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

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Abstract

Background—Studies have examined the association between acetaminophen (APAP) use and asthma; however, their interpretation is limited by a number of methodological issues.

Objective—We sought to investigate the association between recent and chronic prescription acquired acetaminophen use and asthma.

Methods—This was a retrospective case control study using 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, gender, and region were randomly chosen. APAP exposure, dose and duration were measured in the 7 and 30 days (recent) and in the 1-year (chronic) look-back period. 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.

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Conflicts of interest : None

Results—There were 28,892 cases and 86,676 controls with mean age 42.7 years and 37.7% were males. 22.6% cases and 18.2% controls had APAP exposure in the pre-index year with mean cumulative doses of 78.7 gm and 59.8 gm respectively. There was no significant association between recent prescription APAP exposure and asthma (7 days: OR = 1.02, p = 0.74; 30 days: OR = 0.97, p = 0.38). Cumulative prescription APAP dose in the year prior increased asthma risk compared to APAP nonusers (<=1 kg: OR = 1.09, p <0.001 and >1 kg: OR = 1.60, p=0.02). Duration of prescription APAP use >30 days was associated with elevated asthma risk (OR = 1.39, p <0.001).

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

Keywords

Asthma; Acetaminophen; Pharmacoepidemiology; Acetaminophen toxicity

Introduction

Acetaminophen (APAP) is a widely used analgesic and antipyretic drug in the U.S. with annual sales around $1 billion.[1] Although considered relatively safe, concerns are being expressed over excessive APAP consumption. The organs principally affected by APAP overdose are the liver and kidneys, but dose-dependent lung toxicity may also occur.[2] Instances of acute lung injury in patients with APAP-induced fulminant hepatic failure have been reported previously.[3] Advanced liver disease itself is associated with hypoxemia and respiratory failure by various mechanisms[4] suggesting that the lung injury may be a result of physiological changes related to hepatic dysfunction rather than the direct effect of APAP. Although the exact cause of lung injury among APAP-induced fulminant liver failure cases is not clear, possible reasons cited 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 APAP metabolites on the lung.[3] It has also been suggested that APAP-induced glutathione depletion, independent of advanced liver disease, leads to lung damage and regular APAP users without liver manifestations may be at an increased risk of asthma.[5] A review of publications on this topic[2] reports an association between APAP use and the development of asthma symptoms, but mechanistic studies in humans to support these associations have not been performed. Alterations in lung glutathione levels[6] and/or metabolic activation of acetaminophen[7], or cyclo-oxygenase mediated effects[2] may represent important mechanisms in the pathogenesis of asthma based on data from experimental animal models.

The hypothesis of an association between APAP use and asthma was first proposed about a decade ago.[8] At the population level, associations between per capita APAP consumption and the prevalence of asthma have been reported.[8] The prevalence of asthma in the U.S. has increased over the last thirty years for reasons not completely understood.[2] Due to a surge in asthma prevalence that occurred concurrently with increasing APAP use, there is renewed interest about the role of acetaminophen in the development of asthma.[2;8]

Several reviews on this topic suggest a positive link between acetaminophen use and the risk of asthma in adults and children[9–11], but whether this association is causal or not remains debatable.[12] The interpretation of epidemiological studies [7;13–15] supporting the APAP-asthma association in adults is limited by a number of issues like lack of rigorous case definitions and not controlling for key confounders.[2] Moreover, these studies have measured

APAP use in terms of 'frequency of use' rather than the dose which plays a major role in determining the degree of glutathione depletion. Finally, except for one study[13], others have used prevalent asthma cases instead of incident cases and there is no way of knowing if APAP use preceded asthma or vice versa. According to our knowledge there are no large scale claims based studies examining the association between APAP use and asthma. One of the reasons could be incomplete APAP-exposure ascertainment due to incomplete recording of over the counter (OTC) APAP use. Chronic prescription-acquired APAP use has increased in the past few years, which parallels increases in the use of APAP-opioid combination products.[16;17] Our previous claims-based study of annual APAP use reported approximately 30% of acetaminophen users with potential peak APAP consumption more than the maximum recommended daily dose (4 grams per day) based exclusively on prescription claims indicating that administrative claims data do capture high risk APAP 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 biased by knowledge about the study outcome.[18] Given these advantages and a lack of claims based studies examining the APAP-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 non-hepatic outcomes (renal disease and asthma) using a retrospective case-control study design.[19] The data source used was a 10% random sample of the IMS LifeLink Health Plans commercial claims data from 1997–2009. This dataset consists of claims from over 98 managed care organizations in the U.S. and is representative of the commercially insured population in the U.S. with respect to age, gender, and region. The data includes pharmacy claims, inpatient and outpatient claims and enrollment information for about 6 million individuals. The data contains records for both OTC and prescription APAP containing products billed as a prescription claim. The APAP 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 >=18 years of age with at least one incident primary diagnosis of asthma (493.xx)[20] between January 1st 1998 to December 31st 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 (Appendix 1, 2, 3) to exclude persons with possible manifestations of the disease. We also excluded cases with previous liver, kidney or lung transplant, those on immunosuppressant therapy or those with liver, renal, respiratory-tract cancer or secondary malignancies.

Controls

Three controls for every case matched on age, gender 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 an index date the same 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 same as that of the cases. Selection of cases and controls is depicted in Figure 1.

Acetaminophen exposure measures

APAP containing products were identified using unique Generic Product Identifier (GPI codes) in the data. We measured any APAP 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 APAP 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 (PADD) in the pre-index month: Dose obtained by summing the APAP doses contained in all prescriptions in the 30 days pre-index divided by the total days of APAP use.
3. Cumulative dose in the pre-index year: The sum of APAP doses from all acetaminophen-containing prescriptions during the pre-index year.

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

Other covariates

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

- Medical conditions: These were measured in the 365 days 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 cancer [29] (Appendix 4).
- 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 APAP use models. Use of beta blockers[25], antibiotics[30] and non-steroidal anti-inflammatory drugs[31] was measured. We also controlled for use of single-ingredient unmixed opioid-analgesics since their use is linked to respiratory depression.[32]
- 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 also included a binary term for APAP use in the 30 days pre-index to control for recent use of APAP for the chronic APAP 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. Chi-square tests were used to conduct bivariate comparisons between the characteristics of cases and controls. Adjusted and unadjusted conditional logistic regression models were used to determine the effect of recent and chronic APAP use on the risk of asthma. Odds ratios (OR) 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, Cary, North Carolina). This study was approved by the Institutional review board of the University of Arkansas for Medical Sciences.

Results

28,892 incident asthma cases and 86,676 controls were included in the study (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 was significantly higher among the cases compared to the controls (Table 2). 1415 cases (4.9%) and 3271 controls (3.8%) were exposed to acetaminophen for at least one day in the 30 days pre-index with mean maximum daily doses of 3,393.5 mg and 3,346.4 mg respectively (Table 3). 6,537 cases (22.6%) and 15,809 controls (18.2%) had APAP exposure in the pre-index year with mean cumulative doses of 78.7 gm and 59.8 gm respectively. The mean total days of APAP 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/APAP combinations (Table 3).

There was no significant association between any of the adjusted recent APAP 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 ratio of 1.5, the power of our study was >80% to detect significant differences with all the recent APAP variables (data not shown).

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

Discussion

In our sample, recent prescription acquired APAP use did not increase the risk of asthma. This is in agreement with studies reporting no-significant asthma risk with infrequent (< monthly) APAP use or use for up to 22 days in a month.[13;14] Although there are no studies reporting an association between recent APAP use and asthma, acute APAP 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 APAP use, however, increased the risk of asthma by 10 – 60% compared to APAP non-users. This is consistent with a recent meta-analysis that reported a 74% increased asthma risk (a pooled OR of 1.74) among adult acetaminophen users compared to non-users.[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 APAP-induced glutathione depletion in the lungs is dose-dependent.[2] Consistent with the existing epidemiologic literature[13;14], asthma risk also increased with APAP use duration.

Our results are biologically plausible based on pathophysiological mechanisms describing APAP-induced lung toxicity. The primary organs affected by APAP overdose are the liver and the kidneys. However, APAP 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 sub-clinical disease.[14] Other mechanisms of APAP-induced lung injury are through the lack of inhibition of the cycloxygenase enzyme and through increased IgE antibody levels as a result of antigenic activity of acetaminophen.[34] According to our knowledge, there is a paucity of research about the detailed mechanisms of APAP-induced lung injury, particularly about the time of onset of lung injury after APAP consumption in humans. If it is true that APAP 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 unrecognized in aspirin-sensitive asthmatics since the effect of acetaminophen on the lungs is smaller and of slower onset than with aspirin.[14] This finding, although in asthmatic individuals, provides some evidence of the slow onset of lung injury with acetaminophen. While an association between chronic APAP 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 APAP-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 towards the null. This is why we refer to ‘potential’ maximum and average daily doses, however, PMDD was not significantly related to asthma in our study and this calculation does not affect our other APAP dose measures. A larger concern is not accounting for un-recorded over the counter (OTC) acetaminophen use that could bias our results. The APAP product market consists of 48% prescription and 52% OTC products[35]; so we may have accounted for approximately half of all APAP use with our data and our calculated APAP use measures may perhaps be understated substantially. If the misclassification is non-differential, ie., an equal proportion of cases and controls are misclassified, our results would most likely be biased towards the null. If a greater proportion of cases which exhibited higher comorbidity levels than controls use unrecorded APAP, they could be differentially misclassified as non-exposed and the results would also bias our results towards the ‘null’. While this could be a reason for the lack of an association between recent APAP use and asthma, the same consideration makes our observed association between chronic-APAP use and asthma more plausible; perhaps the strength of association 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 APAP products in the pre-index period to manage early manifestations of asthma. However, 93.5% of all APAP prescriptions of cases were opioid-APAP 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 APAP use and cough-cold APAP product use was slightly higher in controls compared to cases. Hence bias due to reverse causality is unlikely to be a significant concern.

Opioid analgesics have been linked to respiratory depression.[32] Since an overwhelming majority of the APAP prescriptions in our sample were for opioid-APAP 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 un-mixed opioids. 1.9% of the cases and 1.4% of controls used un-mixed opioids in the pre-index year and in spite of controlling for this, we observed a positive association between chronic APAP use and asthma. The models without this adjustment provided similar results. Respiratory depression is kept to a minimum in chronic pain patients 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 American Pain Society states that opioid induced respiratory depression is a short lived phenomenon and generally occurs in opioid-naïve patients than patients 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] and this would support the notion that it is APAP and not the opioids in these combination products that are associated with asthma in our chronic use models.

Given the increased odds of asthma with chronic APAP consumption, clinical decisions guiding APAP use should be based on a thorough risk-benefit assessment of APAP. A clinical trial reports the use of 4gm/day of APAP for 12 months to be safe and effective in 287 osteoarthritis patients.[40] However, this trial did not measure lung-disorders as one of their outcomes and there is no way of knowing if lung function was affected with APAP use for a year. Adequately powered clinical trials measuring lung function with chronic APAP use are needed to more clearly elucidate the asthma risks of chronic APAP to aid its risk-benefit assessment. Common alternatives to APAP may be non-steroidal anti-inflammatory drugs and opioid analgesics. However, these are associated with a number of adverse events[41–43] and a thorough comparison of risk-benefit profile of APAP and other analgesic alternatives should be used to guide clinical and policy recommendations about APAP 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 asthma.[44] Since we selected controls from amongst 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 APAP use, we used a somewhat arbitrary time-window of 1 year. Third, our study only included the subjects >= 18 years of age. The incidence of asthma is greater in pediatrics compared to adults, and if acetaminophen was the preferred analgesic in individuals with a previous 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 and environmental exposure to allergens and anthropometric measures, and therefore the possibility of omitted variable bias cannot be excluded.

Conclusion

Consistent with 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 APAP 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 APAP, particularly in those with symptoms of asthma because the most common substitute analgesics, NSAIDS, have been linked to asthma. Epidemiologic studies with more complete APAP use measures, including OTC and prescription acquired use, are warranted to confirm our findings in addition to more basic research to determine the time of onset of lung injury and the causal pathways of asthma associated with APAP use.

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Appendix 1–ICD-9-CM Codes for Asthma and related conditions

Table 1.1

Case definitions (used for identifying incident asthma cases)

Code	Description
493.0x	Extrinsic asthma
493.1x	Intrinsic asthma
493.2x	Chronic obstructive asthma
493.8x	Other forms of asthma
493.9x	Asthma, unspecified

Table 1.2

ICD-9 codes for exclusions of asthma cases 1 year before the index date (used along with table 1.1)

Code	Description
786.05	Shortness of breath
786.07	Wheezing
786.2x	Cough
786.09	Other respiratory distress, insufficiency
162	Malignant neoplasm of trachea, bronchus, and lung
209.21	malignant carcinoid tumor of bronchus
231.2	Carcinoma in situ of respiratory system: Bronchus and lung
V10.11	Personal history of malignant neoplasm: Bronchus and lung
996.84	Complications of transplanted organ: Lung
V426	Organ or tissue replaced by transplant: Lung
32850, 32851, 32852, 32854	Lung transplant CPT codes

Appendix 2–ICD-9-CM Codes for Hepatotoxicity and related conditions

Code	Description
570	Acute and subacute necrosis of liver
572.2	Hepatic encephalopathy
573.3	Hepatitis, unspecified
572.4	Hepatorenal syndrome

Code	Description
286.7	Acquired coagulation factor deficiency
571.xx	Chronic liver disease and cirrhosis
572.xx	Liver abscess and sequelae of chronic liver disease
573.xx	Other disorders of liver
070.0–070.9	Viral hepatitis
277.3	Amyloidosis
751.62	Congenital cystic disease of liver
271.0	Glycogen infiltration of liver
789.1	Hepatomegaly not otherwise specified
452	Portal vein thrombosis
095.3	Syphilis of liver
091.62	Secondary syphilitic hepatitis
130.5	Hepatitis due to toxoplasmosis
155.xx	Neoplasm of the liver and intrahepatic bile ducts
782.4	Jaundice, unspecified, not of newborn
996.82	Complications of transplanted organ: Liver
V427	Organ or tissue replaced by transplant: Liver
47125, 47130, 47135,, 47140-42	Liver transplant CPT codes

Appendix 3–ICD-9-CM Codes for Nephrotoxicity and related conditions

Code	Description
580.xx	Acute glomerulonephritis
581.xx	Nephrotic syndrome
582.xx	Chronic glomerulonephritis
583.xx	Nephritis and nephropathy, not specified as acute or chronic
584.xx	Acute kidney failure
585.xx	CHRONIC RENAL FAILURE
586	Renal failure, unspecified
587	Renal sclerosis, unspecified
588.xx	Disorders resulting from impaired renal function
589.xx	Small kidney of unknown cause
591	HYDRONEPHROSIS
593.xx	Other disorders of kidney and ureter
596.xx	Other disorders of bladder

Code	Description
600.xx	Hyperplasia of prostate
753.1x	Cystic kidney disease
189.0 189.1 209.24, V1052, V1053	Cancer of the kidney and renal pelvis
996.81	Complications of transplanted organ: kidney
V420	Organ or tissue replaced by transplant: kidney
50320, 50323, 50325, 50327, 50328, 50329, 50340, 50360, 50365, 50370, 50380, 50547	Kidney transplant CPT codes

Appendix 4–ICD-9-CM codes of medical conditions used as covariates for asthma

Medical conditions	ICD-9-CM codes
Contact dermatitis and other eczema	692.xx
Acute respiratory infections	460.xx – 466.xx
Chronic obstructive pulmonary disease and allied conditions	491.xx, 492.xx, 494.xx, 496.xx
Allergic rhinitis	477.xx
Esophageal reflux	530.81
Cancer	Based on AHRQ Clinical Classification Software Designation (Cancer codes from cluster 2, http://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixCMultiDX.txt)

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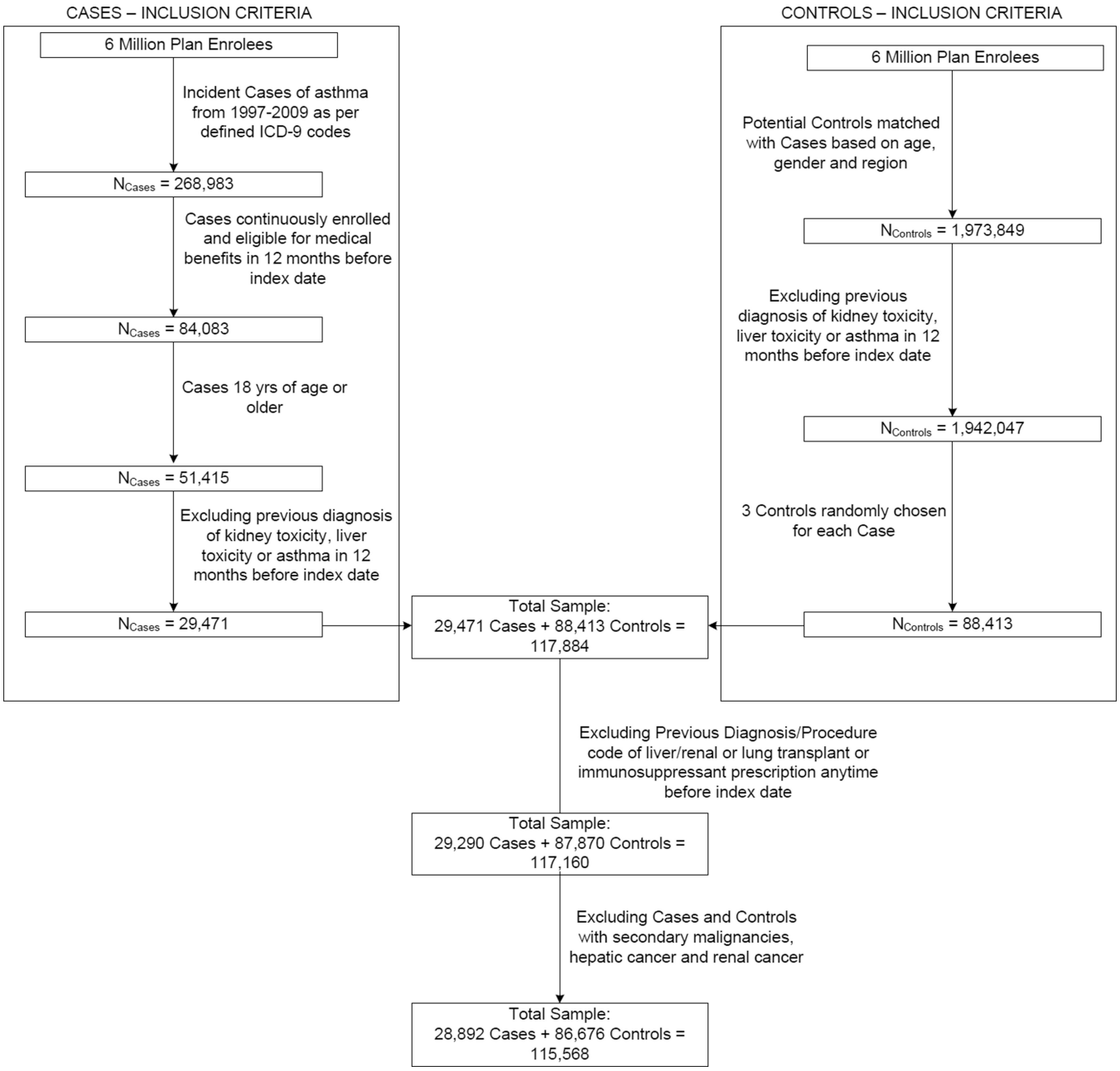

Figure 1.
Flowchart of Case and Control Selection

Table 1

Description of Recent and Chronic Acetaminophen Exposure Measures

APAP use measure	Definition/Description	Categories	Reference group
Recent APAP exposure measures : measured in the 7 days pre-index			
APAP exposure in the 7 day pre-index period	Use of an APAP containing prescription for at least one day in the 7 days pre-index period	Yes/No	No APAP exposure in the 7 day pre-index period
Potential Maximum daily dose (PMDD) in the 7 day pre-index period	The highest potential APAP 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 <= 4gm/day PMDD > 4gm/day	No APAP use (PMDD = 0 gm/day)
Recent APAP exposure measures : measured in the 30 days pre-index			
APAP exposure in the 30 days pre-index period	Use of an APAP containing prescription for at least one day in the 30 day pre-index period	Yes/No	No APAP exposure in the 30 days pre-index period
Potential Maximum daily dose (PMDD) in the 30 days pre-Index	The highest potential APAP 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 <= 4gm/day PMDD > 4gm/day	No APAP use (PMDD = 0 gm/day)
Potential average daily dose (PADD) in the pre-index month	Dose obtained by summing up the APAP doses contained in all prescriptions in the 30 days pre-index and dividing by the total days of APAP use in the 30 days pre-index period.	PADD <= 4gm/day PADD > 4gm/day	No APAP use (PADD = 0 gm/day)
Chronic APAP exposure measures : measured in the pre-index year			
Cumulative dose (CD) for one year pre-index	Sum of APAP doses in all APAP containing prescriptions in the pre-index year	CD <= 1kg CD > 1kg	No APAP use (CD = 0 kg)
Duration of APAP use	Total number of days of APAP use in the pre-index year	1 to 30 days 31 to 365 days	No APAP use
Combination of dose and duration of APAP use	Joint effect of APAP dose and duration of APAP use in the pre-index year	PMDD <= 4gm/day & duration <= 30 days PMDD <= 4gm/day & duration > 30 days PMDD > 4gm/day & duration <= 30 days PMDD > 4gm/day & duration > 30 days	No APAP use (PMDD = 0 and duration = 0)

APAP : Acetaminophen; CD: Cumulative dose; PADD: Potential average daily dose; PMDD: potential maximum daily dose

Table 2

Demographic, Comorbidity and Drug Exposure Variables for Asthma Cases and Matched Controls : Pharmetrics Claims Data 1997–2009

Variable	Cases		Controls	
	N = 28,892		N = 86,676	
Demographic variables				
Age (Mean, SD)				
Age at index date (years)	42.77	15.1	42.77	15.1
Gender (n,%)				
male	10878	37.7%	32634	37.7%
Region (n,%)				
East	6717	23.3%	20151	23.3%
West	4125	14.3%	12375	14.3%
Mid West	11207	38.8%	33621	38.8%
South	6843	23.7%	20529	23.7%
Health system variables (n,%)				
Medicaid	927	3.2%	1598	1.8%
Commercial HMO	7791	27.0%	24280	28.0%
Medicare	942	3.3%	2402	2.8%
non-HMO commercial and unknown type	19232	66.6%	58396	67.4%
Pre-index exposure to drugs that increase the risk of asthma (n,%)				
Antibiotic exposure - 30 days	4327	15.0%	6091	7.0%
Antibiotic exposure - 365 days	14325	49.6%	32227	37.2%
NSAID exposure - 30 days	942	3.3%	1920	2.2%
NSAID exposure - 365 days	5094	17.6%	12004	13.9%
Beta blocker exposure - 30 days	1432	5.0%	3992	4.6%
Beta blocker exposure - 365 days	1906	6.6%	5256	6.1%
Use of unmixed-opioids – 365 days	565	1.9%	1247	1.4%
Comorbidity variables in the 365 days pre-index (n,%)				
Eczema	1640	5.7%	3614	4.2%
Respiratory tract infection	10424	36.1%	14712	17.0%
Rhinitis	5307	18.4%	5091	5.9%
COPD	1546	5.4%	1042	1.2%
GERD	1674	5.8%	3151	3.6%
Cancer	2003	6.9%	5557	6.4%

COPD : Chronic obstructive pulmonary disease ; GERD: Gastro-esophageal reflux disease; NSAID: Non-steroidal anti-inflammatory drugs.

p-values for all variables < 0.05

Table 3

Prescription Acquired Acetaminophen Exposure, Doses and Durations of Use for Asthma Cases and Matched Controls in the Pre-Index Period

Variable	Cases		Controls	
	N = 28,892		N = 86,676	
Acetaminophen exposure variables				
APAP exposure for at least one day - 7 days (n,%)	798	2.8%	1721	2.0%
APAP exposure for at least one day - 30 days (n,%)	1415	4.9%	3271	3.8%
APAP exposure for at least one day – 365 days (n,%)	6537	22.6%	15809	18.2%
Maximum daily dose in the 7 days pre-index				
MDD (mg) - 7 days (Mean [a], SD)	3004.4	4871.3	2947.2	7533.1
MDD (<= 4gm/day) - 7 days (n,%)	690	2.4%	1486	1.7%
MDD (> 4gm/day) - 7 days (n,%)	108	0.4%	235	0.3%
Maximum daily dose in the 30 days pre-index				
MDD (mg) - 30 days (Mean [b]†, SD)	3393.5	5219.0	3346.4	6279.2
MDD (<= 4gm/day) - 30 days (n,%)	1148	4.0%	2632	3.0%
MDD (> 4gm/day) - 30 days (n,%)	267	0.9%	639	0.7%
Average daily dose in the 30 days pre-index				
ADD (mg) - 30 days (Mean [b], SD)	2940	4133.0	2946.4	4374.0
ADD (<= 4gm/day) - 30 days (n,%)	1240	4.3%	2819	3.3%
ADD (> 4gm/day) - 30 days (n,%)	35	0.6%	45	0.5%
Cumulative dose in the pre-index year				
Cumulative dose (gm) in the pre-index year (Mean [b],SD)	78.7	224.6	59.8	157.1
Cumulative dose (<= 1kg) (n,%)	6488	22.5%	15734	18.2%
Cumulative dose (> 1kg) (n,%)	49	0.2%	75	0.1%
Duration of APAP use in the pre-index year				
Total days of APAP use (Mean [c],SD)	32.2	67.9	24.7	57.6
Total days of APAP use (<= 30 days) (n,%)	5309	18.4%	13559	15.6%
Total days of APAP use (> 30 days) (n,%)	1228	4.3%	2250	2.6%
PMDD and Duration of APAP use in the pre-index year				
PMDD <= 4gm and total days <= 30 days (n,%)	4002	13.9%	10294	11.9%
PMDD <= 4gm and total days > 30 days (n,%)	654	2.3%	1161	1.3%
PMDD > 4gm and total days <= 30 days (n,%)	1307	4.5%	3265	3.8%
PMDD > 4gm and total days > 30 days (n,%)	574	2.0%	1089	1.3%
Types of APAP prescriptions for 22,346 APAP users				
Opioid/APAP combinations	19740	93.5%	39480	92.5%
Cough-cold products	10	0.1%	72	0.2%
Non-opioid combination analgesics	1260	6.0%	2924	6.9%
APAP only [d]	97	0.5%	226	0.5%

ADD : Average daily dose; APAP : Acetaminophen; MDD : Maximum daily dose

[a]mean values calculated for 798 cases and 1721 controls

[b] mean values calculated for 1415 cases and 3271 controls

[b], [‖], [¶] mean values calculated for 6537 cases and 15809 controls

[d] not significant at alpha = 0.05

Table 4

Adjusted and Unadjusted Odds Ratios of Acute Acetaminophen Exposure (Reference Group: No APAP Exposure)

Variable	No of cases	No. of controls	Unadjusted OR	Adjusted OR[a] (95% CI)	P value
	N = 28,892	N = 86,676			
APAP Exposure for at least one day in the 7 days pre-index					
APAP exposure - 7 days	798	1721	1.40 (1.29 – 1.53)	1.02 (0.93 – 1.11)	0.74
APAP Exposure for at least one day in the 30 days pre-index					
APAP exposure - 30 days	1415	3271	1.31 (1.23 – 1.40)	0.97 (0.90 – 1.04)	0.38
Maximum daily dose – 7 days preindex					
MDD (<= 4gm) – 7 days	690	1486	1.40 (1.28 – 1.54)	1.03 (0.93 – 1.13)	0.62
MDD (>4gm) – 7 days	108	235	1.39 (1.11 – 1.74)	0.96 (0.75 – 1.23)	0.74
Maximum daily dose - 30 days preindex					
MDD (<= 4gm) – 30 days	1148	2632	1.32 (1.24 – 1.42)	0.98 (0.90 – 1.05)	0.53
MDD (>4gm) – 30 days	267	639	1.27(1.10 – 1.46)	0.94 (0.81 – 1.10)	0.45
Average daily dose – 30 days preindex					
ADD (<= 4gm)	1240	2819	1.33 (1.25 – 1.43)	0.98 (0.91 – 1.06)	0.66
ADD (> 4gm)	175	452	1.17 (0.99 – 1.40)	0.88 (0.73 – 1.06)	0.18

ADD : Average daily dose ; APAP : Acetaminophen ; MDD : Maximum daily dose ;

[a]Analyses adjusted for (1) drug exposure variables (30 days pre-index) – antibiotics, non-steroidal anti-inflammatory drugs, beta blockers (2) diagnosis variables (365 days preindex) - eczema, rhinitis, chronic obstructive pulmonary disease, respiratory tract infections, gastrointestinal reflux disease, cancer (3) unmixed opioid-use in pre-index year and (4) health system variables – Medicare, Medicaid, Commercial health maintenance organization

Table 5

Adjusted and Unadjusted Odds Ratios of Chronic Acetaminophen Exposure (Reference Group: No APAP Exposure)

Variable	No. of Cases N = 28,892	No. of Controls N = 86,676	Unadjusted OR (95% CI)	Adjusted OR[d] (95% CI)	P value
Cumulative dose in the pre-index year					
<= 1kg [a]	6488	15734	1.31 (1.26 – 1.35)	1.09 (1.05 – 1.13)	<.001
> 1kg [a]	49	75	2.08 (1.45 – 2.98)	1.60 (1.09 – 2.37)	0.02
APAP use 30days preindex	1415	3271	-	0.96 (0.89 – 1.03)	0.24
Total APAP use duration in the pre-index year					
<= 30days [b]	5309	13559	1.24 (1.20 – 1.28)	1.07 (1.03 – 1.11)	0.01
> 30days [b]	1228	2250	1.74 (1.62 – 1.87)	1.39 (1.27 – 1.53)	<.001
APAP use 30days preindex	1415	3271	-	0.87 (0.80 – 0.95)	0.01
Categories of PMDD in the pre-index year and the total days of APAP use					
PMDD <= 4gm and total days <= 30 days [c]	4002	10294	1.23 (1.18 – 1.28)	1.06 (1.02 – 1.11)	0.01
PMDD <= 4gm and total days > 30 days [c]	654	1161	1.79 (1.63 – 1.98)	1.44 (1.29 – 1.61)	<.001
PMDD > 4gm and total days <= 30 days [c]	1307	3265	1.27 (1.19 – 1.36)	1.09 (1.01 – 1.17)	0.01
PMDD > 4gm and total days > 30 days [c]	574	1089	1.68 (1.51 – 1.86)	1.34 (1.19 – 1.52)	<.001
APAP use 30days preindex	1415	3271	-	0.87 (0.80 – 0.95)	0.01

Reference Category: No APAP exposure

[a] coefficients of the two categories were marginally different, p = 0.0521

[b] p <0.001 for trend

[c] Coefficients on categories I & II and categories III & IV were significantly different, p <0.0001 and p = 0.0020 respectively

[d] Analyses adjusted for the following (1)Acute APAP exposure in the 30 days pre-index (2) drug exposure variables (365 days pre-index) – antibiotics, non-steroidal anti-inflammatory drugs, beta blockers (3) diagnosis variables (365 days pre-index) - eczema, rhinitis, chronic obstructive pulmonary disease, respiratory tract infections, gastrointestinal reflux disease, cancer and (4) health system variables (365 days pre-index) – Medicare, Medicaid, Commercial health maintenance organization (5)use of unmixed opioids in the pre-index year