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Acute and Chronic Acetaminophen Use and Renal Disease: A Case-Control Study Using Pharmacy and Medical Claims

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Abstract

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

OBJECTIVE—To study the association between acute and chronic prescription-acquired APAP use and renal disease.

METHODS—This was a retrospective case-control study of medical and pharmacy claims of a 10% random sample of the enrollees from the IMS LifeLink Health Plans commercial claims dataset for dates of service from January 1, 1997, through December 31, 2009. Subjects were continuously enrolled and aged 18 years or older. Cases had at least 1 incident claim of renal disease defined by ICD-9-CM codes in the primary diagnosis field. Controls were randomly selected from individuals without evidence of renal disease, liver disease, or asthma in medical claims and matched to cases in a 3-to-1 ratio based on 3 variables (age, gender, and geographic region). APAP exposure, dose, and duration were measured in the 7 and 30 days (acute) and in the 1-year (chronic) look-back periods. Multivariable conditional logistic regression was used to estimate the risk of APAP exposure adjusted for comorbidities, use of other nephrotoxic drugs, and health system factors.

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RESULTS—There were 4,724 cases and 14,172 controls with a mean (SD) age of 60.8 (17.8) years, and 52.6% were males; 10.9% of cases and 4.2% of controls had APAP exposure in the 30 days pre-index with mean potential maximum daily doses of 3,846.5 mg and 3,190.8 mg, respectively. Acute APAP exposure was significantly associated with renal disease, and the risk decreased with longer look-back periods (7 days: adjusted odds ratio [OR]=1.93, 95% CI=1.61-2.30); 30 days: OR=1.71, 95% CI=1.48-1.97). Cumulative APAP dose greater than 1 kg and APAP use for longer than 30 days in the pre-index year were not significantly associated with an increased risk of renal disease (both *P* values=0.900).

CONCLUSIONS—Acute prescription-acquired APAP use was associated with renal disease, while chronic use was not. Because this study assessed APAP use in pharmacy claims, further research accounting for OTC APAP use is warranted before the safety of chronic APAP consumption can be firmly established.

Acetaminophen (APAP), a widely used analgesic and antipyretic, is one of the most commonly used drugs in the United States.[1,2] In 2004, APAP was ranked first among the 30 most commonly used prescription and over-the-counter (OTC) drugs in the United States.[1] Further, Vicodin (APAP-hydrocodone combination) was prescribed 128 million times in 2009 and topped the Forbes list of America's most prescribed medicines.[3] Although the drug is considered relatively benign, concerns are increasing over the excessive consumption of APAP. In the United States, 26,000 hospitalizations and 458 deaths due to APAP overdose have been reported annually,[4] and from 1993 through 2007, more than 700,000 emergency department visits were attributable to APAP overdoses.[5] Although the organ primarily affected is the liver, there has also been evidence of renal injury.[6] Some temporal and clinical evidence suggests that liver damage often precedes renal damage, but there are some reports of renal disease without significant hepatic injury, indicating that the mechanisms of organ injury may differ.[6] Ingestion of APAP in doses exceeding 4 grams (gm) per day can lead to acute renal failure in individuals without risk factors, whereas lower doses may lead to renal damage in individuals with chronic liver disease, those with concurrent alcohol consumption, and those with increased activity of the cytochrome P-450 enzyme system.[6]

While APAP-induced hepatotoxicity has been widely studied, mechanisms of renal toxicity are less clear. Cytochrome P-450 enzymes, glutathione S-transferase, prostaglandin endoperoxidase synthase (PGES) and N-deacetylase are hypothesized to be involved in APAP-induced renal toxicity.[7] Like hepatic cells, renal microsomes also oxidize APAP to an arylating intermediate product via the P-450 dependent mechanism indicating a biochemical mechanism of toxicity similar to that in the liver. The glutathione (GSH)-conjugate of a secondary metabolite is also thought to be involved in APAP-induced renal disease in CD-1 mice. Renal toxicity due to chronic APAP exposure depends on PGES according to studies on rabbit renal microsomes. It was found that human kidney medulla microsomes also catalyzed the PGES-based metabolic activation of APAP at rates similar to those in rabbit kidney microsomes. Variations in APAP-induced renal toxicity have been observed across different species and gender.[7] Another possible mechanism of renal injury is due to oxidative stress and tumor necrosis factor (TNF)-α production. A study reported oxidative stress-induced renal damage after APAP administration in rats.[8]

Incidents of acute renal toxicity after large acute APAP doses were reported in a case series[9] and a few case reports.[10,11] Several epidemiologic and clinical studies have examined the association between lifetime APAP use and renal disease.[12-17] A European autopsy study on 616 individuals reported a decreased prevalence of analgesic nephropathy in spite of the use of APAP-containing analgesics, indicating no renal disease with chronic APAP use.[12] While some epidemiologic case-control studies supported this finding,[14,17] a few others found a positive association between chronic APAP use and renal disease.[13,15,16] However, the interpretation of these studies is limited by a number of methodological limitations, such as the inability to clearly establish temporality of exposure prior to outcome, including other analgesics in exposure measures, and recall bias. To our knowledge, no population-based studies using large insurance claims datasets have studied the link between APAP use and renal disease.

Administrative claims data include records for a large number of patients for long time periods and can be particularly useful for the study of rare events.[18] Retrospective, interview-based studies may be subject to recall bias if the cases remember and report their drug exposure more accurately than the controls. However, pharmacy claims record the start and end dates (fill date + days supply) of a prescription and the amount of drug prescribed and are therefore not biased by knowledge about the study outcome.[18] In an analysis of IMS LifeLink Health Plans' pharmacy claims data, Gokhale and Martin (2012) found that the annual mean cumulative APAP dose increased from 55.3 gm per year in 2001 to 81.9 gm per year in 2008, indicating an increase in chronic prescription-acquired APAP use.[19] This change parallels increases in the use of APAP-opioid combination products (mean number of prescriptions and dose per enrollee) in the United States.[20] A study of annual APAP use based exclusively on pharmacy claims data reported that approximately 30% of APAP users had a potential maximum daily dose exceeding the currently recommended maximum daily dose (4 gm per day), indicating that administrative claims data do capture high risk APAP use.[19] Given the lack of previous claims-based studies examining the association between APAP use and renal disease and the rarity of the outcome, we investigated the association between acute and chronic prescription-acquired APAP use and renal disease using a large, nationally representative commercial insurance dataset.

Methods

Study Design and Data Source

This study was part of a larger project examining associations between acute and chronic APAP use and hepatic (liver disease) and nonhepatic (renal disease and asthma) outcomes, using a retrospective case-control study design. Data from 1997-2009 on a 10% random sample of the enrollees in the IMS LifeLink Health Plans were used for this study. This data source consists of claims from more than 98 U.S. managed care organizations and is representative of the commercially insured population in the country with respect to age, gender, and region. The data include pharmacy claims, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, procedure codes, and patient enrollment information for more than 6 million individuals followed for an average of 2.5 years. The data contain records for both OTC and prescription APAP-containing

products that have been billed as pharmacy claims; however, it is unlikely that many plans reimburse OTC APAP prescriptions, and less than 5% of APAP claims were for OTC products during the study period. The APAP records in the dataset have been used in a previous examination of APAP use and overuse patterns.[19]

Cases

Eligible cases were individuals aged 18 years or older with at least 1 incident primary diagnosis code of acute renal failure (ICD-9-CM codes 584.5-584.9), chronic kidney disease (585.xx); renal failure unspecified (586.xx); nephritis (580.0, 580.4, 580.81, 580.89, 580.9, 582.0-582.2, 582.4, 582.81, 582.89, 582.9, 583.0-583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9); ; nephrotic syndrome (581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581,9); renal sclerosis unspecified (587.xx); renal osteodystrophy (588.0); Other specified disorders resulting from impaired renal function (588.8); unspecified disorder resulting from impaired renal function (588.9); nephrogenic diabetes insipidus (588.1); unilateral small kidney (589.0); bilateral small kidney (589.1); and small kidney unspecified (589.9) from January 1, 1998, through December 31, 2009.[21] The sensitivity and specificity of the ICD-9-CM codes for acute renal failure are 35.4% and 97.7%, respectively.[22] We supplemented our case definition to include persons with primary diagnoses for chronic renal disease based on another claims-based study defining renal disease;[21] this decision was made to increase the sensitivity of our measure at the potential expense of decreasing the specificity. For case selection, only the claims from inpatient hospitalization records, emergency room visits, surgical records, and outpatient visits were used. Claims with record type “ancillary” were excluded because they imply events incidental to direct care of patients (e.g., x-rays, transportation services).

APAP-induced renal disease may or may not be preceded by hepatotoxicity.[6] Therefore, cases of renal disease were checked for evidence of liver disease (acute liver necrosis, hepatitis, hepatic coma, hepatorenal syndrome, and coagulopathy; Appendix) in the 10 days before the renal disease diagnosis. It is likely that patients would not have been prescribed APAP after a liver disease diagnosis. If the index date was the diagnosis date of renal disease for patients with preceding liver disease, it would be likely that these patients would not consume APAP in the pre-index period after their liver disease diagnosis and bias the results toward no association. To address this potential bias, for patients with liver disease in the 10-day window prior to incident renal disease, the index date was the date of diagnosis of liver disease. For those patients without prior liver disease, the index date was the date of diagnosis of renal disease.

All cases were required to have continuous health plan enrollment in the pre-index year. Since this study was a part of a larger project with 3 outcomes, to keep the methods consistent, cases with diagnoses of liver disease, renal disease, or asthma in the pre-index year were excluded. These exclusion codes (Appendix) contained a broader set of conditions than the case definitions to exclude persons with possible manifestations of each disease. We also excluded cases with previous liver, kidney or lung transplant; those on immunosuppressant therapy (except corticosteroids); and those with liver, renal, respiratory-tract cancer, or secondary malignancies.

Controls

In order to increase statistical power, 3 controls per case matched on age, gender, and geographic location (East, Midwest, South and West) were randomly selected from a group of individuals without ICD-9-CM codes for renal disease, liver disease, or asthma (Appendix) in any of the 4 diagnosis fields. Controls were assigned an index date the same as that of the corresponding case and were required to have continuous plan enrollment in the pre-index year. We excluded controls with a previous diagnosis of APAP poisoning (ICD-9-CM code 965.4x).[23] Other exclusion criteria were the same as those for the cases (Figure 1).

APAP Exposure Measures

APAP containing products were identified using unique Medi-Span Generic Product Identifier (GPI, Medi-Span, Indianapolis, IN) codes in the data. We measured any APAP exposure, doses, and durations of APAP use for acute (7 and 30 days pre-index) and chronic (365 days pre-index) look-back periods (Table 1). Doses were calculated as follows:

1. Potential maximum daily dose (PMDD) in the 7-day and 30-day pre-index periods: This was highest potential APAP dose in any 1 day calculated in the pre-index period using the days supply, strength, and quantity fields in the data. Overlapping prescriptions were identified using fill dates and days supply, and the daily doses were summed to obtain the potential maximum dose. For example, for a patient with an APAP claim on January 1 for a 13-day supply of 52 tablets at 500 milligrams [mg] per tablet (daily dose of 2,000 mg per day); a second APAP claim on January 3 for a 7-day supply, 42 tablets at 325 mg per tablet (daily dose of 1,950 mg per day); and an index date of January 11, the PMDD in the 7 days pre-index was 3,950 mg.
2. Potential average daily dose (PADD) in the pre-index month: Dose obtained by summing the APAP dose contained in all prescriptions in the 30 days pre-index divided by the total days of APAP use. For example using the scenario above, 3 days supply of the first pharmacy claim occured after the index date and are not counted (12 tablets), and the PADD is ([40 tablets at 500 mg] + [42 tablets at 325 mg]) ÷ 10 days (January 1 through January 10) = 3,365 mg.
3. Cumulative dose in the pre-index year: The sum of APAP doses from all APAP-containing prescriptions during the pre-index year.

Other Covariates

Using the enrollment information and pre-index medical and pharmacy claims, we obtained data on the following potential risk factors for renal disease:

- Medical conditions: These were measured in the 365-day pre-index period (in any of the 4 diagnosis fields) for both acute and chronic analyses and consisted of hypertension,[24,25] kidney infections,[26] heart disease,[24,27] substance abuse (alcohol/illicit drug use and abuse),[23,28,29] diabetes,[23,30] metabolic variables (gout and malnutrition),[28,31] and cancer[32] (Appendix).

- Drug variables: Drug exposure (at least 1 day supply in the pre-index period) was measured in the 30 days pre-index for analyses of acute APAP exposure and in the 365 days pre-index for analyses of chronic APAP exposure. Use of the following drugs was identified using GPI codes: antibiotics,[28] nonsteroidal anti-inflammatory drugs (NSAIDs),[33,34] diuretics,[33] angiotensin-converting enzyme (ACE) inhibitors,[33] corticosteroids,[33] oral anticoagulants,[33] and miscellaneous drugs.[28,33]
- Health system variables: Using the enrollment information, we obtained data on insurance payer/plan type.

Since hypertension and diabetes are important risk factors for kidney disease,[25] we explored the possibility of these diseases being potential effect measure modifiers and included interaction terms between these factors and APAP use. In addition to the above covariates, we also included in the chronic APAP use models a binary term for APAP use in the 30 days pre-index to control for short-term use of APAP. We could not adjust for race since it was not available in the dataset.

Analysis

We measured baseline descriptive characteristics of the sample in the acute and chronic pre-index periods. Adjusted and unadjusted conditional logistic regression models were used to determine the effect of acute and chronic APAP use on the risk of renal failure. We used likelihood ratio chi-square tests to compare adjusted models with and without the interaction terms. Collinearity among predictor variables was tested using phi coefficients; no exploratory variables had a phi coefficient exceeding 0.5. Odds ratios (ORs) and 95% confidence interval (CI) estimates were calculated. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). This study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

Results

From about 6 million plan enrollees in the data source, we obtained 45,843 incident cases of renal disease, of which 16,163 met the 12-month pre-index continuous enrollment and age criteria (Figure 1). We excluded those with certain prior medical conditions and drug use to arrive at a final sample of 4,724 cases. The case diagnoses included acute renal failure (n=1,921), chronic renal failure (n=1,905), nephritis (n=631) and other kidney diseases (n=267). From the same parent population, there were 1,366,555 age-, region- and gender-matched controls meeting the enrollment criteria. On applying further exclusion criteria, we obtained 1,257,240 individuals from whom 3 controls were randomly chosen for every case to get a total of 14,172 controls. The mean (standard deviation [SD]) age of our sample was 60.8 (17.8) years, and 52.6% were male (Table 2). Prevalence of drug use and medical conditions that increase the risk of renal disease were significantly higher among the cases compared with the controls, and 601 (12.7%) cases had evidence of liver disease in the 10 days before the diagnosis of renal disease.

Descriptive analyses of the APAP use variables for the cases and controls are shown in Table 3. APAP was used for at least 1 day in the pre-index year by 1,366 cases (28.9%) and 2,347 controls (16.6%). Mean cumulative doses in the pre-index year for cases and controls

were 117.92 gm and 83.49 gm, respectively. In the 30 days pre-index, 517 (10.9%) cases and 599 (4.2%) controls used APAP with mean PMDDs of 3,846.50 mg and 3,190.80 mg respectively. The total number of days of APAP use during the pre-index year was higher for cases compared with controls (47.7 days and 35.2 days, respectively). More than 95% of all APAP containing prescriptions were for opioid/APAP combinations in both cases and controls.

We first ran models with interaction terms between APAP use and hypertension and diabetes. The likelihood ratio test between the models with and without the diabetes-APAP interaction term was not significant (data not shown). The likelihood ratio test was significant between the models with and without the hypertension-APAP interaction term (P <0.05; data not shown), suggesting a better model fit with the interaction term. However, the ORs calculated based on the variance-covariance matrix and coefficients obtained from the conditional logistic regression models (as explained by Hosmer and Lemeshow[35]) were in opposite of the anticipated direction (APAP exposure in nonhypertensive patients conferring higher risk than APAP exposure with hypertension). Given these findings and the lack of pathophysiological evidence of the joint effect of APAP and hypertension on renal disease, our final models included no interaction terms.

Adjusted and unadjusted odds ratios of acute and chronic APAP use measures are shown in Table 4. Unadjusted odds of renal disease for patients with any APAP exposure in the 7 and 30 days pre-index were 3.17 and 2.80 times that of APAP nonusers, respectively. After controlling for covariates, the ORs decreased to 1.93 (95% CI=1.61-2.30) and 1.71 (95% CI=1.48-1.97) for 7- and 30-day pre-index exposure, respectively. Compared with nonusers, there was a 4.60-fold elevated risk (95% CI=2.87-7.39) of renal disease with PMDD exceeding 4 gm in the 7 days pre-index. This was significantly greater than the risk conferred by PMDD of 4 gm per day or less (OR=1.68, 95% CI=1.38-2.03; P<0.001 for trend). Potential maximum and average daily doses in the 30 days pre-index were significantly associated with renal disease, but a significant dose-dependent relationship was not observed (P=0.23 and P=0.57 for trend, respectively). To explore other possible dose thresholds, we re-categorized the APAP daily doses using the cut-offs of 3.25 gm per day and 2.6 gm per day (instead of 4 gm per day), but the risk at lower doses continued to be higher than that of nonusers (data not shown).

Cumulative dose of at least 1 kilogram (kg) in the pre-index year increased the renal disease risk by 13% (OR=1.13, 95% CI=1.01-1.26) compared with APAP nonuse (Table 4). Only 15 (0.3%) cases and 20 (0.1%) controls had a cumulative dose exceeding 1 kg, and we obtained a nonsignificant estimate for this category (P=0.900). We performed a power analysis using the Epicalc package in version 2.6.1 of R statistical software (open-source software available at http://www.r-project.org/)[36] and found only a 15.6% power to detect a significant difference between cases and controls for cumulative dose exceeding 1 kg.

Having the last day of APAP use (recency based on fill date and days supply) within 0-30 days pre-index was associated with a significantly greater risk of renal disease (OR=1.84, 95% CI=1.59-2.13) compared with having the last day of APAP use between the 31st and 365th day pre-index (OR=1.13, 95% CI=1.01-1.26, P for trend <0.001; Table 4). The total

duration of APAP use up to 30 days was significantly associated with renal disease while duration longer than 30 days was not.

Discussion

In the present study sample, any APAP exposure in the 7 and 30 days pre-index increased the risk of renal disease by about 70%-90% compared with no APAP use, and the risk was 3.6 times greater when the PMDD exceeded 4 gm in the 7-day pre-index window. The risk associated with APAP use decreased with a longer look-back period of 30 days. Although APAP is generally considered to be safe at therapeutic doses (up to 4 grams per day), we found a 60% increased risk of renal disease with these doses in spite of controlling for potential confounders.

It has been suggested that the risk of renal disease with therapeutic APAP doses is high among individuals with genetic alterations in acetylation processes, which are often ethnicity dependent.[37] These genetic polymorphisms may be in part responsible for the elevated risks we observed at low levels of APAP use. Unfortunately we could not investigate this possibility empirically without the ability to measure genetic or even ethnic differences in our data.

To aid clinical decision making about APAP use, we estimated the number needed to harm (NNH)[38] based on the ORs in our study and literature-based incidence rate of renal disease (0.18%).[39,40] The NNH should, however, be interpreted with caution since it is based on OR, which is only an approximation of the relative risk. For the 7 days pre-index, the NNH was 819 (95% CI=541-1,466) with PMDD up to 4 grams and 156 (95% CI=88-299) with PMDD greater than 4 grams, corresponding to absolute risk increases of 0.11% and 0.64%, respectively. This result implies that within a period of 7 days, only 156 individuals would have to be treated with APAP at a PMDD of more than 4gm per day to observe 1 additional case of renal disease. With no known clinical benefit of APAP at doses exceeding 4 gm and given our findings combined with those of other studies that found APAP toxicity at more than recommended doses, the observed renal disease risk is concerning. Actions to curb the use of more than the recommended dose of APAP are warranted. Decisions about APAP use should be based on a comparison of the benefit-risk of APAP and alternative drugs, such as NSAIDS and narcotic analgesics not containing APAP. However, these alternatives are also associated with a number of adverse events,[41,42] and a thorough risk-benefit assessment using NNH, quality-of-life studies, alcohol use, and ethnicity considerations among other factors should guide recommendations about APAP use. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Risk-Benefit Management Working Group also suggests calculating relative-value adjusted NNH (RV-NNH), which incorporates patient preferences for avoidance of negative clinical outcomes.[43]

APAP has a narrow therapeutic-to-toxic ratio, and the U.S. Food and Drug Administration (FDA) advisory committees have recommended lowering of the maximum daily dose from the current 4 gm per day to 3.25 gm per day.[2,44] Although this change has not yet been implemented, dose-lowering efforts are being undertaken by some manufacturers of APAP products. For example, Johnson & Johnson's McNeil Consumer Healthcare Division

recently announced lowering the maximum recommended daily dose on its OTC APAP product label to 3 gm per day.[45] Our results demonstrate an increased renal disease risk at daily doses above and below 4 gm and therefore offer support to lowering the dose; however, further research is needed to confirm the safety of the potential new dose limit.

The FDA also recently mandated limiting the maximum APAP strength in each tablet of prescription-combination products to 325 mg.[46] We previously tested the potential impact of this policy and found that if the dose is limited to 325 mg, the proportion of APAP overusers would reduce by more than one-half.[19] After more robust confirmatory evidence has been acquired, such regulatory changes to APAP products should be considered to help reduce acute APAP overuse and possible resultant renal disease.

Improved labeling of APAP products could also be considered as a means of preventing APAP overuse. Some examples are clear instructions on the maximum number of tablets/ doses that can be consumed in a day, enhancing the prominence of the word "acetaminophen" instead of using abbreviations like APAP, and including warnings about APAP toxicity and concurrent use with other acetaminophen-containing products.[2]

Cumulative doses of more than1 kg and longer durations of APAP use (more than 30 days) were not associated with renal disease in our sample. While insufficient statistical power could be a reason for this finding, some alternative explanations should be considered. A previous study of trends in APAP use and overuse, also based on IMS claims data, found that 1% of APAP users in calendar year 2008 (1,707 APAP users) had annual cumulative APAP dose greater than 1 kg.[19] Of these, 853 individuals had pharmacy claims for more than 13 kg of APAP, which is approximately equivalent to using 35 gm per day for 365 days. Similar patterns were observed in previous years from 2001-2007. However, in spite of using the same claims database, we found few cases of renal disease among individuals with chronic APAP use in the present study. The fact that these persons prescribed cumulative APAP did not meet our case definition lends some support to the lack of an association for long-term chronic use.

The majority of the existing evidence based on clinical and some epidemiologic studies of chronic APAP use supports a lack of association between cumulative lifetime APAP dose and renal disease.[12,14,17,47,48] One clinical trial reported APAP to be effective and well tolerated among 287 osteoarthritis patients and identified no instances of hepatic or renal failure or serum creatinine levels at or above 1.5 times the upper limit of the reference range at APAP doses of 4 gm per day for up to 12 months (annual cumulative dose of 1.460 kg).[47] Another clinical trial in 88 osteoarthritis patients randomized to APAP (dose 2.6 gm per day of APAP for up to 2 years; equivalent to annual cumulative dose 0.95 kg) also did not report the occurrence of any hepatic or renal adverse events.[48] A European clinical autopsy study on 616 adults and 2 epidemiologic case-control studies examining analgesic use (including APAP) also support the lack of association between lifetime APAP use and renal disease.[12,14,17] Contrary to these results, a few case-control studies suggest an increased risk of renal disease with chronic APAP use.[13,15,16] However, the epidemiologic studies were based on self-reports of lifetime APAP exposure and may be subject to recall bias. Our claims-based study found no association between chronic APAP use and renal disease and

adds to the majority of the literature suggesting the lack of such an association. However, given the conflicting evidence, further research is needed to firmly establish the safety of chronic APAP consumption.

There are reports in the literature about chronic high-dose APAP use without any ill effects.[49] Although regeneration of hepatocytes is hypothesized to be the reason for an auto-protective effect against APAP-induced hepatotoxicity,[50] according to our knowledge there is no published evidence about auto-protection against APAP-induced renal disease. Pathophysiological research is warranted to determine if such a mechanism exists.

Limitations

Given the ubiquitous availability of APAP in the U.S. OTC and prescription markets, significant challenges exist in accurately assessing APAP exposure in any research setting, and our results, like those of all past epidemiologic studies of APAP use, are limited by potential exposure misclassification bias. First, we could not account for OTC (or prescription) APAP use not recorded as a pharmacy claim ; therefore, the calculated APAP doses are likely understated. Since the APAP product market consists of 52% OTC products,[51] we may have accounted for only one-half of all APAP use with our data, which would suggest that our calculated APAP doses may be understated substantially. On the other hand, our PMDD calculations were based on days supply and fill dates, and we assumed that overlapping prescriptions were used concurrently. This method could have overestimated the PMDD in some instances. Overestimates could also have occurred for APAP opioid combinations that were diverted and not consumed by the recipient. About 95% of the APAP prescription products used in the present study were opioid-APAP combinations, many of which would be prescribed “as needed,” and this use pattern could overstate the actual APAP doses consumed. For these reasons, we used the terms “potential” maximum and average daily doses; however, this potential overestimation of dose is likely a smaller concern relative to the possible underestimation due to unrecorded OTC APAP use. For these reasons, our observed renal disease risk at doses up to 4 grams per day should be interpreted with caution, and further studies with complete information on APAP doses and genetic predisposition are warranted to confirm this risk at lower doses of APAP.

Second and related, although the exact extent of OTC APAP use captured in this data source cannot be determined, there undoubtedly were a nontrivial number of persons misclassified as nonexposed when they used OTC APAP exclusively. If this misclassification was nondifferential (i.e., equal proportions of cases and controls misclassified), our results would be biased towards the null. It is possible that the cases with higher comorbidity burden would have more access to providers, and this channeling and differential misclassification would bias the results away from the null. We recognize that accurately assessing APAP exposure is challenging, and our data offer a new perspective on the associations between APAP use and renal disease with some advantages over past survey-based epidemiologic studies that are subject to recall bias and an inability to accurately identify the dates and doses of use.

Third, since our data source did not include clinical measures, we exclusively used ICD-9-CM codes to define renal disease cases. Given the low sensitivity (35.4%) of claims-based

ICD-9-CM diagnosis codes for acute renal failure, we might not have captured all true cases with renal failure.[22]

Fourth, in the absence of a well-established definition of "chronicity" of APAP use, our time window of 1 year was somewhat arbitrary but has been used by a clinical trial that studied the adverse events of long-term APAP use.[47] Fifth, since we required the cases in our sample to be free from a diagnosis of renal disease and related conditions only in the pre-index year, the incident cases in our study are actually "incident episodes" of renal disease. However, given the relatively rare occurrence of renal disease, its chronicity, and the regular follow-up care, this methodological decision may not have a substantial impact on study results. Sixth, since this was an insurance database, we did not have data on factors like body-mass index, obesity, smoking status, ethnicity, and educational level, and we cannot exclude the possibility of omitted variable bias. Finally, limitations typical of a case-control design should be considered. Specifically, we could not directly calculate incidence ratios of renal disease, and the ORs obtained are only approximations of the relative risk.

Conclusions

Acute APAP exposure is associated with renal disease, and the risk increases substantially when daily doses exceed 4 gm per day. Lowering the recommended maximum daily APAP dose, improved labeling of APAP products, restructuring pharmacy benefits to deter high daily APAP or APAP/opioid combination use, and regulatory changes to APAP products should be considered to reduce potential APAP overuse and resultant renal disease. In keeping with published clinical and epidemiologic evidence, we found that the renal disease risk decreased with longer look-back periods, and chronic use was not associated with renal disease.. However, our interpretation is limited by potentially incomplete APAP exposure ascertainment, and further research is warranted to establish the risks and safety of APAP consumption.

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Appendix

Appendix

CPT and ICD-9-CM Codes

Codes for baseline kidney disease[a]	Description
591	Hydronephrosis
593.3	Stricture or kinking of ureter
593.4	Other ureteric obstruction
593.5	Hydroureter
593.7	Vesicoureteral reflux
593.8	Other specified disorders of kidney and ureter

Codes for baseline kidney disease[a]	Description
593.9	Unspecified disorders of kidney and ureter
596.0	Bladder neck obstruction
600	Hyperplasia of prostate
753.1	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

Codes for secondary malignancies and immunosuppressant drugs	
196.0, 196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 209.71,197.0, 197.7, 209.72, 198.3 ,198.5, 209.73, 198.3, 197.1,197.2, 197.3, 197.4, 197.5, 197.6,197.8, 198.0, 198.1,198.2, 198.4, 198.6, 198.7,198.81, 198.82, 198.89, 209.74, 511.81, 789.51	Secondary malignancies
9940 (first 4 digits of GPI codes)	Immunosuppressant drugs
Codes for liver disease	
570	Acute and subacute necrosis of liver
572.2	Hepatic encephalopathy
573.3	Hepatitis, unspecified
572.4	Hepatorenal syndrome
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
Asthma and related conditions	
493.0x	Extrinsic asthma

Codes for secondary malignancies and immunosuppressant drugs	
493.1x	Intrinsic asthma
493.2x	Chronic obstructive asthma
493.81	Exercise induced bronchospasm
493.82	Cough variant asthma
493.9x	Asthma, unspecified
786.05	Shortness of breath[b]
786.07	Wheezing[b]
786.2x	Cough[b]
786.09	Other respiratory distress, insufficiency[b]
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
Codes for covariates	
291.xx, 303.xx, 305.0x	Alcohol use and abuse
304.xx, 305.xx except 305.0x and 305.1x	Illicit drug use and abuse
260.xx-269.xx	Nutritional deficiencies
250.xx	Diabetes
401.xx-405.xx	Hypertension
590.xx	Infections of the kidney
599.0x	Urinary tract infections
411.xx-413.xx	Angina
410.xx-414.xx	Coronary heart disease
274.xx	Gout
Based on AHRQ Clinical Classification Software Designation[c]	Cancer

AHRQ=Agency for Healthcare Research and Quality; CPT=Current Procedural Terminology; GPI=Generic Product Identifier; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification.

[a] Refers to 1 year prior to the index date. At least 1 of these codes or a case identification code for renal disease as specified in the Methods section resulted in exclusion from the sample.

[b] There are many reasons other than asthma for cough, wheezing, shortness of breath or other respiratory distress, but to get a clean sample, we excluded patients with these symptom codes.

[c] Cancer codes from cluster 2: http://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixCMultiDX.txt.

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What is already known about this subject

- Ingestion of large acetaminophen (APAP) doses leads to renal failure in individuals without risk factors, whereas a smaller dose may lead to renal damage in individuals with concurrent alcohol consumption, increased activity of cytochrome P-450 enzymes, or chronic liver disease.
- Several epidemiologic and clinical studies have examined the relationship between lifetime APAP use and analgesic nephropathy or renal disease with the majority of the evidence suggesting a lack of such an association. However, some interview-based epidemiologic studies report a positive association between cumulative lifetime APAP dose and renal disease. The epidemiologic studies depended on self-reported lifetime APAP exposure and could be subject to recall bias/exposure misclassification. Moreover, some of the above studies used prevalent renal disease cases, a method that could lead to reverse-causality bias.
- According to our knowledge, there have been no large-scale administrative claims-based studies examining the association between APAP and renal disease.

What this study adds

- Acute prescription-acquired APAP use was associated with an increased risk of renal disease in a dose- and time-dependent manner in a large commercially representative sample. In the 7 days prior to the index claim with a renal disease diagnosis, potential maximum daily dose of more than 4 gm per day increased the risk of renal disease by approximately 4 times compared to nonusers.
- Lowering the recommended maximum daily APAP dose; improved labeling with clear and concise instructions on maximum number of tablets/doses; and regulatory changes to APAP products, such as reducing the maximum strength for APAP-combination tablets to 325 mg, should be considered to reduce potential acetaminophen overuse and resultant renal disease.
- Chronic APAP use did not confer an increased risk of renal disease in our sample, but further studies are needed to confirm the safety of chronic APAP consumption.

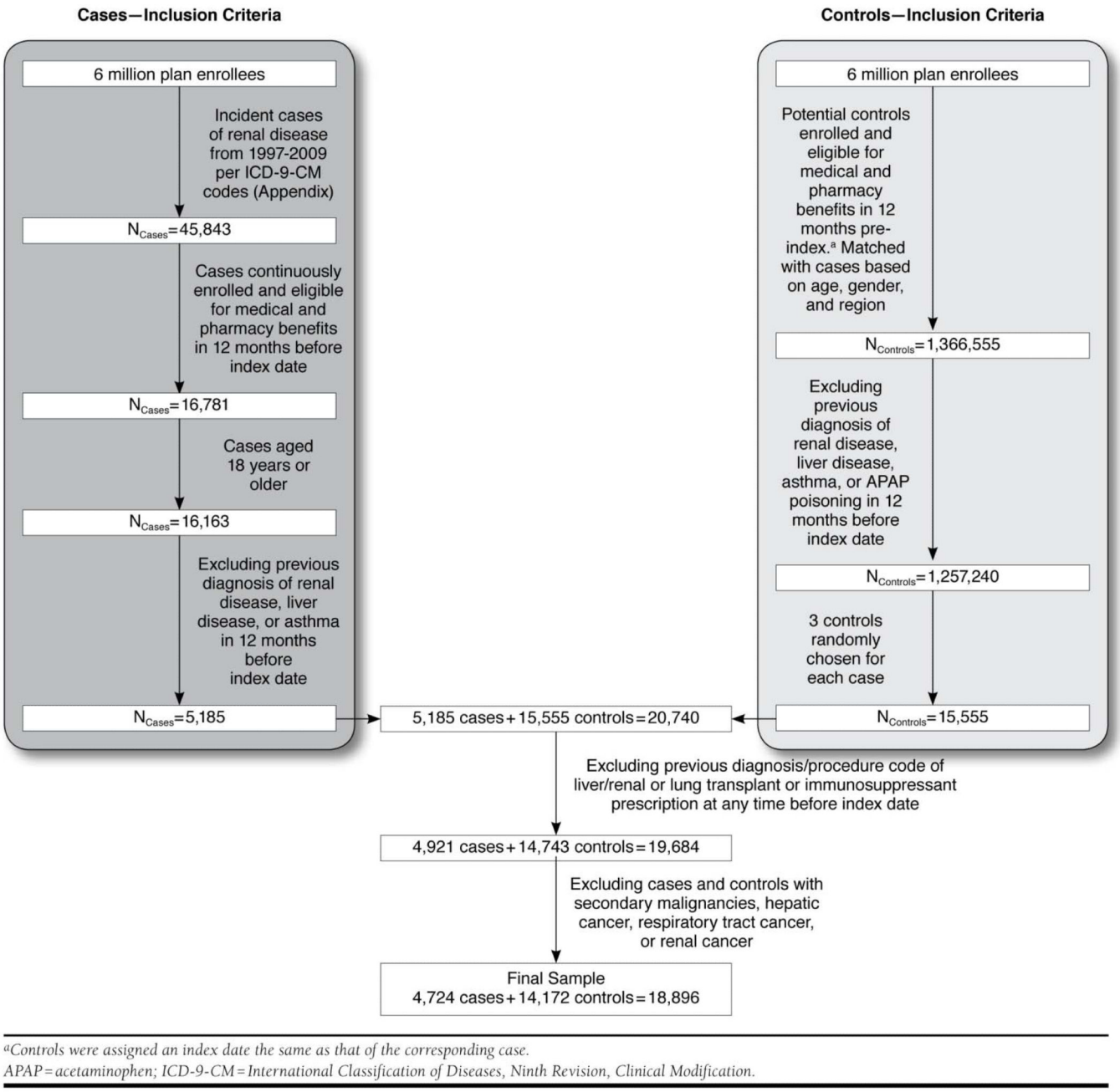

Figure 1.
Case-Control Selection Flowchart

Table 1

Description of Acute and Chronic Acetaminophen Exposure Measures

APAP Use Measure	Definition/Description	Categories	Time Period(s) Measured
Acute APAP exposure measures			
APAP exposure		Yes No[a]	7 days pre-index and 30 days pre-index
Potential PMDD	The highest potential APAP dose on any day. Calculated using the days supply, strength, and quantity fields. Overlapping prescriptions were identified using fill dates and days supply, and the daily doses were summed to obtain the PMDD.	PMDD <=4 gm per day PMDD >4 gm per day PMDD=0 gm per day[a]	7 days pre-index and 30 days pre-index
PADD in the pre-index month	Sum of the APAP doses contained in all prescriptions ÷ total days of APAP use	PADD <=4 gm per day PADD >4 gm per day PADD=0 gm per day[a]	30 days pre-index
Chronic APAP exposure measures (measured in the pre-index year)			
CD for 1 year before the index date	Sum of APAP doses in all APAP containing prescriptions in the pre-index year	CD <=1 kg CD >1 kg CD=0 kg[a]	Pre-index year
Recency of APAP use	Number of days between the index date and the last day of APAP use in the pre-index period	0-30 days pre-index 31-365 days pre-index No APAP use[a]	Pre-index year
Duration of APAP use	Total number of days of APAP use in the pre-index year	1-30 days 31-365 days No APAP use[a]	Pre-index year

APAP=acetaminophen; CD=cumulative dose; gm=grams; kg=kilograms; PADD= potential average daily dose; PMDD=potential maximum daily dose.

[a]Indicates reference group; all reference groups indicate no APAP use.

Table 2

Demographic, Comorbidity, and Drug Exposure Variables for Renal Disease Cases and Matched Controls (Pharmetrics Claims Data 1997-2009)

Variable	Cases n=4,724		Controls n=14,172	
Demographic variables				
Age				
Age at index date in years - mean [SD]	60.8	[17.8]	60.8	[17.8]
Gender	**n**	**%**	**n**	**%**
Male	2,485	52.6	7,455	52.6
Region				
East	946	20.0	2,838	20.0
West	746	15.8	2,238	15.8
Midwest	1,682	35.6	5,046	35.6
South	1,350	28.6	4,050	28.6
Health system variables				
Medicaid	95	2.0	104	0.7
Commercial HMO	944	19.9	2,735	19.3
Medicare	972	20.6	2,516	17.7
Non-HMO commercial and unknown type	2,713	57.4	8,817	62.2
Case definitions				
Acute renal failure	1,921	40.7	-	-
Chronic renal failure	1,905	40.3	-	-
Nephritis	631	13.4	-	-
Other kidney diagnoses[a]	267	5.6	-	-
Exposure to other potentially nephrotoxic drugs pre-index[b,c]				
Antibiotic exposure—30 days	645	13.6	851	6.0
Antibiotic exposure—365 days	2,079	44.0	4,603	32.5
NSAID exposure—30 days	431	9.1	686	4.8
NSAID exposure—365 days	1,040	22.0	2,008	14.2
Miscellaneous drug[d] exposure—30 days	85	1.8	135	0.9
Miscellaneous drug[d] exposure—365 days	144	3.0	233	1.6
Diuretic exposure—30 days	1,131	23.9	1,309	9.2
Diuretic exposure—365 days	1,459	30.8	1,877	13.2
ACE inhibitor exposure—30 days	1,008	21.3	1,334	9.4
ACE inhibitor exposure—365 days	1,281	27.1	1,677	11.8
Corticosteroid exposure—30 days	142	3.0	168	1.2
Corticosteroid exposure—365 days	461	9.8	844	5.9
Oral anticoagulant exposure—30 days	166	3.5	272	1.9
Oral anticoagulant exposure—365 days	238	5.0	386	2.7
Comorbidity variables in the 365 days pre-index[c]				

Variable	Cases n=4,724		Controls n=14,172	
Individuals with liver disease diagnosis in the 10 days prior to the diagnosis of kidney disease[e]	601	12.7	-	-
Heart disease	986	20.9	1182	8.3
Hypertension	3,058	64.7	4,679	33.0
Kidney infections	1,024	21.7	1,014	7.2
Substance abuse	266	5.6	291	2.0
Diabetes	1,542	32.6	1,655	11.7
Metabolic variables	344	7.3	344	2.4
Cancer	702	14.9	1,548	10.9

ACE=angiotensin-converting enzyme inhibitor; HMO-health maintenance organization; NSAID=nonsteroidal anti-inflammatory drug; SD=standard deviation.

[a] Other kidney diagnoses: impaired renal function necrosis, impaired renal function not otherwise specified, unilateral small kidney, bilateral small kidney, small kidney unspecified.

[b] At least 1-day supply in the pre-index period. The 30-day period is the 30 days immediately preceding the index date.

[c] For all comparisons shown in the category, values of cases and controls significantly different at alpha=0.05.

[d] Miscellaneous drugs=carbamazepine, phenobarbital, phenytoin, rifampin, hydralazine, acyclovir, primidone, antithyroid drugs, cisplatin.

[e] For these individuals, the index date was defined as the date of diagnosis of liver disease; for other cases, it was the date of diagnosis of renal disease.

Table 3

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

Variable	Cases n=4,724		Controls n=14,172	
Acetaminophen use variables	**n**	**%**	**n**	**%**
APAP exposure for at least 1 day in 7 days	343	7.3	344	2.4
APAP exposure for at least 1 day in 30 days	517	10.9	599	4.2
APAP exposure for at least 1 day in 1 year	1,366	28.9	2,347	16.6
PMDD in the 7 days pre-index				
Mean[a] [SD] mg	2,935.3	[3,641.0]	2,664.1	[2,331.8]
<= 4 gm per day n (%)	282	(5.9)	311	(6.6)
> 4 gm per day n (%)	61	(1.3	33	(0.7)
PMDD in the 30 days pre-index				
Mean[b], [SD] mg	3,846.5	11,049.8	3,190.8	[3,140.4]
<= 4 gm per day n (%)	404	(8.6)	483	(3.4)
> 4 gm per day n(%)	113	(2.4)	116	(0.8)
PADD in the 30 days pre-index				
Mean[c] [SD] mg	3,389.5	[10,895.7]	2,862.1	[2,950.7]
<= 4 gm per day n (%)	450	(9.5)	520	(3.7)
> 4 gm per day n (%)	67	(1.4)	79	(0.6)
Cumulative dose in the pre-index year				
Mean[c] [SD] gm	117.9	[442.5]	83.5	[188.9]
<= 1 kg n (%)	1,351	(28.6)	2,327	(16.4)
> 1 kg n (%)	15	(0.3)	20	(0.1)
Total days of APAP use in the pre-index year				
Mean[c] [SD] total days	47.7	82.3	35.2	70.9
<= 30 days n (%)	982	(20.8)	1,846	(13.0)
> 30 days n (%)	384	(8.1)	501	(3.5)
Recency of APAP use in the pre-index year				
Within the most 30 pre-index days n (%)	517	(10.9)	599	(4.2)
More than 30 days pre-index n (%)	849	(17.9)	1,748	(12.3)
Types of APAP prescription for 3,713 APAP users[d]	**n**	**%**	**n**	**%**
Opioid/APAP	4,968	95.7	6,875	95.0
Cough/cold products	27	0.5	10	0.1
Non-narcotic/APAP combinations	132	2.5	253	3.5
Only APAP	64	1.2	93	1.3

ADD=average daily dose; APAP=acetaminophen; gm=grams; kg=kilograms; mg=milligrams; PADD=potential average daily dose; PMDD=potential maximum daily dose; SD=standard deviation.

[a] Mean values calculated for 343 cases and 344 controls.

[b] Mean values calculated for 517 cases and 599 controls.

[c] Mean values calculated for 1,366 cases and 2,347 controls.

[d] The denominator is the total number of APAP claims: 5,191 APAP claims for cases and 7,231 APAP claims for controls.

Table 4

Conditional Logistic Regression Analyses of Renal Disease: Adjusted and Unadjusted Odds Ratios for Acetaminophen Exposure Variables

Variable	Cases (n)	Controls (n)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	*P* Value
Acute APAP exposure[b]					
APAP exposure for at least 1 day in the 7 days pre-index					
7 days pre-index	343	344	3.17 (2.71-3.69)	1.93 (1.61-2.30)	<0.001
APAP exposure for at least 1 day in the 30 days pre-index					
30 days pre-index	517	599	2.80 (2.48-3.17)	1.71 (1.48-1.97)	<0.001
Maximum daily dose: 7 days pre-index					
MDD <= 4 gm[c]	282	311	2.88 (2.44-3.40)	1.68 (1.38-2.03)	<0.001
MDD >4 gm[c]	61	33	5.86 (3.83-8.97)	4.60 (2.87-7.39)	<0.001
Maximum daily dose: 30 days pre-index					
MDD <= 4 gm	404	483	2.72 (2.37-3.11)	1.64 (1.40-1.92)	<0.001
MDD > 4 gm	113	116	3.16 (2.43-4.11)	2.01 (1.49-2.70)	<0.001
Average daily dose: 30 days pre-index					
ADD <= 4 gm	450	520	2.81 (2.46-3.20)	1.68 (1.44-1.96)	<0.001
ADD > 4 gm	67	79	2.75 (1.99-3.82)	1.89 (1.30-2.74)	<0.001
Chronic APAP Exposure[b]					
Cumulative dose in the pre-index year					
<= 1 kg	1,351	2,327	2.06 (1.91-2.23)	1.13 (1.01-1.26)	0.030
> 1 kg	15	20	2.64 (1.35-5.18)	0.97 (0.45-2.12)	0.900
APAP use in the 30 days pre-index	517	599	-		<0.001
Recency of APAP exposure					
0-30 days[c]	517	599	3.07 (2.71-3.48)	1.84 (1.59-2.13)	<0.001
> 30 days[c]	849	1,748	1.73 (1.57-1.89)	1.13 (1.01-1.26)	0.030
Total APAP use duration in the pre-index year					
1-30 days	982	1,846	1.89 (1.73-2.06)	1.15 (1.03-1.28)	0.020
> 30 days	384	501	2.73 (2.38-3.14)	1.00 (0.81-1.23)	0.900
APAP use in the 30 days pre-index	517	599	-	1.73 (1.44-2.07)	<0.001

ACE=angiotensin-converting enzyme; APAP=acetaminophen; CI=confidence interval; OR=odds ratio.

[a] Likelihood ratio chi-square statistic, which tests the null hypothesis that all model coefficients are zero (0) was P<0.001 for all models. All models adjusted for the following: (a) acute APAP use in the 30 days pre-index; (b) drugs in the 365 days pre-index (antibiotics, nonsteroidal anti-inflammatory drugs, miscellaneous drugs [carbamazepine, phenobarbital, phenytoin, rifampin, hydralazine, acyclovir, primidone, antithyroid drugs, cisplatin], diuretics, ACE inhibitors, corticosteroids, oral anticoagulants; (c) diagnoses in the 365 days pre-index (heart disease, hypertension, kidney infections, substance abuse, diabetes, metabolic variables, cancer); and (d) health system variables (Medicaid, Medicare, commercial health maintenance organization). Additionally, models of chronic APAP exposure adjusted for acute APAP use in the 30 days pre-index.

[b] For all APAP exposure variables, the reference group was no APAP exposure.

[c] P<0.001 for trend.