos que podrían aumentar el riesgo de asma y factores asociados al sistema de salud, se utilizó la regresión logística condicionada.

RESULTADOS: Se evaluaron 28,892 casos y 86,676 controles. La edad promedio fue de 42.7 años y 37.7% eran varones. 22.6% casos y 18.2% controles tuvieron exposición a APAP en el período de referencia con dosis acumuladas de 78.7 gramos y 59.8 gramos, respectivamente. No se encontró una diferencia significativa entre exposición reciente a APAP y asma (7 días: OR = 1.02, p = 0.74; 30 días: OR = 0.97, p = 0.38). La

dosís acumulada de APAP durante el año anterior aumentó el riesgo de asma al compararse con los que no habían usado APAP (≤ 1 kg: OR = 1.09, $p < 0.001$ y > 1 kg: OR = 1.60; $p = 0.02$). La duración de la terapia con APAP mayor de 30 días estuvo asociada con un aumento en el riesgo de asma (OR = 1.39, $p < 0.001$).

CONCLUSIONES: El uso crónico de APAP obtenido mediante receta médica estuvo asociado con un aumento en el riesgo de asma mientras que el uso reciente no lo estuvo. Sin embargo, el uso de APAP sin receta no pudo capturarse en este estudio. Es necesario realizar estudios epidemiológicos adicionales que tomen en consideración la exposición a APAP (con receta y sin receta) e investigaciones sobre los mecanismos fisiopatológicos que pudieran confirmar los hallazgos de este estudio.

Traducido por Homero A Monsanto

RÉSUMÉ

L'Utilisation d'Acétaminophène sur Ordonnance et le Risque d'Asthme chez les Adultes: Une Étude cas-Témoin.

M Kelkar, MA Cleves, HR Foster, WR Hogan, LP James, et BC Martin

Ann Pharmacother 2012;46:1598-608.

HISTORIQUE: Des études ont examiné le lien entre l'utilisation d'acétaminophène (PAAP) et l'asthme. éthodologie: Il s'agissait d'une étude rétrospective cas-témoin d'un échantillon aléatoire de 10% des données de réclamation d'IMS LifeLink de 1997 à 2009. Les cas retenus devaient avoir fait l'objet d'au moins une réclamation pour diagnostic d'asthme.

Des contrôles appariés 3:1 pour l'âge, le sexe et la région ont été aléatoirement choisis. L'exposition à l'acétaminophène, la dose et la durée ont été mesurées dans les 7 et 30 jours (utilisation récente) et dans l'année (utilisation chronique) précédant le diagnostic (date index). La régression logistique conditionnelle à variables multiples a été utilisée pour estimer le risque d'asthme, relié à l'utilisation d'acétaminophène, ajusté pour les comorbidités, les autres médicaments augmentant le risque d'asthme et les facteurs reliés au système de santé.

RÉSULTATS: Il y avait 28,892 cas et 86,676 contrôles âgés en moyenne de 42.7 ans dont 37.7% étaient des hommes. 22.6% des cas et 18.2% des contrôles ont été exposés au PAAP dans l'année précédant la date index avec une dose cumulative moyenne de 78.7 g et 59.8 g respectivement. Il n'y avait pas de lien significatif entre l'exposition récente au PAAP sur ordonnance et l'asthme (7 jours: RC = 1.02; $p = 0.74$; 30 jours: RC = 0.97; $p = 0.38$). La dose cumulative de PAAP sur ordonnance dans l'année précédente augmentait le risque d'asthme comparativement à ceux n'utilisant pas de PAAP (≤ 1 kg: RC = 1.09; $p < 0.001$ et > 1 kg: RC = 1.60; $p = 0.02$). La durée d'utilisation de PAAP sur ordonnance > 30 jours était reliée à un risque augmenté d'asthme (RC = 1.39; $p < 0.001$).

CONCLUSIONS: L'utilisation chronique de PAAP sur ordonnance était reliée à un risque augmenté d'asthme alors qu'une utilisation récente ne l'était pas. Cependant, l'utilisation de PAAP en vente libre n'était pas documentée dans cette étude. Davantage d'études épidémiologiques tenant compte de l'exposition totale au PAAP et des recherches sur les mécanismes physiopathologiques sont nécessaires pour confirmer ces liens.

Traduit par Louis Boisvert