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CLINICAL AND ECONOMIC CHARACTERISTICS OF EMERGENCY DEPARTMENT VISITS DUE TO ACETAMINOPHEN TOXICITY IN THE UNITED STATES

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Preliminary findings of this study were presented as a plenary presentation at The Western States Conference for Pharmacy Residents, Fellows, Preceptors and Sponsors, May 21-24, 2012, Pacific Grove, California, USA, and as a poster at the American Society of Health-System Pharmacists ASHP Summer Meeting and Exhibition, May 31-June 4, 2014, Las Vegas, Nevada, USA

ABSTRACT

Objectives: To estimate the number of acetaminophen (APAP) toxicity-related emergency department (ED) visits and to assess their associated clinical and economic burden in the U.S. from 2006-2010.

Design: Cross-sectional, retrospective, large-scale database study.

Setting: Non-federal, non-rehabilitation, community emergency departments in the U.S.

Participants: Inclusion criteria included any-listed diagnosis identifying poisoning by aromatic analgesics paracetamol/acetaminophen or associated supplementary code. Generalized linear models were used to investigate the association between outcomes of inpatient admission, mortality, requirement of invasive mechanical ventilation, charges, and inpatient lengths of stay based upon patient, hospital, and clinical characteristics.

Results: Across the 625.2 million ED visits in the U.S. from 2006-2010, 411,811 APAP-related toxicity ED visits were, with 45.5% resulting in inpatient admission, 4.7% requiring invasive mechanical ventilation, and 0.6% involving death. The incidence was 27.10 per 100,000 U.S. population overall, exceeding 70 per 100,000 at age 2 and ages 16-18. The total national bill was

$1.06 billion per year (USD 2014), and predominantly involved females (65.5%) and intentional self-harm (58.4%), which were notably higher within the 12-20 age category ($female_{12\text{-}20\ years}$=74.8%, intentional $self\text{-}harm_{12\text{-}20\ years}$=71.4%). Behavioral and mental health comorbidities were relatively common and associated with an increased relative risk of admission and likelihood of charges almost entirely across all age categories of ≥12 years within the multivariable analyses. The number of ED visits did not appreciably change over time, decreasing by <2% from 2006 to 2010 (n=1,351). Multivariable results also suggested no consistently change in outcomes across the study's time horizon.

Conclusions: A substantial public health impact of APAP toxicity-related cases was observed in the U.S. from 2006-2010, with incidences peaking at age 2 and ages 16-18. After controlling for numerous factors, no consistent change was observed over the five-year time horizon concerning outcomes of admission, mortality, invasive mechanical ventilation, charges, or length of stay.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study draws upon an estimated 130 million ED visits per year within the U.S. to report national estimates of case incidence and to provide assessments of clinical and economic outcomes.
- No specific categorization existed to classify cases as being unsupervised ingestions or therapeutic misadventures (e.g., overuse, medication errors), the type of APAP product consumed (e.g., single-agent, combination products, tablets, liquid), and the amount ingested or serum levels observed.
- The use of n-acetyl cysteine (NAS) or gastric decontamination was also not consistently captured within the dataset, nor was a designation of acute liver injury directly attributable to acetaminophen (APAP) toxicity.

INTRODUCTION

As one of the most frequently-used analgesic and antipyretics worldwide, acetaminophen (APAP) is a common single or combination agent within numerous over-the-counter (OTC) and prescription products.[1] Though considered generally safe at approved doses, APAP has a known and established toxicity pattern at higher doses.[2] Of all pharmaceuticals involved in human overdoses, analgesics are considered the most frequently involved.[2] U.S. poison center data indicate that APAP combinations were associated with the fourth highest number of fatalities compared to other medications in 2012, with APAP overdose being principal cause of toxic drug ingestion that ultimately contributed to 39% of all acute liver failures.[2,3] Hepatotoxicity is a well-recognized adverse event associated with APAP overdose that may result in liver failure and death.[4] The percentage of APAP-induced acute liver failure cases increased from 28% in 1998 to 51% in 2003, establishing this medication as the most common cause of acute liver failure in the U.S.[4] Overall, previous studies have suggested that APAP overdoses leads annually to 56,000-78,000 emergency department (ED) visits, 26,000-34,000 hospitalizations, and an estimated 500 deaths.[5-8]

The U.S. Food and Drug Administration (FDA) has issued several updates in recent years involving APAP to increase the safety and limit the toxicity of the drug.[9-13] In 1998, to illustrate, an updated warning label concerning APAP use and alcohol consumption was issued to limit the possibility of hepatotoxicity.[9,11,13] In 2002, an additional recommendation to place more comprehensive hepatotoxicity warnings on all APAP products was issued.[9,11,13] By 2009, APAP labeling was changed to highlight APAP within combination products. Further, warnings were placed on all prescription APAP products indicating the risk of liver injury and the possibility of

a rare but serious hypersensitivity reaction when APAP is used.[9,10] The amount of APAP in children's liquid medications was standardized by manufactures to 160 mg/5 mL, and concentrated infant drops were discontinued in 2009.[12] By 2013, another warning was issued that highlighted the association of APAP with fatal skin reactions.[9,10] In 2014, in response to the increasing number of cases of APAP toxicity, the FDA limited the amount of APAP found in prescription combination products to 325 mg per tablet or capsule.[11] Given the aforementioned, the overall purpose of this investigation was to estimate the number of APAP toxicity-related ED visits and to assess their associated clinical and economic burden in the U.S. from 2006-2010. More specifically, the objectives were to assess the relationships between outcomes of inpatient admission, mortality, requirement of invasive mechanical ventilation, charges, and inpatient lengths of stay based upon patient, hospital, and clinical characteristics.

METHODS

This cross-sectional, retrospective investigation utilized 2006-2010 Nationwide Emergency Department Sample (NEDS) from the Agency for Healthcare Research and Quality (AHRQ).[14] These data comprise nationally-representative case presentations across hospital-based EDs within non-federal, non-rehabilitation, community facilities and generalizing, overall, to approximately 130 million ED visits that occur in the U.S. per year.[14] Given the fully de-identified and anonymized, this research is classified as exempt via human subjects protection.[14]

Consistent with previous research, ED visits involving APAP toxicity were identified based on the inclusion criteria of any-listed diagnosis according to International Classification of Disease, 9th edition, Clinical Manifestations (ICD-9-CM) codes identifying poisoning by aromatic analgesics paracetamol/acetaminophen (i.e., 965.4) or associated supplementary code (i.e., E850.4: accidental poisoning by aromatic analgesics paracetamol/acetaminophen).[5-8,15,16]

Previous research has addressed the challenges in the sensitivity and specificity of utilizing diagnosis or supplementary codes to identify acetaminophen toxicity-related cases, suggesting that the use of these aforementioned codes remains a valid approach.[15] All ages were investigated and stratified according to the following age categories: A) 0-11 years; B) 12-20 years; C) 21-64 years; and ≥65 years.

Clinical outcomes assessed were admission to an inpatient setting from the ED, mortality, and requirement of invasive mechanical ventilation (i.e., as a proxy for acute respiratory distress syndrome and supportive care measures associated with APAP toxicity disease progression or acute liver failure).[17,18] Economic outcomes analyzed involved inflation-adjusted charges (USD 2014) and inpatient length of stay. Independent predictor variables analyzed were patient demographics (i.e., age category, sex, income quartile, age, primary payer, rural location defined by communities ≤50,000 residents), ED and hospital characteristics (geographic region, urban/rural location, teaching status), clinical case-mix disease severity measured via Elixhauser comorbidities (a validated case-mix risk severity measure comprised of 30 disease states), designation of intentional self-harm, and year (2006-2010).[14,19] Notably, if any given Elixhauser comorbidity was observed in <0.01% of cases within any age category, it was omitted to allow for appropriate statistical inference; peptic ulcer disease with bleeding was consistently observed to be <0.01% of cases and summarily removed from the study.[6,7]

Multivariable analyses for outcomes of admission to an inpatient setting from the ED and mortality were conducted using a multinomial logit regression, specifying treat-and-release ED cases as a baseline comparator.[20,21] The requirement of invasive mechanical ventilation was analyzed via a logistic regression. Generalized linear models were used to analyze inflation-adjusted charges and inpatient length of stay, specified by a gamma distribution with log link and

negative binomial distribution with log link, respectively.[21] Accordingly, results may be interpreted generally as relative risk measures, superficially as: a relative risk ratio (RRR) in a multinomial regression; an odds ratio (OR) in a logistic regression; an exponentiated beta value (exp(b)) in a gamma regression; and an incidence rate ratio (IRR) in a negative binomial regression.[21] Therein, estimated coefficients may be interpreted as suggesting a reduced likelihood (<1.00), suggesting no difference in likelihood (=1.00), and suggesting an increased likelihood (>1.00).

The Simes (1986) procedure to control for false discovery rates was used to control for multiple comparisons across age categories within the analysis of invasive mechanical ventilation, charges, and length of stay, yielding critical p-values for significance of 0.028, 0.036, and 0.024, respectively.[22] Inherently controlling for multiple comparisons by definition, the multinomial regression of disposition from the ED used an alpha level of 0.05 for significance and established treat-and-release cases as the baseline comparator. Due to the complex nature of sampling employed by the NEDS, Taylor-series weighting procedures were incorporated to yield national estimates.[14] All analyses were conducted using SAS 9.2 (Cary, North Carolina) and STATA SE 12.1 (College Station, Texas).

RESULTS

Across the 625.2 million ED visits in the U.S. from 2006-2010, APAP-related toxicity was observed among 411,881 ED visits, with peaks occurring at approximately ages 0-5, 15-20, and 35-45 years (Figure 1). The incidence of APAP toxicity-related ED visits according to age per 100,000 per U.S. population was 27.10 overall and, by age category: 17.29 for ages 0-11; 63.17 for ages 12-20; 27.77 for ages 21-64; and 8.18 for ages 65 and over. Reflected in Figure 2, peak incidences exceeding 70 per 100,000 U.S. population were observed at age 2 (78.39 per

100,000) and ages 16-18 (76.16, 77.52, and 74.00 per 100,000, respectively). Inpatient admissions averaged 12.46 per 100,000 US population, lowest among <12 years (0.50 per 100,000) and highest within cases from 12-20 (23.34 per 100,000); peaks were noted at ages 18 (33.55 per 100,000) and 19 (31.07 per 100,000).

In general, cases involved females (65.5%) averaging 29.3 (±17.6) years of age with 3.1 (±4.4) days for inpatient lengths of stay, and involved intentional self-harm (58.4%). Within the 12-20 age category, cases were markedly female (74.8%) and involving intentional self-harm (71.4%). Among the APAP-related cases presenting to the ED, 45.4% resulted in direct inpatient admission, highest in percentage terms among cases age ≥65 years (66.0%) even though this age category constituted an age-adjusted 5.68 admissions per 100,000 U.S. population. Those treated-and-released directly in the ED involved 37.4% of cases, particularly characteristic among cases <12 years (92.7%).

The most common Elixhauser comorbidities observed were depression (25.0%), drug abuse (15.6%), psychoses (15.3%), alcohol abuse (13.7%), and fluid and electrolyte disorders (13.6%); no Elixhauser comorbidities were noted among 38.0%. Inpatient mortality was low (0.6%), and the requirement of invasive mechanical ventilation was 4.7%. The total national bill across the five-year time horizon was $5.30 billion (USD 2014), equating to $12,766 (±28414) per case. The full descriptive statistics appear in Table 1.

<TABLE 1>

Multivariable Analysis: Inpatient Admission, Mortality, Invasive Mechanical Ventilation

Results of the multinomial logit regression of patient disposition from the ED (Table 2) indicated that numerous patient, hospital, and clinical characteristics were associated with an increased likelihood of admission or death. After statistically controlling for numerous factors,

rural patient residence suggested a significant ($p<0.05$) increased relative risk of admission among the 0-11, 12-20, and 21-64 year-old categories ($RRR_{0-11}=2.26$, $RRR_{12-20}=1.30$, $RRR_{21-64}=1.24$). Intentional self-harm was also associated with over a 3x increase odds of admission across all age categories ≥12 years ($p<0.05$), was almost perfectively predictive of mortality cases among those 12-20 years of age, and was associated with a 8.57x ($p<0.001$) for those ≥65 years.

Comorbidities of liver disease, coagulopathy, fluid and electrolyte disorders, and weight loss/cachexia were associated with significant ($p<0.05$) and large relative risks for both admission and mortality across age groups (sample size permitting for analysis). Specifically among pediatric cases <12 years, other neurological disorders, fluid and electrolyte disorders, and blood or deficiency anemia were significantly associated with increased admission ($p<0.05$). Across other age categories concerning admissions alone, comorbid conditions of valvular disease, peripheral vascular disorders, hypertension with complications, other neurological disorders, obesity, deficiency or other anemia, alcohol abuse, psychoses, and depression were significantly associated with an increased relative risk across all age groups ($p<0.05$). Over time, no sustained decrease in admissions or mortality were observed consistently across age categories over time.

The requirement of invasive mechanical ventilation (Table 3) indicated that chronic pulmonary disease, coagulopathy, and fluid and electrolyte disorders were significant predictors among cases ≥12 years ($p<0.028$). Intentional self-harm was associated with a 1.49x higher odds among those aged 21-64 years, and a 2.42x higher odds among cases ≥65 years ($p<0.028$). Other neurological disorders, blood loss or deficiency anemia, alcohol abuse, drug abuse, and psychoses were associated with an increased odds ($p<0.028$) among 12-20 and 21-64 age groups.

Due to the relatively small number of cases within the 12-20 age group, several factors had near-perfect associations with invasive mechanical ventilation. Notably, over time, no consistent change in odds of invasive mechanical ventilation across years was observed from 2006.

Multivariable Analysis: Charges, Length of Stay

The multivariable analysis of charges and length of stay (Table 4) indicated varying associations with these economic outcomes. Suggestive of greater intensities of care required across all age categories, consistently significant increased charges and lengths of stay were associated with liver disease ($p<0.036$ for charges, $p<0.024$ for length of stay), while weight loss/cachexia and coagulopathy were significant across age groups 21-64 and ≥65 and HIV/AIDS was significant in the 21-64 age category. Increased charges alone were associated with intentional self-harm and most Elixhauser comorbidities: heart failure; hypertension with complications; other neurological disorders; coagulopathy; fluid and electrolyte disorders; blood loss or deficiency anemia; alcohol abuse; psychoses; and depression ($p<0.036$). No consistent change across age categories was noted over time for either charges or length of stay.

DISCUSSION

This investigation examined nationally-representative cases of APAP toxicity-associated ED visits in the U.S. from 2006-2010, assessing the independent associations between outcomes of inpatient admission, mortality, required use of invasive mechanical ventilation, charges, and lengths of stay based upon several patient, clinical, and hospital characteristics. Overall, 411,881 ED visits were observed (82,376 per year), equating to 27.10 ED visits per 100,000 US population annually and summing to a national bill of $1.06 billion per year (USD 2014). Some 37.2% were treated-and-released directly from the ED (30,783 per year), 45.5% were admitted to the inpatient setting (37,877 per year), and 0.6% involved death (484 per year). The number of

ED presentations did not appreciably change over time, decreasing by <2% from 2006 to 2010 (n=1,351), though representing a change from 27.15 to 25.78 visits per 100,000 U.S. population annually overall.

Comparatively, Nouraj et al. (2006) estimated that attributable APAP overdoses from 1993-1999 were lower than aforementioned findings, with approximately 56,000 ED visits, 26,000 hospitalizations, and 458 deaths per year, wherein Li and Martin (2011) also reported a decrease in rates from 2001-2007 to slightly less than 45,000 ED visits per year.[5,8] From 1993-1999, Li and Martin (2011) found a lower number of ED visits, at 21.03 visits per 100,000 persons per year and decreasing to 15.21 from 2000-2007.[8] It is critical to note that Nouraj et al. (2006) and Li and Martin (2011) utilized different national data than the present study, data that has explicitly been identified as having a discrepancy in the number of cases associated with intentional APAP overdose-related visits; unintentional poisonings, however, appear to be similar across various data sources.[5-8] Manthripragada et al. (2011) presented results illustrating differences present within nationally-representative studies, wherein the number of APAP toxicity-associated ED visits may be potentially underestimated perhaps by one-third to one-half.[6] More closely paralleling the present study, Budnitz et al. (2011) reported 78,414 annual ED visits associated with APAP overdoses from 2005-2006 using data from the National Electronic Injury Surveillance System (NEISS), while Manthripragada et al. (2011) found an age-adjusted rate of 13.9 hospitalizations per 100,000 U.S. population from 2000-2006.[6,7] Also consistent with the current work, a decrease in the number of ED visits or hospitalizations over time relating to APAP overdose was not observed.[6]

The average age in the present study was 29.3 years, with 60.0% of ED visits occurring across the 21-64 year age group. Though constituting 16.2% and 11.1% of the U.S. population,

some 10.3% and 25.9% of cases, respectively, involved persons 0-11 and 12-20 years of age. Furthermore, ED presentations exceeding 50 visits per 100,000 persons per year were noted from ages 1-2 and 15-22, peaking at over 70 per 100,000 specifically at age 2 and ages 16-18. Broader surveillance figures suggest that age-adjusted overall nonfatal injuries relating to poisoning of any type was 36.14 per 100,000 in 2013, though the crude rate for ages 1-2 is 12.27 per 100,000 and is 35.79 per 100,000 for ages 15-22.[23] Prior investigations suggest a substantially large number of APAP toxicity-related ED visits occur among young children, adolescents, and young adults; Li and Martin (2011) reported 72.42 visits per 100,000 for cases under 5 years, 61.91 per 100,000 for ages 15-17, and 40.92 per 100,000 for ages 18-24.[7,8,24,25] Budnitz et al. (2011), found that 13.4% of APAP overdose ED visits were attributed to unsupervised ingestions by children 5 years of age and under, a finding which has been observed across other work.[7,27,28] Others have found higher risks for APAP toxicity-related ED visits due, in part, to single-ingredient unintentional overdose or high use of APAP products.[24,25,28]

A majority of cases in the current work involved female sex (65.5%) and intentional self-harm (58.4%), highest in the 12-20 year age category at 74.8% female and 71.4% intentional self-harm. Similar to Li and Bradly (2011), behavioral and mental health comorbidities were common and represented the largest proportions of Elixhauser comorbidities including depression (25.0%), psychoses (15.3%), drug abuse (15.6%), and alcohol abuse (13.7%). Notably, these comorbid conditions were also associated with increased relative risk of admission and likelihood of charges almost entirely across all age categories of ≥12 years within the multivariable analyses. Over most age categories ≥12 years, intentional self-harm was generally associated with increased odds of admission, mortality, requirement of invasive mechanical ventilation, charges, and length of stay. Budnitz et al. (2011) reported that 69.8% of

ED visits involving APAP overdoses from 2006-2007 were associated with self-directed violence, peaking among those between 15-24 years of age, with 75% ultimately resulting in either psychiatric or inpatient hospitalizations.[7] Surveillance data also suggest that one-quarter of all ED cases for intentional poisoning involve APAP.[23] Budnitz et al. (2011) also noted that females had the highest rates of intentional self-harm, especially as adolescents or young adults.[7] It has been noted in prior work that suicide attempts via toxic medication ingestion is more frequently observed among adolescents and often associated with impulsivity, of which toxic APAP ingestion has been classified.[7,29,30,31] Importantly, Manthripragada et al. (2011) emphasized that discerning whether self-harm was intentional versus accidental remains challenging to ascertain via secondary data, potentially resulting in the misclassification of cases involving non-accidental poisoning via supplementary ICD-9 codes (i.e., E-codes) or differences in hospital reporting requirements.[6,32,33]

Results of the multivariable analysis indicated that rural patient residence (municipalities ≤50,000 persons) was associated with a higher odds of admission across age categories <65 years. Among age categories ≥12 years, an increased relative risk of admission and mortality was associated with liver disease, coagulopathy, fluid and electrolyte disorders, and weight loss/cachexia. With some exceptions, increased odds of invasive mechanical ventilation, charges, and lengths of stay were also observed with these comorbidities as well. As Li and Martin (2011) reported a 8.62x higher odds of ED visits attributed to APAP toxicity with alcohol abuse or dependence ($p<0.001$), findings from the current work also suggest over a 2x higher relative risk of admission (age categories ≥12 years), a 1.75x higher relative risk of mortality (ages 21-64), over 1.19x higher charges (age categories ≥12 years), and 1.26x or greater odds of invasive mechanical ventilation (ages 12-20 and 21-64). Pediatric admissions <12 years were

associated with other neurological disorders, fluid and electrolyte disorders, and blood loss or deficiency anemia; Budnitz et al. (2011) reported that most of the unsupervised ingestions of APAP were observed among children <6 years, typically treated-and-released from the ED setting via gastric decontamination or n-acetyl cysteine (NAS) treatment.[7]

Although findings from this study provide updated information concerning the burden of APAP-related ED visits in the U.S., some important study limitations exist. While similar coding algorithms were used as other retrospective studies to identify APAP-toxicity cases, no specific categorization was present that may have classified cases as being unsupervised ingestions or therapeutic misadventures (e.g., overuse, medication errors), the type of APAP product consumed (e.g., single-agent, combination products, tablets, liquid), and the estimated amount ingested or serum levels observed.[5-8,15,16] In this context, Budnitz et al. (2011) reported that 13.4% of APAP toxicity-related ED visits were attributed to unsupervised ingestions and 16.7% involved therapeutic misadventures, with slightly over half involving overuse of agents versus dosage confusion or APAP over-ingestion from multiple source products.[7] The use of NAS or gastric decontamination was also not consistently captured within the dataset, nor was a designation of acute liver injury directly attributable to APAP toxicity.[6,7] Generalizations of findings beyond acute care settings are not appropriate to estimate the prevalence of APAP poisoning in the U.S., as cases presenting to poison centers or within ambulatory practices are not captured. Finally, given the time horizon of this study and available data, continued work is warranted to study the impact of more recent APAP dose limitations established by the FDA in addition to studies focusing directly upon consumer perceptions, attitudes, beliefs, knowledge, and health literacy.[9-13,34-45]

CONCLUSION

This nationally-representative study of ED visits in the U.S. highlights a substantial public health impact of APAP toxicity-related cases from 2006-2010. Overall, 82,376 cases per year were observed, summing to a national bill of $1.06 billion. The ED visit average rate across all ages was 27.10 ED visits per 100,000 U.S. population, exceeding 70 per 100,000 age 2 and ages 16-18. After controlling for numerous factors, no consistent temporal change was observed during the five-year time horizon concerning outcomes of admission, mortality, invasive mechanical ventilation, charges, or length of stay.

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CONTRIBUTIONS

AA and GHS conducted the initial planning of this investigation. AA, LK, and GHS were involved in formalizing and executing the study methodology, analysis, interpretation of results, and drafting and revisions of the manuscript. GHS was involved in the acquisition of data and overall study supervision.

COMPETING INTEREST STATEMENTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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TABLE 1. Descriptive Statistics of ED Cases Associated with APAP Toxicity According to Age Category in the U.S., 2006-2010.

	Age 11 Years and Below (N = 42,623)	Age 12-20 Years (N = 106,725)	Age 21-64 Years (N = 246,640)	Age 65 Years and Above (N = 15,893)	Overall (N = 411,881)
PATIENT CHARACTERISTICS					
Age (mean ± standard deviation)	2.2 ±1.7	16.9 ±2.1	36.4 ±11.4	75.2 ±7.9	29.3 ±17.6
Female Sex	48.3%	74.8%	64.4%	68.0%	65.5%
Payer, Commercial Insurance	38.1%	26.4%	20.4%	1.6%	23.1%
Medicare	<0.1%	0.2%	10.0%	88.3%	9.5%
Medicaid	48.9%	51.5%	35.1%	7.8%	39.7%
Other	12.8%	21.8%	34.5%	2.3%	27.7%
Income Quartile, Lowest	24.3%	23.2%	28.1%	24.4%	26.3%
2nd Quartile	28.3%	27.5%	28.5%	27.0%	28.2%
3rd Quartile	25.5%	25.6%	24.5%	25.4%	24.9%
4th Quartile	21.9%	23.8%	18.9%	23.3%	20.6%
Rural Residence	19.6%	16.7%	17.1%	17.9%	17.3%
HOSPITAL CHARACTERISTICS					
Region, Northeast	14.4%	16.2%	15.6%	16.4%	15.6%
Midwest	25.6%	18.2%	26.4%	21.0%	26.6%
South	32.1%	30.0%	34.7%	34.5%	33.2%
West	18.1%	25.6%	23.3%	28.2%	24.5%
Rural Facility	18.5%	15.3%	15.3%	16.2%	15.6%
Teaching Facility	38.9%	39.9%	39.5%	35.7%	39.4%
CLINICAL CHARACTERISTICS					
Congestive Heart Failure	<0.1%	<0.1%	0.7%	8.8%	0.8%
Valvular Disease	<0.1%	0.1%	0.6%	3.3%	0.5%
Pulmonary Circulation Disorders	<0.1%	<0.1%	0.2%	1.4%	0.2%
Peripheral Vascular Disorders	<0.1%	<0.1%	0.3%	3.8%	0.3%
Hypertension with Complications	0.0%	0.1%	0.7%	7.6%	0.7%
Paralysis	<0.1%	0.1%	0.4%	1.5%	0.3%
Other Neurological Disorders	0.3%	2.2%	7.4%	14.6%	5.6%
Chronic Pulmonary Disease	2.0%	4.9%	7.8%	19.2%	6.9%
Diabetes with Complications	0.0%	0.1%	0.5%	2.0%	0.4%

Hypothyroidism	<0.1%	0.5%	2.9%	11.9%	2.3%
Renal Failure	<0.1%	0.1%	0.8%	7.3%	0.8%
Liver Disease	<0.1%	0.2%	2.2%	1.7%	1.4%
HIV/AIDS	0.0	<0.1%	0.2%	0.0	<0.1%
PUD, excluding bleeding	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%
Lymphoma	0.0	<0.1%	0.1%	<0.1%	<0.1%
Metastatic Cancer	0.0	<0.1%	0.1%	1.0%	0.2%
Solid Tumor	0.0	<0.1%	0.3%	2.1%	0.2%
Rheumatoid Arthritis/Collagen Vascular Disease	0.0	0.1%	0.9%	3.1%	0.7%
Coagulopathy	<0.1%	0.5%	2.3%	4.2%	1.7%
Obesity	<0.1%	1.2%	3.3%	2.4%	2.4%
Weight Loss/Cachexia	<0.1%	<0.1%	0.8%	3.2%	0.6%
Fluid and Electrolyte Disorders	0.7%	8.1%	17.2%	29.4%	13.6%
Blood Loss or Deficiency Anemia	0.1%	1.5%	4.3%	12.3%	3.4%
Alcohol Abuse	0.0	5.7%	19.8%	8.6%	13.7%
Drug Abuse	<0.1%	12.1%	20.3%	6.3%	15.6%
Psychoses	<0.1%	11.2%	19.8%	13.3%	15.3%
Depression	<0.1%	27.4%	28.4%	22.6%	25.0%
No Elixhauser Comorbidities Present	96.4%	47.0%	25.7%	12.6%	38.0%
Intentional Self-Harm	<0.1%	71.4%	64.2%	34.9%	58.4%
CALENDAR YEAR					
2006	18.1%	21.1%	19.5%	17.5%	19.7%
2007	21.0%	20.5%	19.6%	17.0%	19.9%
2008	21.8%	21.1%	20.6%	20.1%	20.8%
2009	20.8%	19.7%	20.4%	21.8%	20.3%

2010	18.3%	17.6%	20.0%	23.6%	19.3%
OUTCOMES					
Disposition, treat and release	92.7%	38.4%	28.1%	23.8%	37.4%
Transfer	2.5%	22.4%	14.0%	6.3%	14.7%
Admission	2.9%	37.0%	55.1%	66.0%	45.4%
Death	0.0%	0.1%	0.7%	3.4%	0.6%
Other	1.9%	2.2%	1.9%	0.5%	1.9%
Average ED and Inpatient Charge (USD 2014) (mean ± standard deviation)	$1,343 ±3162	$7,884 ±13034	$15,824 ±31404	$28,631 ±50515	$12,766 ±28414
Annual: Total National Bill (USD 2014) (mean ± standard deviation)	$11.45 million	$168.28 million	$789.11 million	$91.00 million	$1,059.86 million
2006-2010: Total National Bill (USD 2014) (mean ± standard deviation)	$0.06 billion	$0.84 billion	$3.95 billion	$0.46 billion	$5.30 billion
Inpatient Length of Stay (mean ± standard deviation)	1.8±1.8	2.3±2.2	3.2±4.5	4.9±6.9	3.1±4.4
Invasive Mechanical Ventilation	<0.1%	1.2%	6.8%	8.6%	4.7%
ED Visits per 100,000 persons per year[A]	17.29	63.17	27.77	8.18	27.10
Inpatient Admissions per 100,000 persons per year[A]	0.50	23.34	15.50	5.68	12.46

ED: emergency department; APAP: acetaminpophen;

[A] Base U.S. populations for 2006-2010 obtained from the Centers for Disease Control and Prevention, National Vital Statistics System, Vintage 2012 bridged-race post-census U.S. resident population estimates

TABLE 2. Patient Disposition of Admission or Mortality versus Treat-and-Release from APAP-Toxicity-Related Presentation to the ED, 2006-2010.

	Age 11 Years and Below (N = 42,623)		Age 12-20 Years (N = 106,725)		Age 21-64 Years (N = 246,640)		Age 65 Years and Above (N = 15,893)	
	Admission [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]
PATIENT CHARACTERISTICS								
Age	1.11** (1.03,1.19)	--	1.09*** (1.06,1.11)	1.49* (1.01,2.19)	1.01*** (1.01,1.02)	1.05*** (1.04,1.06)	1.00 (0.99,1.01)	1.09** (1.03,1.14)
Female Sex	1.01 (0.77,1.33)	--	0.97 (0.89,1.06)	1.94 (0.28,13.60)	0.90*** (0.85,0.95)	0.96 (0.76,1.22)	1.24 (0.99,1.56)	0.54 (0.25,1.15)
Payer (vs. Commercial Insurance) Medicare	--	--	0.54* (0.30,0.97)	omitted[A]	0.83** (0.75,0.92)	0.87 (0.59,1.28)	1.17 (0.49,2.78)	0.12** (0.03,0.55)
Medicaid	0.62** (0.45,0.86)	--	0.97 (0.87,1.07)	0.42 (0.09,1.85)	1.02 (0.94,1.11)	0.90 (0.64,1.27)	0.64 (0.25,1.69)	0.04** (0.01,0.28)
Other	0.58* (0.37,0.92)	--	0.86* (0.76,0.98)	0.32 (0.07,1.46)	0.90* (0.83,0.98)	0.87 (0.62,1.22)	0.31* (0.10,0.93)	omitted[A]
Income Quartile (vs. Lowest) 2nd Quartile	1.12 (0.79,1.59)	--	1.13* (1.00,1.27)	2.50 (0.21,29.40)	1.05 (0.97,1.14)	0.93 (0.67,1.28)	0.84 (0.61,1.14)	0.23* (0.07,0.74)
3rd Quartile	0.75 (0.48,1.16)	--	1.15* (1.02,1.29)	13.40* (1.59,113.21)	1.08 (0.98,1.20)	1.21 (0.86,1.69)	1.08 (0.75,1.54)	1.03 (0.32,3.24)
4th Quartile	0.90 (0.58,1.39)	--	1.24** (1.07,1.43)	omitted[A]	1.26*** (1.13,1.41)	1.20 (0.83,1.73)	1.18 (0.83,1.69)	1.76 (0.64,4.85)
Rural Residence	2.26* (1.19,4.30)	--	1.30* (1.06,1.60)	0.82 (0.18,3.78)	1.24** (1.07,1.44)	1.21 (0.72,2.03)	1.36 (0.76,2.43)	1.88 (0.44,7.97)
HOSPITAL CHARACTERISTICS								
Rural Location	0.53 (0.26,1.12)	--	0.79* (0.62,0.99)	1.48 (0.15,14.19)	0.67*** (0.56,0.80)	0.42** (0.21,0.81)	0.63 (0.35,1.14)	1.27 (0.34,4.68)
Teaching Facility	3.13*** (2.17,4.50)	--	1.55*** (1.35,1.79)	5.08 (0.82,31.72)	0.98* (0.86,1.12)	1.04 (0.79,1.37)	1.31* (1.03,1.68)	1.58 (0.68,3.66)
Region (vs. Northeast) Midwest	0.72 (0.47,1.12)	--	0.96 (0.81,1.14)	1.18 (0.11,13.16)	0.87 (0.72,1.04)	0.59* (0.40,0.90)	0.63* (0.44,0.90)	0.48 (0.16,1.45)
South	0.79 (0.51,1.22)	--	0.85 (0.72,1.02)	1.92 (0.17,21.10)	0.86 (0.72,0.99)	0.79 (0.55,1.14)	0.85 (0.61,1.18)	0.36* (0.14,0.92)
West	0.65 (0.39,1.08)	--	0.62*** (0.52,0.74)	0.39 (0.01,12.73)	0.51*** (0.43,0.59)	0.52** (0.35,0.77)	0.54** (0.38,0.77)	0.26* (0.08,0.82)
CLINICAL CHARACTERISTICS								
Congestive Heart Failure	--	--	--	--	1.48 (0.95,2.31)	1.67 (0.80,3.49)	3.36*** (2.01,5.63)	1.64 (0.55,4.87)
Valvular Disease	--	--	3.94* (1.15,13.50)	omitted[A]	4.47*** (2.70,7.40)	2.06 (0.60,7.01)	3.64** (1.67,7.92)	3.55 (0.51,24.58)
Pulmonary Circulation Disorders	--	--	--	--	2.35*	8.50**	3.70	omitted[A]

					(1.03,5.40)	(2.54,28.43)	(0.39,35.40)	
Peripheral Vascular Disorders	--	--	--	--	3.15*** (1.55,6.37)	2.64 (0.59,11.89)	2.88** (1.32,6.28)	5.77 (0.96,34.48)
Hypertension with Complications	--	--	2.46*** (1.53,3.96)	omitted[A]	2.27** (1.32,3.92)	1.66 (0.59,4.68)	5.74*** (2.32,14.21)	0.66 (0.06,6.75)
Paralysis	--	--	1.54 (0.31,7.54)	omitted[A]	3.28*** (1.90,5.65)	11.47*** (4.84,27.23)	1.75 (0.57,5.38)	1.20 (0.14,10.13)
Other Neurological Disorders	24.83*** (10.48,58.83)	--	3.14*** (2.40,4.12)	50.97*** (10.75,241.71)	2.19*** (1.95,2.47)	2.21*** (1.55,3.15)	1.97*** (1.40,2.78)	1.48 (0.67,3.27)
Chronic Pulmonary Disease	1.94 (0.95,3.96)	--	2.35*** (1.93,2.86)	omitted[A]	2.01*** (1.78,2.28)	1.29 (0.83,2.00)	3.21*** (2.27,4.54)	5.16** (1.75,15.25)
Diabetes with Complications	--	--	0.97 (0.58,1.64)	omitted[A]	4.52*** (2.55,8.01)	3.57* (1.01,12.64)	2.34 (0.62,8.88)	16.60 (0.12,225.36)
Hypothyroidism	--	--	1.04 (0.58,1.85)	omitted[A]	2.67*** (2.16,3.31)	1.52 (0.77,2.99)	2.15*** (1.43,3.24)	2.17 (0.75,6.33)
Renal Failure	--	--	2.11 (0.24,18.52)	omitted[A]	2.39*** (1.51,3.80)	3.16** (1.38,7.25)	0.50 (0.22,1.12)	1.06 (0.13,8.44)
Liver Disease	--	--	2.98* (1.03,8.64)	omitted[B]	12.13*** (5.98,24.60)	47.89*** (21.53,106.52)	omitted[B]	omitted[B]
HIV/AIDS	--	--	--	--	2.18 (0.82,5.83)	6.86* (1.35,34.92)	--	--
Lymphoma	--	--	--	--	1.43 (0.60,3.43)	4.24 (0.69,25.95)	--	--
Metastatic Cancer	--	--	--	--	6.08*** (2.22,16.67)	30.32*** (8.35,110.18)	3.18 (0.78,13.04)	1.76 (0.29,10.55)
Solid Tumor	--	--	--	--	1.97* (1.09,3.55)	5.77** (2.13,15.59)	2.41 (0.98,5.91	5.46 (0.94,31.63)
Rheumatoid Arthritis/Collagen Vascular Disease	--	--	0.80 (0.21,3.07)	omitted[A]	2.66*** (1.89,3.76)	2.28 (0.95,5.43)	3.32* (1.24,8.90)	omitted[A]
Coagulopathy	--	--	21.75*** (7.70,61.42)	178.62*** (10.96,291.11)	16.06*** (9.70,26.57)	72.42*** (39.91,131.40)	omitted[B]	omitted[B]
Obesity	--	--	6.29*** (3.95,10.01)	omitted[A]	4.96*** (3.32,6.27)	5.55*** (3.08,10.02)	5.43** (1.68,17.54)	0.10 (0.01,1.37)
Weight Loss	--	--	--	--	20.51*** (7.35,57.18)	25.74*** (7.64,86.71)	19.01** (2.50,144.65)	283.59*** (17.45,468.08)
Fluid and Electrolyte Disorders	20.75*** (9.22,46.70)	--	6.78*** (5.70,8.07)	8.91** (2.48,31.96)	7.97*** (7.09,8.96)	28.45*** (21.84,37.07)	9.77*** (6.85,13.92)	56.28*** (22.19,142.71)
Blood Loss or Deficiency Anemia	13.27** (2.65,66.38)	--	4.17*** (2.83,6.15)	omitted[A]	4.46*** (3.64,5.46)	3.34*** (2.22,5.04)	2.64*** (1.72,4.04)	0.15 (0.01,4.35)
Alcohol Abuse	--	--	2.32*** (1.94,2.77)	1.16 (0.09,14.53)	2.53*** (2.33,2.75)	1.75*** (1.34,2.29)	2.96*** (1.76,4.95)	3.27 (0.71,15.09)
Drug Abuse	--	--	2.02*** (1.77,2.30)	3.02 (0.59,15.37)	2.37*** (2.17,2.59)	1.58** (1.17,2.13)	1.71 (0.96,3.04)	0.59 (0.06,5.44)
Psychoses	--	--	5.13*** (4.48,5.89)	4.46 (0.91,21.85)	4.44*** (4.00,4.93)	1.42 (1.00,2.03)	6.41*** (3.88,10.57)	6.46 (0.84,49.84)
Depression	--	--	1.71***	3.46	1.75***	1.10	1.95***	1.88

			(1.55,1.88)	(0.94,12.70)	(1.62,1.89)	(0.82,1.48)	(1.44,2.64)	(0.79,4.49)
Intentional Self-Harm	--	--	3.40*** (3.07,3.77)	omitted[B]	3.03*** (2.81,3.26)	1.69*** (1.30,2.21)	4.89*** (3.59,6.64)	8.57*** (3.97,18.49)
CALENDAR YEAR								
2007 (vs. 2006)	0.78 (0.48,1.28)	--	0.92 (0.80,1.06)	0.95 (0.17,5.34)	0.99 (0.88,1.11)	1.01 (0.69,1.49)	1.29 (0.92,1.81)	1.97 (0.39,9.87)
2008 (vs. 2006)	0.79 (0.49,1.26)	--	0.79** (0.68,0.92)	0.65 (0.07,5.73)	0.82** (0.72,0.94)	0.82 (0.56,1.21)	0.94 (0.67,1.32)	3.13 (0.96,10.19)
2009 (vs. 2006)	0.67 (0.40,1.11)	--	0.84* (0.72,0.98)	0.30 (0.03,3.17)	0.87 (0.77,1.00)	0.58* (0.38,0.88)	0.79 (0.55,1.13)	2.23 (0.65,7.64)
2010 (vs. 2006)	0.74 (0.45,1.22)	--	0.88 (0.74,1.03)	0.56 (0.06,5.18)	0.83** (0.73,0.95)	0.78 (0.53,1.13)	1.03 (0.74,1.45)	2.57 (0.72,9.18)

ED: emergency department; RRR = relative risk ratio
omitted[A] = variable omitted due to near-perfect association with survival (i.e., OR <0.01)
omitted[B] = variable omitted due to near-perfect association with mortality (i.e., RRR>10000)
'- -' = variable omitted due to small sample size (n<0.01%)
*** statistically significant at p<0.001
** statistically significant at p<0.01
* statistically significant at p<0.05

TABLE 3. Invasive Mechanical Ventilation among APAP-Toxicity-Related Cases Presenting to the ED According to Age Category, 2006-2010.

	Age 11 Years and Below (N = 42,623)	Age 12-20 Years (N = 106,725)	Age 21-64 Years (N = 246,640)	Age 65 Years and Above (N = 15,893)
	Invasive Mechanical Ventilation [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]
PATIENT CHARACTERISTICS				
Age	--	1.26* (1.16,1.36)	1.03* (1.02,1.03)	0.96* (0.95,0.98)
Female Sex	--	0.46* (0.35,0.60)	0.85* (0.78,0.92)	1.12 (0.84,1.50)
Payer (vs. Commercial Insurance) Medicare	--	0.62 (0.15,2.58)	0.82* (0.72,0.95)	1.03 (0.37,2.84)
Medicaid	--	0.92 (0.67,1.28)	1.05 (0.94,1.17)	1.52 (0.52,4.45)
Other	--	1.01 (0.71,1.43)	0.78* (0.70,0.87)	0.46 (0.12,1.79)
Income Quartile (vs. Lowest) 2nd Quartile	--	0.92 (0.63,1.35)	1.10 (0.99,1.23)	1.12 (0.76,1.65)
3rd Quartile	--	0.92 (0.62,1.37)	1.23* (1.08,1.39)	1.01 (0.69,1.48)
4th Quartile	--	0.92 (0.61,1.40)	1.08 (0.95,1.24)	0.91 (0.58,1.41)
Rural Residence	--	1.96 (0.97,3.99)	1.25 (1.01,1.55)	1.07 (0.55,2.10)
HOSPITAL CHARACTERISTICS				
Rural Location	--	0.38* (0.16,0.91)	0.61* (0.47,0.77)	0.57 (0.26,1.26)
Teaching Facility	--	1.51* (1.12,2.03)	1.10 (0.98,1.22)	1.27 (0.95,1.71)
Region (vs. Northeast) Midwest	--	0.79 (0.53,1.18)	0.87 (0.75,1.01)	0.88 (0.56,1.36)
South	--	0.77 (0.51,1.17)	0.99 (0.86,1.15)	0.90 (0.59,1.36)
West	--	0.72 (0.45,1.13)	0.94 (0.81,1.08)	0.90 (0.57,1.42)
CLINICAL CHARACTERISTICS				
Congestive Heart Failure	--	--	1.61* (1.17,2.21)	1.39 (0.86,2.25)
Valvular Disease	--	8.31* (1.91,36.10)	1.12 (0.78,1.62)	0.77 (0.35,1.73)

Pulmonary Circulation Disorders	--	--	2.66* (1.46,4.86)	0.83 (0.27,2.53)
Peripheral Vascular Disorders	--	--	1.25 (0.70,2.21)	1.06 (0.56,2.02)
Hypertension with Complications	--	2.48* (1.11,5.56)	0.86 (0.54,1.36)	2.01 (0.91,4.45)
Paralysis	--	omitted[A]	1.95* (1.29,2.94)	0.26 (0.03,2.25)
Other Neurological Disorders	--	7.11* (5.00,10.11)	1.88* (1.66,2.13)	1.10 (0.76,1.60)
Chronic Pulmonary Disease	--	1.79* (1.09,2.92)	1.34* (1.18,1.51)	1.75* (1.26,2.44)
Diabetes with Complications	--	0.79 (0.13,4.81)	0.91 (0.56,1.46)	0.62 (0.21,1.79)
Hypothyroidism	--	0.87 (0.25,3.09)	0.91 (0.75,1.11)	0.56* (0.35,0.89)
Renal Failure	--	1.78 (0.18,17.95)	1.25 (0.82,1.92)	0.42 (0.19,0.94)
Liver Disease	--	2.49 (0.44,14.03)	2.23* (1.77,2.81)	2.47* (1.17,5.21)
AIDS	--	--	2.11* (1.23,3.60)	--
Lymphoma	--	--	1.93 (0.84,4.40)	--
Metastatic Cancer	--	--	1.68 (0.79,3.59)	0.47 (0.09,2.47)
Solid Tumor	--	--	0.68 (0.32,1.44)	0.27 (0.06,1.22)
Rheumatoid Arthritis/Collagen Vascular Disease	--	omitted[A]	1.59* (1.18,2.14)	0.48 (0.18,1.25)
Coagulopathy	--	2.58* (1.13,5.89)	2.48* (2.10,2.94)	2.17* (1.27,3.70)
Obesity	--	0.98 (0.29,3.29)	1.11 (0.91,1.36)	0.49 (0.17,1.35)
Weight Loss/Cachexia	--	--	1.90* (1.43,2.53)	1.92* (1.13,3.28)
Fluid and Electrolyte Disorders	--	5.84* (4.26,8.00)	4.08* (3.75,4.43)	2.26* (1.71,3.00)
Blood Loss or Deficiency Anemia	--	2.07* (1.33,3.97)	1.36* (1.17,1.58)	1.15 (0.79,1.67)
Alcohol Abuse	--	1.90* (1.34,2.71)	1.26* (1.16,1.37)	0.78 (0.47,1.29)
Drug Abuse	--	1.50* (1.10,2.04)	1.16* (1.06,1.27)	0.62 (0.32,1.18)
Psychoses	--	1.62* (1.12,2.35)	1.51* (1.37,1.67)	1.28 (0.91,1.80)

Depression	--	1.10 (0.81,1.49)	1.04 (0.95,1.14)	0.87 (0.61,1.23)
Intentional Self-Harm	--	1.34 (0.96,1.87)	1.49* (1.35,1.63)	2.42* (1.80,3.25)
CALENDAR YEAR				
2007 (vs. 2006)	--	0.99 (0.64,1.55)	0.99 (0.86,1.14)	1.02 (0.63,1.67)
2008 (vs. 2006)	--	0.98 (0.64,1.51)	1.05 (0.92,1.20)	0.81 (0.53,1.25)
2009 (vs. 2006)	--	0.94 (0.60,1.48)	0.92 (0.81,1.05)	1.07 (0.69,1.65)
2010 (vs. 2006)	--	0.96 (0.63,1.46)	0.95 (0.83,1.10)	1.12 (0.73,1.71)

OR = odds ratio; CI = confidence interval

omitted[A] = variable omitted due to near-perfect association with no requirement of intubation (i.e., OR <0.01)

'- -' = variable omitted due to small sample size (n<0.01%)

* Statistically significant below the computed Simes (1986) false discovery rate p-value (p<0.036)

TABLE 4. Total Charges and Inpatient Length of Stay among APAP-Toxicity-Related Cases Presenting to the ED According to Age Category, 2006-2010.

	Age 11 Years and Below (N = 42,623)		Age 12-20 Years (N = 106,725)		Age 21-64 Years (N = 246,640)		Age 65 Years and Above (N = 15,893)	
	Charges [*exp(b)*,95th CI]	**LoS** [*IRR*,95th CI]	**Charges** [*exp*(b),95th CI]	**LoS** [*IRR*,95th CI]	**Charges** [*exp(b)*,95th CI]	**LoS** [*IRR*,95th CI]	**Charges** [*exp(b)*,95th CI]	**LoS** [*IRR*,95th CI]
PATIENT CHARACTERISTICS								
Age	1.04* (1.01,1.07)	1.03 (0.99,1.07)	1.05* (1.04,1.06)	0.99 (0.98,1.01)	1.01* (1.01,1.01)	1.01* (1.01,1.01)	1.00 (1.00,1.01)	1.01 (1.00,1.01)
Female Sex	0.94 (0.86,1.02)	1.07 (0.88,1.31)	0.97 (0.93,1.01)	1.00 (0.95,1.05)	0.96* (0.93,0.98)	0.97* (0.94,0.99)	0.91 (0.83,1.01)	0.94 (0.85,1.03)
Payer (vs. Commercial)								
Medicare	--	--	0.93 (0.65,1.33)	1.55 (0.90,2.65)	0.98 (0.94,1.03)	1.01 (0.96,1.06)	1.14 (0.83,1.56)	1.18 (0.81,1.72)
Medicaid	0.81* (0.71,0.92)	0.96 (0.79,1.16)	0.92* (0.87,0.96)	0.94* (0.89,0.98)	0.96* (0.93,0.98)	0.86* (0.83,0.91)	0.92 (0.65,1.31)	1.12 (0.74,1.69)
Other	0.89 (0.71,1.05)	1.08 (0.75,1.55)	0.87* (0.82,0.92)	0.92* (0.87,0.98)	0.97 (0.94,1.01)	0.94* (0.90,0.98)	0.56* (0.36,0.86)	0.93 (0.58,1.49)
Income Quartile (vs. Lowest)								
2nd Quartile	1.06 (0.95,1.18)	1.27 (0.97,1.66)	1.04 (0.98,1.10)	1.05 (0.99,1.11)	1.01 (0.97,1.04)	0.99 (0.95,1.02)	0.98 (0.86,1.11)	0.99 (0.88,1.12)
3rd Quartile	1.06 (0.88,1.28)	1.33 (0.95,1.88)	1.03 (0.97,1.10)	1.05 (0.98,1.12)	1.01 (0.96,1.06)	1.00 (0.95,1.05)	0.99 (0.87,1.14)	0.92 (0.81,1.04)
4th Quartile	0.95 (0.79,1.14)	1.28 (0.97,1.68)	1.03 (0.95,1.12)	1.00 (0.93,1.07)	1.09* (1.02,1.17)	0.99 (0.94,1.04)	1.13 (0.96,1.33)	0.95 (0.85,1.09)
Rural Residence	1.19 (0.97,1.45)	1.12 (0.71,1.75)	1.00 (0.92,1.08)	0.96 (0.86,1.07)	1.03 (0.96,1.10)	1.01 (0.94,1.09)	0.93 (0.75,1.14)	1.06 (0.88,1.27)
HOSPITAL CHARACTERISTICS								
Rural Location	0.68* (0.55,0.87)	0.86 (0.52,1.43)	0.73* (0.66,0.81)	0.80* (0.71,0.91)	0.66* (0.60,0.72)	0.76* (0.69,0.83)	0.52* (0.42,0.66)	0.67* (0.54,0.82)
Teaching Facility	1.28* (1.10,1.49)	1.23 (0.98,1.54)	1.14* (1.06,1.24)	1.03 (0.96,1.10)	1.06 (0.99,1.13)	1.09* (1.05,1.15)	0.95 (0.84,1.07)	1.02 (0.93,1.13)
Region (vs. Northeast)								
Midwest	0.74* (0.64,0.87)	0.72* (0.55,0.95)	0.78* (0.71,0.86)	0.83* (0.76,0.90)	0.71* (0.65,0.78)	0.79* (0.73,0.85)	0.72* (0.61,0.85)	0.74* (0.66,0.83)
South	0.89 (0.76,1.05)	0.91 (0.68,1.23)	0.88* (0.79,0.98)	0.91* (0.85,0.97)	0.87* (0.79,0.97)	0.90* (0.85,0.96)	0.88 (0.75,1.04)	0.85* (0.75,0.96)
West	0.35* (0.27,0.45)	0.71* (0.54,0.95)	0.64* (0.57,0.73)	0.76* (0.71,0.82)	0.78* (0.70,0.86)	0.82* (0.77,0.87)	0.85 (0.71,1.02)	0.74* (0.65,0.83)
CLINICAL CHARACTERISTICS								
Congestive Heart Failure	--	--	--	--	1.52* (1.30,1.78)	1.31* (1.14,1.50)	1.39* (1.23,1.59)	1.25* (1.12,1.40)
Valvular Disease	--	--	1.36 (0.94,1.96)	0.99 (0.68,1.44)	1.42* (1.23,1.63)	1.06 (0.95,1.18)	1.56* (1.26,1.94)	1.08 (0.91,1.29)
Pulmonary Circulation Disorders	--	--	--	--	1.90* (1.45,2.47)	1.45* (1.19,1.77)	1.27 (0.89,1.81)	1.10 (0.79,1.54)

Peripheral Vascular Disorders	--	--	--	--	1.81* (1.47,2.23)	1.40* (1.12,1.74)	1.18 (0.98,1.42)	1.01 (0.85,1.19)
Hypertension with Complications	--	--	1.51* (1.28,1.79)	1.35* (1.17,1.56)	1.43* (1.19,1.71)	1.23* (1.05,1.45)	1.50* (1.23,1.84)	1.17 (0.99,1.37)
Paralysis	--	--	1.79 (1.03,3.09)	1.02 (0.70,1.48)	1.60* (1.32,1.94)	1.39* (1.19,1.63)	1.94* (1.12,3.36)	2.24 (1.08,4.62)
Other Neurological Disorders	7.00* (2.80,17.49)	1.41 (1.02,1.96)	1.61* (1.45,1.78)	1.05 (0.94,1.17)	1.29* (1.24,1.34)	1.00 (0.97,1.04)	1.15* (1.03,1.29)	1.01 (0.90,1.13)
Chronic Pulmonary Disease	0.98 (0.80,1.20)	0.81 (0.61,1.08)	1.18* (1.11,1.26)	0.97 (0.91,1.04)	1.20* (1.15,1.26)	1.02 (0.98,1.07)	1.37* (1.23,1.52)	1.03 (0.94,1.12)
Diabetes with Complications	--	--	1.02 (0.86,1.20)	0.90 (0.74,1.11)	1.27* (1.11,1.45)	1.07 (0.95,1.22)	1.60 (0.97,2.66)	1.07 (0.79,1.46)
Hypothyroidism	--	--	1.31 (1.00,1.72)	1.39* (1.08,1.79)	1.23* (1.15,1.31)	1.01 (0.94,1.08)	1.12 (1.00,1.25)	0.89 (0.81,0.99)
Renal Failure	--	--	1.41 (0.84,2.37)	0.88 (0.51,1.51)	1.43* (1.23,1.67)	1.16 (1.00,1.33)	1.03 (0.82,1.29)	0.99 (0.80,1.22)
Liver Disease	--	--	1.76* (1.30,2.39)	1.53* (1.15,2.03)	2.00* (1.80,2.23)	1.52* (1.39,1.67)	2.34* (1.66,3.31)	1.52* (1.19,1.95)
HIV/AIDS	--	--	--	--	1.56* (1.18,2.06)	1.30* (1.12,1.52)	--	--
Lymphoma	--	--	--	--	1.16 (0.86,1.57)	1.02 (0.78,1.34)	--	--
Metastatic Cancer	--	--	--	--	1.64* (1.16,2.31)	1.48* (1.07,2.03)	1.38 (0.89,2.15)	1.06 (0.64,1.76)
Solid Tumor	--	--	--	--	1.23 (0.97,1.56)	1.12 (0.92,1.36)	1.02 (0.84,1.24)	0.88 (0.72,1.08)
Rheumatoid Arthritis/Collagen Vascular Disease	--	--	0.71 (0.38,1.32)	0.84 (0.41,1.72)	1.34* (1.21,1.49)	1.12 (1.00,1.25)	1.33* (1.07,1.64)	1.02 (0.83,1.25)
Coagulopathy	--	--	3.04* (2.46,3.78)	1.98* (1.63,2.41)	2.08* (1.91,2.26)	1.48* (1.39,1.59)	1.54* (1.26,1.89)	1.12 (0.92,1.36)
Obesity	--	--	1.58* (1.40,1.79)	1.14 (1.01,1.28)	1.39* (1.31,1.48)	1.11 (1.01,1.22)	1.18 (0.96,1.44)	0.95 (0.76,1.20)
Weight Loss/Cachexia	--	--	--	--	1.99* (1.63,2.42)	1.83* (1.58,2.13)	1.68* (1.32,2.16)	1.58* (1.31,1.89)
Fluid and Electrolyte Disorders	6.46* (3.26,12.81)	1.93* (1.34,2.80)	1.95* (1.84,2.08)	1.04 (0.99,1.09)	1.82* (1.76,1.88)	1.16* (1.13,1.20)	1.81* (1.62,2.02)	1.18* (1.08,1.28)
Blood Loss or Deficiency Anemia	3.02* (1.67,5.47)	1.28 (0.74,2.19)	1.67* (1.43,1.94)	1.20* (1.07,1.36)	1.64* (1.55,1.74)	1.27* (1.17,1.37)	1.40* (1.23,1.59)	1.11 (1.00,1.23)
Alcohol Abuse	--	--	1.23* (1.14,1.31)	1.01 (0.95,1.08)	1.24* (1.21,1.27)	0.98 (0.95,1.01)	1.19* (1.06,1.34)	1.01 (0.88,1.15)
Drug Abuse	--	--	1.19* (1.13,1.20)	1.11* (1.05,1.19)	1.30* (1.26,1.34)	1.11* (1.08,1.15)	1.16 (0.99,1.36)	1.09 (0.95,1.24)
Psychoses	--	--	1.65* (1.57,1.74)	1.01 (0.95,1.08)	1.50* (1.46,1.55)	1.02 (0.98,1.07)	1.50* (1.33,1.70)	1.27* (1.13,1.43)
Depression	--	--	1.27* (1.22,1.33)	0.87* (0.83,0.92)	1.19* (1.16,1.23)	0.84* (0.82,0.87)	1.22* (1.10,1.35)	0.90* (0.83,0.98)

Intentional Self-Harm	--	--	1.40* (1.33,1.49)	1.16* (1.09,1.23)	1.17* (1.13,1.21)	1.09* (1.05,1.13)	1.16* (1.06,1.28)	1.02 (0.94,1.11)
Invasive Mechanical Ventilation	--	--	3.21* (2.84,3.63)	1.60* (1.41,1.82)	3.37* (3.20,3.55)	1.57* (1.50,1.64)	1.39* (1.23,1.59)	1.57* (1.39,1.78)
CALENDAR YEAR								
2007 (vs. 2006)	0.95 (0.80,1.13)	1.12 (0.85,1.47)	0.99 (0.91,1.08)	1.02 (0.95,1.09)	1.04 (0.98,1.10)	1.03 (0.98,1.08)	1.06 (0.90,1.24)	1.01 (0.87,1.17)
2008 (vs. 2006)	1.04 (0.84,1.28)	0.91 (0.68,1.23)	0.99 (0.91,1.08)	0.99 (0.92,1.07)	1.03 (0.97,1.09)	1.03 (0.98,1.07)	1.02 (0.87,1.20)	0.97 (0.85,1.10)
2009 (vs. 2006)	1.01 (0.84,1.22)	0.91 (0.69,1.22)	1.04 (0.96,1.13)	1.01 (0.94,1.09)	1.06 (1.00,1.12)	0.98 (0.93,1.03)	0.97 (0.83,1.12)	0.90 (0.79,1.02)
2010 (vs. 2006)	1.16 (0.97,1.39)	0.89 (0.69,1.15)	1.08 (1.00,1.18)	0.96 (0.90,1.03)	1.07* (1.01,1.14)	0.97 (0.93,1.02)	1.09 (0.93,1.27)	0.94 (0.83,1.07)

exp(b)= exponentiated beta coefficient; IRR = incidence rate ratio; LoS = length of stay; CI = confidence interval

'- -' = variable omitted due to small sample size (n<0.01%)

* Statistically significant below the computed Simes (1986) false discovery rate p-value for charges (p<0.036) and length of stay (p<0.024)

Figure 1. Overall Number of APAP toxicity-related ED Cases According to Age, 2006-2010.

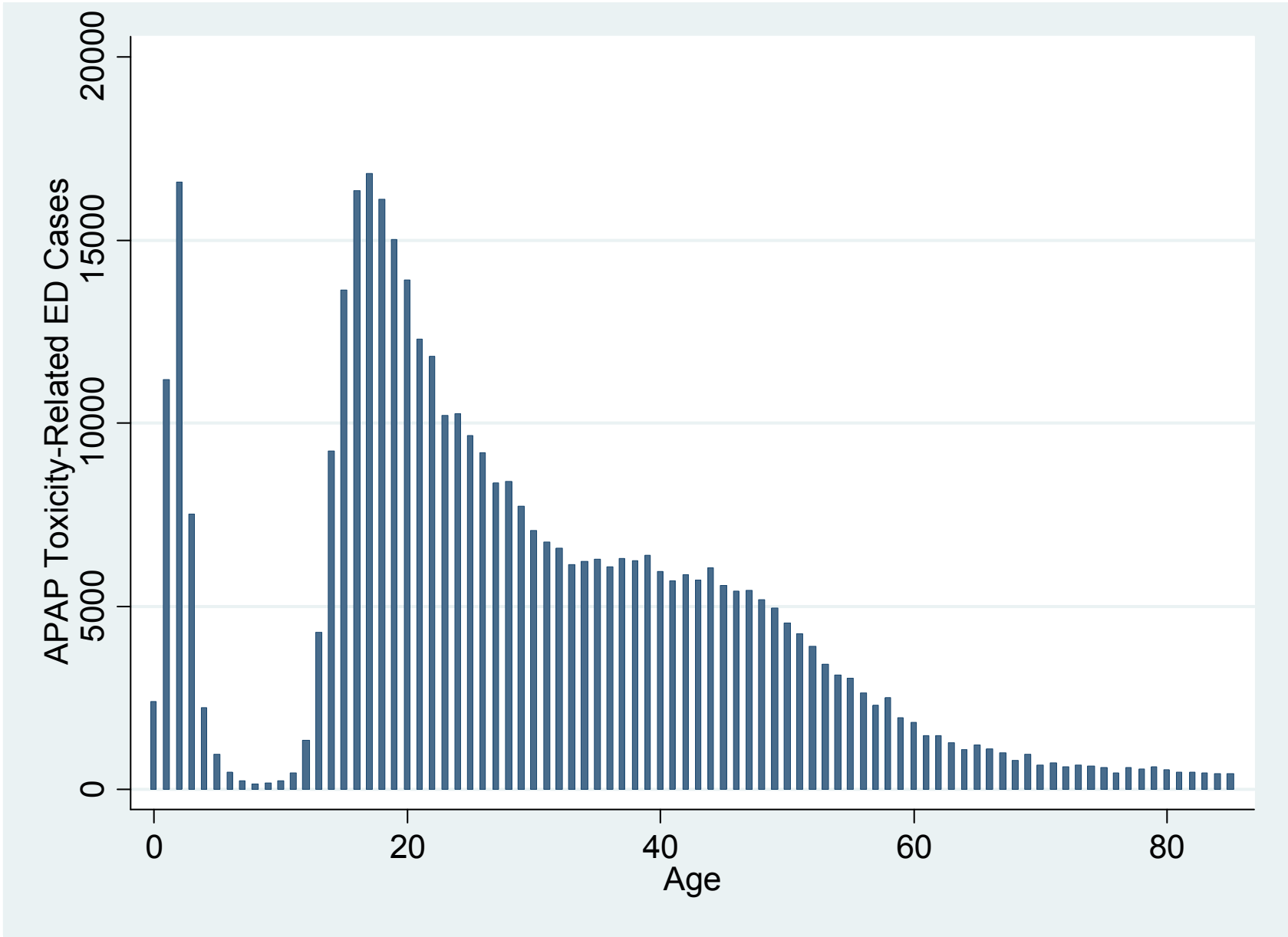
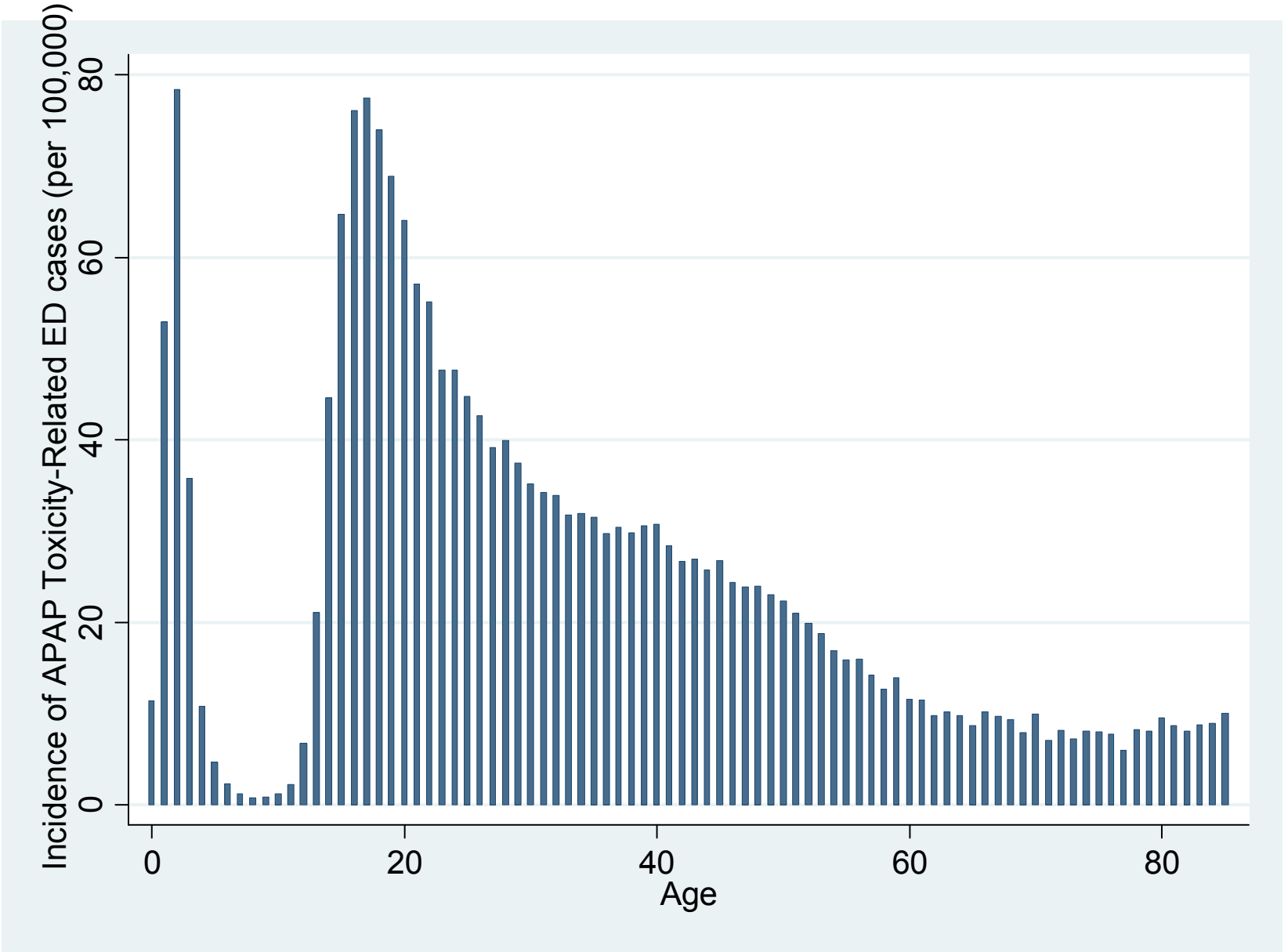


Figure 2. Age-Adjusted of APAP toxicity-related ED Cases per 100,000 U.S. Population, 2006-2010.[A]



[A] Base U.S. populations for 2006-2010 obtained from the Centers for Disease Control and Prevention, National Vital Statistics System, Vintage 2012 bridged-race post-census U.S. resident population estimates

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	None conducted
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7; Tables 1-4
		(b) Give reasons for non-participation at each stage	6-7; Tables 1-4
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-4
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 (descriptives); Table 2-4 (multivariable analysis)
		(*b*) Report category boundaries when continuous variables were categorized	6-7; Tables 1-4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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CLINICAL AND ECONOMIC CHARACTERISTICS OF EMERGENCY DEPARTMENT VISITS DUE TO ACETAMINOPHEN TOXICITY IN THE UNITED STATES

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Preliminary findings of this study were presented as a plenary presentation at The Western States Conference for Pharmacy Residents, Fellows, Preceptors and Sponsors, May 21-24, 2012, Pacific Grove, California, USA, and as a poster at the American Society of Health-System Pharmacists ASHP Summer Meeting and Exhibition, May 31-June 4, 2014, Las Vegas, Nevada, USA.

ABSTRACT

Objectives: To estimate the number of acetaminophen (APAP) toxicity-related emergency department (ED) visits and to assess their associated clinical and economic burden in the U.S. from 2006-2010.

Design: Cross-sectional, retrospective, large-scale database study.

Setting: Non-federal, non-rehabilitation, community emergency departments in the U.S.

Participants: Inclusion criteria included any-listed diagnosis identifying poisoning by aromatic analgesics paracetamol/acetaminophen or associated supplementary code. Generalized linear models were used to investigate the association between outcomes of inpatient admission, mortality, requirement of invasive mechanical ventilation, charges, and inpatient lengths of stay based upon patient, hospital, and clinical characteristics.

Results: Across the 625.2 million ED visits in the U.S. from 2006-2010, 411,811 APAP-related toxicity ED visits were observed, with 45.5% resulting in inpatient admission, 4.7% requiring invasive mechanical ventilation, and 0.6% involving death. The incidence proportion was 27.10 per 100,000 U.S. population overall, exceeding 70 per 100,000 at age 2 and ages 16-18. The

total national bill was $1.06 billion per year (USD 2014), and predominantly involved females (65.5%) and intentional self-harm (58.4%), which were notably higher within the 12-20 age category (female$_{12\text{-}20\ years}$=74.8%, intentional self-harm$_{12\text{-}20\ years}$=71.4%). Behavioral and mental health comorbidities were relatively common and associated with an increased relative risk of admission and likelihood of charges almost entirely across all age categories of ≥12 years within the multivariable analyses. The number of ED visits did not appreciably change over time, decreasing by <2% from 2006 to 2010 (n=1,351). Multivariable results also suggested no consistent change in outcomes across the study's time horizon.

Conclusions: A substantial public health impact of APAP toxicity-related cases was observed in the U.S. from 2006-2010, with incidence proportions peaking at age 2 and ages 16-18. After controlling for numerous factors, no consistent change was observed over the five-year time horizon concerning outcomes of admission, mortality, invasive mechanical ventilation, charges, or length of stay.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study draws upon an estimated 130 million ED visits per year within the U.S. to report national estimates of case incidence and to provide assessments of clinical and economic outcomes.
- No specific categorization existed to classify cases as being unsupervised ingestions or therapeutic misadventures (e.g., overuse, medication errors), the type of APAP product consumed (e.g., single-agent, combination products, tablets, liquid), and the amount ingested or serum levels observed.

- The use of n-acetyl cysteine (NAS) or gastric decontamination was also not consistently captured within the dataset, nor was a designation of acute liver injury directly attributable to acetaminophen (APAP) toxicity.

INTRODUCTION

As one of the most frequently-used analgesic and antipyretics worldwide, acetaminophen (APAP) is a common single or combination agent within numerous over-the-counter (OTC) and prescription products.[1] Though considered generally safe at approved doses, APAP has a known and established toxicity pattern at higher doses.[2] Of all pharmaceuticals involved in human overdoses, analgesics are considered the most frequently involved.[2] U.S. poison center data indicate that APAP combinations were associated with the fourth highest number of fatalities compared to other medications in 2012, with APAP overdose being principal cause of toxic drug ingestion that ultimately contributed to 39% of all acute liver failures.[2,3] Hepatotoxicity is a well-recognized adverse event associated with APAP overdose that may result in liver failure and death.[4] The percentage of APAP-induced acute liver failure cases increased from 28% in 1998 to 51% in 2003, establishing this medication as the most common cause of acute liver failure in the U.S.[4] Overall, previous studies have suggested that APAP overdoses leads annually to 56,000-78,000 emergency department (ED) visits, 26,000-34,000 hospitalizations, and an estimated 500 deaths.[5-8]

The U.S. Food and Drug Administration (FDA) has issued several updates in recent years involving APAP to increase the safety and limit the toxicity associated with use of the medication, presented in Figure 1.[9-13]

<FIGURE 1>

Given the aforementioned, the overall purpose of this investigation was to estimate the number of APAP toxicity-related ED visits and to assess their associated clinical and economic burden in the U.S. from 2006-2010. More specifically, the objectives were to assess the relationships between outcomes of inpatient admission, mortality, requirement of invasive mechanical ventilation, charges, and inpatient lengths of stay based upon patient, hospital, and clinical characteristics.

METHODS

This cross-sectional, retrospective investigation utilized 2006-2010 Nationwide Emergency Department Sample (NEDS) from the Agency for Healthcare Research and Quality (AHRQ).[14] These data comprise nationally-representative case presentations across hospital-based EDs within non-federal, non-rehabilitation, community facilities and generalizing, overall, to approximately 130 million ED visits that occur in the U.S. per year.[14] Given the fully de-identified and anonymized, this research is classified as exempt via human subjects protection.[14]

Consistent with previous research, ED visits involving APAP toxicity were identified based on the inclusion criteria of any-listed diagnosis according to International Classification of Disease, 9th edition, Clinical Manifestations (ICD-9-CM) codes identifying poisoning by aromatic analgesics paracetamol/acetaminophen (i.e., 965.4) or associated supplementary code (i.e., E850.4: accidental poisoning by aromatic analgesics paracetamol/acetaminophen).[5-8,15,16] Previous research has addressed the challenges in the sensitivity and specificity of utilizing diagnosis or supplementary codes to identify acetaminophen toxicity-related cases, suggesting that the use of these aforementioned codes remains a valid approach.[15] All ages were investigated and stratified according to the following age categories: A) 0-11 years; B) 12-20 years; C) 21-64 years; and ≥65 years.

Clinical outcomes assessed were admission to an inpatient setting from the ED, mortality, and requirement of invasive mechanical ventilation (i.e., as a proxy for acute respiratory distress syndrome and supportive care measures associated with APAP toxicity disease progression or acute liver failure).[17,18] Economic outcomes analyzed involved inflation-adjusted charges (USD 2014) and inpatient length of stay. Independent predictor variables analyzed were patient demographics (i.e., age category, sex, income quartile, age, primary payer, rural location defined by communities ≤50,000 residents), ED and hospital characteristics (geographic region, urban/rural location, teaching status), clinical case-mix disease severity measured via Elixhauser comorbidities (a validated case-mix risk severity measure comprised of 30 disease states), designation of intentional self-harm, and year (2006-2010).[14,19] Notably, if any given Elixhauser comorbidity was observed in <0. 1% of cases within any age category, it was omitted to allow for appropriate statistical inference; peptic ulcer disease with bleeding was consistently observed to be <0. 1% of cases and summarily removed from the study.[6,7]

Multivariable analyses for outcomes of admission to an inpatient setting from the ED and mortality were conducted using a multinomial logit regression, specifying treat-and-release ED cases as a baseline comparator.[20,21] The requirement of invasive mechanical ventilation was analyzed via a logistic regression. Generalized linear models were used to analyze inflation-adjusted charges and inpatient length of stay, specified by a gamma distribution with log link and negative binomial distribution with log link, respectively.[21] Accordingly, results may be interpreted generally as relative risk measures, superficially as: a relative risk ratio (RRR) in a multinomial regression; an odds ratio (OR) in a logistic regression; an exponentiated beta value (exp(b)) in a gamma regression; and an incidence ratio (IR) in a negative binomial regression.[21]

Therein, estimated coefficients may be interpreted as suggesting a reduced likelihood (<1.00), suggesting no difference in likelihood (=1.00), and suggesting an increased likelihood (>1.00).

The Simes (1986) procedure to control for false discovery rates was used to control for multiple comparisons across age categories within the analysis of invasive mechanical ventilation, charges, and length of stay, yielding critical p-values for significance of 0.028, 0.036, and 0.024, respectively.[22] Inherently controlling for multiple comparisons by definition, the multinomial regression of disposition from the ED used an alpha level of 0.05 for significance and established treat-and-release cases as the baseline comparator. Due to the complex nature of sampling employed by the NEDS, Taylor-series weighting procedures were incorporated to yield national estimates.[14] All analyses were conducted using SAS 9.2 (Cary, North Carolina) and STATA SE 12.1 (College Station, Texas).

RESULTS

Across the 625.2 million ED visits in the U.S. from 2006-2010, APAP-related toxicity was observed among 411,881 ED visits, with peaks occurring at approximately ages 0-5, 15-20, and 35-45 years (Figure 2). The incidence proportion of APAP toxicity-related ED visits according to age per 100,000 per U.S. population was 27.10 overall and, by age category: 17.29 for ages 0-11; 63.17 for ages 12-20; 27.77 for ages 21-64; and 8.18 for ages 65 and over. Reflected in Figure 3, peak incidence proportions exceeding 70 per 100,000 U.S. population were observed at age 2 (78.39 per 100,000) and ages 16-18 (76.16, 77.52, and 74.00 per 100,000, respectively). Inpatient admissions averaged 12.46 per 100,000 US population, lowest among <12 years (0.50 per 100,000) and highest within cases from 12-20 (23.34 per 100,000); peaks were noted at ages 18 (33.55 per 100,000) and 19 (31.07 per 100,000).

<FIGURE 2>

<FIGURE 3>

In general, cases involved females (65.5%) averaging 29.3 (±17.6) years of age with 3.1 (±4.4) days for inpatient lengths of stay, and involved intentional self-harm (58.4%). Within the 12-20 age category, cases were markedly female (74.8%) and involving intentional self-harm (71.4%). Among the APAP-related cases presenting to the ED, 45.4% resulted in direct inpatient admission, highest in percentage terms among cases age ≥65 years (66.0%) even though this age category constituted an age-adjusted 5.68 admissions per 100,000 U.S. population. Those treated-and-released directly in the ED involved 37.4% of cases, particularly characteristic among cases <12 years (92.7%). The most common Elixhauser comorbidities observed were depression (25.0%), drug abuse (15.6%), psychoses (15.3%), alcohol abuse (13.7%), and fluid and electrolyte disorders (13.6%); no Elixhauser comorbidities were noted among 38.0%. Inpatient mortality was low (0.6%), and the requirement of invasive mechanical ventilation was 4.7%. The total national bill across the five-year time horizon was $5.30 billion (USD 2014), equating to $12,766 (±28414) per case. The full descriptive statistics appear in Table 1.

<TABLE 1>

Multivariable Analysis: Inpatient Admission, Mortality, Invasive Mechanical Ventilation

Results of the multinomial logit regression of patient disposition from the ED (Table 2) indicated that numerous patient, hospital, and clinical characteristics were associated with an increased likelihood of admission or death. After statistically controlling for numerous factors, rural patient residence suggested a significant ($p<0.05$) increased relative risk of admission among the 0-11, 12-20, and 21-64 year-old categories ($RRR_{0-11}=2.26$, $RRR_{12-20}=1.30$, $RRR_{21-64}=1.24$). Intentional self-harm was also associated with over a 3x increase odds of admission across all age categories ≥12 years ($p<0.05$), was almost perfectively predictive of mortality

cases among those 12-20 years of age, and was associated with a 8.57x ($p<0.001$) for those ≥65 years.

<TABLE 2>

Comorbidities of liver disease, coagulopathy, fluid and electrolyte disorders, and weight loss/cachexia were associated with significant ($p<0.05$) and large relative risks for both admission and mortality across age groups (sample size permitting for analysis). Specifically among pediatric cases <12 years, other neurological disorders, fluid and electrolyte disorders, and blood or deficiency anemia were significantly associated with increased admission ($p<0.05$). Across other age categories concerning admissions alone, comorbid conditions of valvular disease, peripheral vascular disorders, hypertension with complications, other neurological disorders, obesity, deficiency or other anemia, alcohol abuse, psychoses, and depression were significantly associated with an increased relative risk across all age groups ($p<0.05$). Over time, no sustained decrease in admissions or mortality were observed consistently across age categories over time.

The requirement of invasive mechanical ventilation (Table 3) indicated that chronic pulmonary disease, coagulopathy, and fluid and electrolyte disorders were significant predictors among cases ≥12 years ($p<0.028$). Intentional self-harm was associated with a 1.49x higher odds among those aged 21-64 years, and a 2.42x higher odds among cases ≥65 years ($p<0.028$). Other neurological disorders, blood loss or deficiency anemia, alcohol abuse, drug abuse, and psychoses were associated with an increased odds ($p<0.028$) among 12-20 and 21-64 age groups. Several factors had near-perfect associations with invasive mechanical ventilation within the 12-20 age group. Notably, over time, no consistent change in odds of invasive mechanical ventilation across years was observed from 2006.

<TABLE 3>

Multivariable Analysis: Charges, Length of Stay

The multivariable analysis of charges and length of stay (Table 4) indicated varying associations with these economic outcomes. Suggestive of greater intensities of care required across all age categories, consistently significant increased charges and lengths of stay were associated with liver disease ($p<0.036$ for charges, $p<0.024$ for length of stay), while weight loss/cachexia and coagulopathy were significant across age groups 21-64 and ≥65 and HIV/AIDS was significant in the 21-64 age category. Increased charges alone were associated with intentional self-harm and most Elixhauser comorbidities: heart failure; hypertension with complications; other neurological disorders; coagulopathy; fluid and electrolyte disorders; blood loss or deficiency anemia; alcohol abuse; psychoses; and depression ($p<0.036$). No consistent change across age categories was noted over time for either charges or length of stay.

<TABLE 4>

DISCUSSION

This investigation examined nationally-representative cases of APAP toxicity-associated ED visits in the U.S. from 2006-2010, assessing the independent associations between outcomes of inpatient admission, mortality, required use of invasive mechanical ventilation, charges, and lengths of stay based upon several patient, clinical, and hospital characteristics. Overall, 411,881 ED visits were observed (82,376 per year), equating to 27.10 ED visits per 100,000 US population annually and summing to a national bill of $1.06 billion per year (USD 2014). Some 37.2% were treated-and-released directly from the ED (30,783 per year), 45.5% were admitted to the inpatient setting (37,877 per year), and 0.6% involved death (484 per year). The number of ED presentations did not appreciably change over time, decreasing by <2% from 2006 to 2010

(n=1,351), though representing a change from 27.15 to 25.78 visits per 100,000 U.S. population annually overall.

Comparatively, Nouraj et al. (2006) estimated that attributable APAP overdoses from 1993-1999 were lower than aforementioned findings, with approximately 56,000 ED visits, 26,000 hospitalizations, and 458 deaths per year, wherein Li and Martin (2011) also reported a decrease in rates from 2001-2007 to slightly less than 45,000 ED visits per year.[5,8] From 1993-1999, Li and Martin (2011) found a lower number of ED visits, at 21.03 visits per 100,000 persons per year and decreasing to 15.21 from 2000-2007.[8] It is critical to note that Nouraj et al. (2006) and Li and Martin (2011) utilized different national data than the present study, data that have explicitly been identified with a discrepancy in the number of cases associated with intentional APAP overdose-related visits, though unintentional poisonings appeared to be similar across various data sources.[5-8] Manthripragada et al. (2011) presented results illustrating differences present within nationally-representative studies, wherein the number of APAP toxicity-associated ED visits may be potentially underestimated perhaps by one-third to one-half.[6] More closely paralleling the present study, Budnitz et al. (2011) reported 78,414 annual ED visits associated with APAP overdoses from 2005-2006 using data from the National Electronic Injury Surveillance System (NEISS), while Manthripragada et al. (2011) found an age-adjusted rate of 13.9 hospitalizations per 100,000 U.S. population from 2000-2006.[6,7] Also consistent with the current work, a decrease in the number of ED visits or hospitalizations over time relating to APAP overdose was not observed.[6]

The average age in the present study was 29.3 years, with 60.0% of ED visits occurring across the 21-64 year age group. Though constituting 16.2% and 11.1% of the U.S. population, some 10.3% and 25.9% of cases, respectively, involved persons 0-11 and 12-20 years of age.

Furthermore, ED presentations exceeding 50 visits per 100,000 persons per year were noted from ages 1-2 and 15-22, peaking at over 70 per 100,000 specifically at age 2 and ages 16-18. Broader surveillance figures suggest that age-adjusted overall nonfatal injuries relating to poisoning of any type was 36.14 per 100,000 in 2013, though the crude rate for ages 1-2 is 12.27 per 100,000 and is 35.79 per 100,000 for ages 15-22.[23] Prior investigations suggest a substantially large number of APAP toxicity-related ED visits occur among young children, adolescents, and young adults; Li and Martin (2011) reported 72.42 visits per 100,000 for cases under 5 years, 61.91 per 100,000 for ages 15-17, and 40.92 per 100,000 for ages 18-24.[7,8,24,25] Budnitz et al. (2011), found that 13.4% of APAP overdose ED visits were attributed to unsupervised ingestions by children 5 years of age and under, a finding which has been observed across other work.[7,27,28] Others have found higher risks for APAP toxicity-related ED visits due, in part, to single-ingredient unintentional overdose or high use of APAP products.[24,25,28]

A majority of cases in the current work involved female sex (65.5%) and intentional self-harm (58.4%), highest in the 12-20 year age category at 74.8% female and 71.4% intentional self-harm. Similar to Li and Bradly (2011), behavioral and mental health comorbidities were common and represented the largest proportions of Elixhauser comorbidities including depression (25.0%), psychoses (15.3%), drug abuse (15.6%), and alcohol abuse (13.7%). Notably, these comorbid conditions were also associated with increased relative risk of admission and likelihood of charges almost entirely across all age categories of ≥12 years within the multivariable analyses. Over most age categories ≥12 years, intentional self-harm was generally associated with increased odds of admission, mortality, requirement of invasive mechanical ventilation, charges, and length of stay. Budnitz et al. (2011) reported that 69.8% of ED visits involving APAP overdoses from 2006-2007 were associated with self-directed

violence, peaking among those between 15-24 years of age, with 75% ultimately resulting in either psychiatric or inpatient hospitalizations.[7] Surveillance data also suggest that one-quarter of all ED cases for intentional poisoning involve APAP.[23] Budnitz et al. (2011) also noted that females had the highest rates of intentional self-harm, especially as adolescents or young adults.[7] It has been noted in prior work that suicide attempts via toxic medication ingestion is more frequently observed among adolescents and often associated with impulsivity, of which toxic APAP ingestion has been classified.[7,29,30,31] Importantly, Manthripragada et al. (2011) emphasized that discerning whether self-harm was intentional versus accidental remains challenging to ascertain via secondary data, potentially resulting in the misclassification of cases involving non-accidental poisoning via supplementary ICD-9 codes (i.e., E-codes) or differences in hospital reporting requirements.[6,32,33]

Results of the multivariable analysis indicated that rural patient residence (municipalities ≤50,000 persons) was associated with a higher odds of admission across age categories <65 years. Among age categories ≥12 years, an increased relative risk of admission and mortality was associated with liver disease, coagulopathy, fluid and electrolyte disorders, and weight loss/cachexia. With some exceptions, increased odds of invasive mechanical ventilation, charges, and lengths of stay were also observed with these comorbidities as well. As Li and Martin (2011) reported a 8.62x higher odds of ED visits attributed to APAP toxicity with alcohol abuse or dependence ($p<0.001$), findings from the current work also suggest over a 2x higher relative risk of admission (age categories ≥12 years), a 1.75x higher relative risk of mortality (ages 21-64), over 1.19x higher charges (age categories ≥12 years), and 1.26x or greater odds of invasive mechanical ventilation (ages 12-20 and 21-64). Pediatric admissions <12 years were associated with other neurological disorders, fluid and electrolyte disorders, and blood loss or

deficiency anemia; Budnitz et al. (2011) reported that most of the unsupervised ingestions of APAP were observed among children <6 years, typically treated-and-released from the ED setting via gastric decontamination or n-acetyl cysteine (NAS) treatment.[7]

Although findings from this study provide updated information concerning the burden of APAP-related ED visits in the U.S., some important study limitations exist. While similar coding algorithms were used as other retrospective studies to identify APAP-toxicity cases, no specific categorization was present that may have classified cases as being unsupervised ingestions or therapeutic misadventures (e.g., overuse, medication errors), the type of APAP product consumed (e.g., single-agent, combination products, tablets, liquid), and the estimated amount ingested or serum levels observed.[5-8,15,16] In this context, Budnitz et al. (2011) reported that 13.4% of APAP toxicity-related ED visits were attributed to unsupervised ingestions and 16.7% involved therapeutic misadventures, with slightly over half involving overuse of agents versus dosage confusion or APAP over-ingestion from multiple source products.[7] The use of NAS or gastric decontamination was also not consistently captured within the dataset, nor was a designation of acute liver injury directly attributable to APAP toxicity.[6,7] Generalizations of findings beyond acute care settings are not appropriate to estimate the prevalence of APAP poisoning in the U.S., as cases presenting to poison centers or within ambulatory practices are not captured. Finally, given the time horizon of this study and available data, continued work is warranted to study the impact of more recent APAP dose limitations established by the FDA in addition to studies focusing directly upon consumer perceptions, attitudes, beliefs, knowledge, and health literacy.[9-13,34-45]

CONCLUSION

This nationally-representative study of ED visits in the U.S. highlights a substantial public health impact of APAP toxicity-related cases from 2006-2010. Overall, 82,376 cases per year were observed, summing to a national bill of $1.06 billion. The ED visit average rate across all ages was 27.10 ED visits per 100,000 U.S. population, exceeding 70 per 100,000 age 2 and ages 16-18. After controlling for numerous factors, no consistent temporal change was observed during the five-year time horizon concerning outcomes of admission, mortality, invasive mechanical ventilation, charges, or length of stay.

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CONTRIBUTIONS

AA and GHS conducted the initial planning of this investigation. AA, LK, and GHS were involved in formalizing and executing the study methodology, analysis, interpretation of results, and drafting and revisions of the manuscript. GHS was involved in the acquisition of data and overall study supervision.

COMPETING INTEREST STATEMENTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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TABLE 1. Descriptive Statistics of ED Cases Associated with APAP Toxicity According to Age Category in the U.S., 2006-2010.

	Age 11 Years and Below (N = 42,623)	Age 12-20 Years (N = 106,725)	Age 21-64 Years (N = 246,640)	Age 65 Years and Above (N = 15,893)	Overall (N = 411,881)
PATIENT CHARACTERISTICS					
Age (mean ± standard deviation)	2.2 ±1.7	16.9 ±2.1	36.4 ±11.4	75.2 ±7.9	29.3 ±17.6
Female Sex	48.3%	74.8%	64.4%	68.0%	65.5%
Payer, Commercial Insurance	38.1%	26.4%	20.4%	1.6%	23.1%
Medicare	≤0.1%	0.2%	10.0%	88.3%	9.5%
Medicaid	48.9%	51.5%	35.1%	7.8%	39.7%
Other	12.8%	21.8%	34.5%	2.3%	27.7%
Income Quartile, Lowest	24.3%	23.2%	28.1%	24.4%	26.3%
2nd Quartile	28.3%	27.5%	28.5%	27.0%	28.2%
3rd Quartile	25.5%	25.6%	24.5%	25.4%	24.9%
4th Quartile	21.9%	23.8%	18.9%	23.3%	20.6%
Rural Residence	19.6%	16.7%	17.1%	17.9%	17.3%
HOSPITAL CHARACTERISTICS					
Region, Northeast	14.4%	16.2%	15.6%	16.4%	15.6%
Midwest	25.6%	18.2%	26.4%	21.0%	26.6%
South	32.1%	30.0%	34.7%	34.5%	33.2%
West	18.1%	25.6%	23.3%	28.2%	24.5%
Rural Facility	18.5%	15.3%	15.3%	16.2%	15.6%
Teaching Facility	38.9%	39.9%	39.5%	35.7%	39.4%
CLINICAL CHARACTERISTICS					
Congestive Heart Failure	≤0.1%	≤0.1%	0.7%	8.8%	0.8%
Valvular Disease	≤0.1%	≤0.1%	0.6%	3.3%	0.5%
Pulmonary Circulation Disorders	≤0.1%	≤0.1%	0.2%	1.4%	0.2%
Peripheral Vascular Disorders	≤0.1%	≤0.1%	0.3%	3.8%	0.3%
Hypertension with Complications	≤0.1%	≤0.1%	0.7%	7.6%	0.7%
Paralysis	≤0.1%	≤0.1%	0.4%	1.5%	0.3%
Other Neurological Disorders	0.3%	2.2%	7.4%	14.6%	5.6%
Chronic Pulmonary Disease	2.0%	4.9%	7.8%	19.2%	6.9%
Diabetes with Complications	≤0.1%	≤0.1%	0.5%	2.0%	0.4%

Hypothyroidism	≤0.1%	0.5%	2.9%	11.9%	2.3%
Renal Failure	≤0.1%	≤0.1%	0.8%	7.3%	0.8%
Liver Disease	≤0.1%	0.2%	2.2%	1.7%	1.4%
HIV/AIDS	≤0.1%	≤0.1%	0.2%	≤0.1%	≤0.1%
PUD, excluding bleeding	≤0.1%	≤0.1%	≤0.1%	≤0.1%	≤0.1%
Lymphoma	≤0.1%	≤0.1%	≤0.1%	≤0.1%	≤0.1%
Metastatic Cancer	≤0.1%	≤0.1%	≤0.1%	1.0%	0.2%
Solid Tumor	≤0.1%	≤0.1%	0.3%	2.1%	0.2%
Rheumatoid Arthritis/Collagen Vascular Disease	≤0.1%	≤0.1%	0.9%	3.1%	0.7%
Coagulopathy	≤0.1%	0.5%	2.3%	4.2%	1.7%
Obesity	≤0.1%	1.2%	3.3%	2.4%	2.4%
Weight Loss/Cachexia	≤0.1%	≤0.1%	0.8%	3.2%	0.6%
Fluid and Electrolyte Disorders	0.7%	8.1%	17.2%	29.4%	13.6%
Blood Loss or Deficiency Anemia	≤0.1%	1.5%	4.3%	12.3%	3.4%
Alcohol Abuse	≤0.1%	5.7%	19.8%	8.6%	13.7%
Drug Abuse	≤0.1%	12.1%	20.3%	6.3%	15.6%
Psychoses	≤0.1%	11.2%	19.8%	13.3%	15.3%
Depression	≤0.1%	27.4%	28.4%	22.6%	25.0%
No Elixhauser Comorbidities Present	96.4%	47.0%	25.7%	12.6%	38.0%
Intentional Self-Harm	≤0.1%	71.4%	64.2%	34.9%	58.4%
CALENDAR YEAR					
2006	18.1%	21.1%	19.5%	17.5%	19.7%
2007	21.0%	20.5%	19.6%	17.0%	19.9%
2008	21.8%	21.1%	20.6%	20.1%	20.8%
2009	20.8%	19.7%	20.4%	21.8%	20.3%

2010	18.3%	17.6%	20.0%	23.6%	19.3%
OUTCOMES					
Disposition, treat and release	92.7%	38.4%	28.1%	23.8%	37.4%
Transfer	2.5%	22.4%	14.0%	6.3%	14.7%
Admission	2.9%	37.0%	55.1%	66.0%	45.4%
Death	≤0.1%	≤0.1%	0.7%	3.4%	0.6%
Other	1.9%	2.2%	1.9%	0.5%	1.9%
Average ED and Inpatient Charge (USD 2014) (mean ± standard deviation)	$1,343 ±3162	$7,884 ±13034	$15,824 ±31404	$28,631 ±50515	$12,766 ±28414
Annual: Total National Bill (USD 2014) (mean ± standard deviation)	$11.45 million	$168.28 million	$789.11 million	$91.00 million	$1,059.86 million
2006-2010: Total National Bill (USD 2014) (mean ± standard deviation)	$0.06 billion	$0.84 billion	$3.95 billion	$0.46 billion	$5.30 billion
Inpatient Length of Stay (mean ± standard deviation)	1.8±1.8	2.3±2.2	3.2±4.5	4.9±6.9	3.1±4.4
Invasive Mechanical Ventilation	≤0.1%	1.2%	6.8%	8.6%	4.7%
ED Visits per 100,000 persons per year[A]	17.29	63.17	27.77	8.18	27.10
Inpatient Admissions per 100,000 persons per year[A]	0.50	23.34	15.50	5.68	12.46

ED: emergency department; APAP: acetaminpophen

[A] Base U.S. populations for 2006-2010 obtained from the Centers for Disease Control and Prevention, National Vital Statistics System, Vintage 2012 bridged-race post-census U.S. resident population estimates

TABLE 2. Patient Disposition of Admission or Mortality versus Treat-and-Release from APAP-Toxicity-Related Presentation to the ED, 2006-2010.

	Age 11 Years and Below (N = 42,623)		Age 12-20 Years (N = 106,725)		Age 21-64 Years (N = 246,640)		Age 65 Years and Above (N = 15,893)	
	Admission [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]
PATIENT CHARACTERISTICS								
Age	1.11** (1.03,1.19)	--	1.09*** (1.06,1.11)	1.49* (1.01,2.19)	1.01*** (1.01,1.02)	1.05*** (1.04,1.06)	1.00 (0.99,1.01)	1.09** (1.03,1.14)
Female Sex	1.01 (0.77,1.33)	--	0.97 (0.89,1.06)	1.94 (0.28,13.60)	0.90*** (0.85,0.95)	0.96 (0.76,1.22)	1.24 (0.99,1.56)	0.54 (0.25,1.15)
Payer (vs. Commercial Insurance) Medicare	--	--	0.54* (0.30,0.97)	omitted[A]	0.83** (0.75,0.92)	0.87 (0.59,1.28)	1.17 (0.49,2.78)	0.12** (0.03,0.55)
Medicaid	0.62** (0.45,0.86)	--	0.97 (0.87,1.07)	0.42 (0.09,1.85)	1.02 (0.94,1.11)	0.90 (0.64,1.27)	0.64 (0.25,1.69)	0.04** (0.01,0.28)
Other	0.58* (0.37,0.92)	--	0.86* (0.76,0.98)	0.32 (0.07,1.46)	0.90* (0.83,0.98)	0.87 (0.62,1.22)	0.31* (0.10,0.93)	omitted[A]
Income Quartile (vs. Lowest) 2nd Quartile	1.12 (0.79,1.59)	--	1.13* (1.00,1.27)	2.50 (0.21,29.40)	1.05 (0.97,1.14)	0.93 (0.67,1.28)	0.84 (0.61,1.14)	0.23* (0.07,0.74)
3rd Quartile	0.75 (0.48,1.16)	--	1.15* (1.02,1.29)	13.40* (1.59,113.21)	1.08 (0.98,1.20)	1.21 (0.86,1.69)	1.08 (0.75,1.54)	1.03 (0.32,3.24)
4th Quartile	0.90 (0.58,1.39)	--	1.24** (1.07,1.43)	omitted[A]	1.26*** (1.13,1.41)	1.20 (0.83,1.73)	1.18 (0.83,1.69)	1.76 (0.64,4.85)
Rural Residence	2.26* (1.19,4.30)	--	1.30* (1.06,1.60)	0.82 (0.18,3.78)	1.24** (1.07,1.44)	1.21 (0.72,2.03)	1.36 (0.76,2.43)	1.88 (0.44,7.97)
HOSPITAL CHARACTERISTICS								
Rural Location	0.53 (0.26,1.12)	--	0.79* (0.62,0.99)	1.48 (0.15,14.19)	0.67*** (0.56,0.80)	0.42** (0.21,0.81)	0.63 (0.35,1.14)	1.27 (0.34,4.68)
Teaching Facility	3.13*** (2.17,4.50)	--	1.55*** (1.35,1.79)	5.08 (0.82,31.72)	0.98* (0.86,1.12)	1.04 (0.79,1.37)	1.31* (1.03,1.68)	1.58 (0.68,3.66)
Region (vs. Northeast) Midwest	0.72 (0.47,1.12)	--	0.96 (0.81,1.14)	1.18 (0.11,13.16)	0.87 (0.72,1.04)	0.59* (0.40,0.90)	0.63* (0.44,0.90)	0.48 (0.16,1.45)
South	0.79 (0.51,1.22)	--	0.85 (0.72,1.02)	1.92 (0.17,21.10)	0.86 (0.72,0.99)	0.79 (0.55,1.14)	0.85 (0.61,1.18)	0.36* (0.14,0.92)
West	0.65 (0.39,1.08)	--	0.62*** (0.52,0.74)	0.39 (0.01,12.73)	0.51*** (0.43,0.59)	0.52** (0.35,0.77)	0.54** (0.38,0.77)	0.26* (0.08,0.82)
CLINICAL CHARACTERISTICS								
Congestive Heart Failure	--	--	--	--	1.48 (0.95,2.31)	1.67 (0.80,3.49)	3.36*** (2.01,5.63)	1.64 (0.55,4.87)
Valvular Disease	--	--	3.94* (1.15,13.50)	omitted[A]	4.47*** (2.70,7.40)	2.06 (0.60,7.01)	3.64** (1.67,7.92)	3.55 (0.51,24.58)
Pulmonary Circulation Disorders	--	--	--	--	2.35*	8.50**	3.70	omitted[A]

					(1.03,5.40)	(2.54,28.43)	(0.39,35.40)	
Peripheral Vascular Disorders	--	--	--	--	3.15*** (1.55,6.37)	2.64 (0.59,11.89)	2.88** (1.32,6.28)	5.77 (0.96,34.48)
Hypertension with Complications	--	--	2.46*** (1.53,3.96)	omitted[A]	2.27** (1.32,3.92)	1.66 (0.59,4.68)	5.74*** (2.32,14.21)	0.66 (0.06,6.75)
Paralysis	--	--	1.54 (0.31,7.54)	omitted[A]	3.28*** (1.90,5.65)	11.47*** (4.84,27.23)	1.75 (0.57,5.38)	1.20 (0.14,10.13)
Other Neurological Disorders	24.83*** (10.48,58.83)	--	3.14*** (2.40,4.12)	50.97*** (10.75,241.71)	2.19*** (1.95,2.47)	2.21*** (1.55,3.15)	1.97*** (1.40,2.78)	1.48 (0.67,3.27)
Chronic Pulmonary Disease	1.94 (0.95,3.96)	--	2.35*** (1.93,2.86)	omitted[A]	2.01*** (1.78,2.28)	1.29 (0.83,2.00)	3.21*** (2.27,4.54)	5.16** (1.75,15.25)
Diabetes with Complications	--	--	0.97 (0.58,1.64)	omitted[A]	4.52*** (2.55,8.01)	3.57* (1.01,12.64)	2.34 (0.62,8.88)	16.60 (0.12,225.36)
Hypothyroidism	--	--	1.04 (0.58,1.85)	omitted[A]	2.67*** (2.16,3.31)	1.52 (0.77,2.99)	2.15*** (1.43,3.24)	2.17 (0.75,6.33)
Renal Failure	--	--	2.11 (0.24,18.52)	omitted[A]	2.39*** (1.51,3.80)	3.16** (1.38,7.25)	0.50 (0.22,1.12)	1.06 (0.13,8.44)
Liver Disease	--	--	2.98* (1.03,8.64)	omitted[B]	12.13*** (5.98,24.60)	47.89*** (21.53,106.52)	omitted[B]	omitted[B]
HIV/AIDS	--	--	--	--	2.18 (0.82,5.83)	6.86* (1.35,34.92)	--	--
Lymphoma	--	--	--	--	1.43 (0.60,3.43)	4.24 (0.69,25.95)	--	--
Metastatic Cancer	--	--	--	--	6.08*** (2.22,16.67)	30.32*** (8.35,110.18)	3.18 (0.78,13.04)	1.76 (0.29,10.55)
Solid Tumor	--	--	--	--	1.97* (1.09,3.55)	5.77** (2.13,15.59)	2.41 (0.98,5.91	5.46 (0.94,31.63)
Rheumatoid Arthritis/Collagen Vascular Disease	--	--	0.80 (0.21,3.07)	omitted[A]	2.66*** (1.89,3.76)	2.28 (0.95,5.43)	3.32* (1.24,8.90)	omitted[A]
Coagulopathy	--	--	21.75*** (7.70,61.42)	178.62*** (10.96,291.11)	16.06*** (9.70,26.57)	72.42*** (39.91,131.40)	omitted[B]	omitted[B]
Obesity	--	--	6.29*** (3.95,10.01)	omitted[A]	4.96*** (3.32,6.27)	5.55*** (3.08,10.02)	5.43** (1.68,17.54)	0.10 (0.01,1.37)
Weight Loss	--	--	--	--	20.51*** (7.35,57.18)	25.74*** (7.64,86.71)	19.01** (2.50,144.65)	283.59*** (17.45,468.08)
Fluid and Electrolyte Disorders	20.75*** (9.22,46.70)	--	6.78*** (5.70,8.07)	8.91** (2.48,31.96)	7.97*** (7.09,8.96)	28.45*** (21.84,37.07)	9.77*** (6.85,13.92)	56.28*** (22.19,142.71)
Blood Loss or Deficiency Anemia	13.27** (2.65,66.38)	--	4.17*** (2.83,6.15)	omitted[A]	4.46*** (3.64,5.46)	3.34*** (2.22,5.04)	2.64*** (1.72,4.04)	0.15 (0.01,4.35)
Alcohol Abuse	--	--	2.32*** (1.94,2.77)	1.16 (0.09,14.53)	2.53*** (2.33,2.75)	1.75*** (1.34,2.29)	2.96*** (1.76,4.95)	3.27 (0.71,15.09)
Drug Abuse	--	--	2.02*** (1.77,2.30)	3.02 (0.59,15.37)	2.37*** (2.17,2.59)	1.58** (1.17,2.13)	1.71 (0.96,3.04)	0.59 (0.06,5.44)
Psychoses	--	--	5.13*** (4.48,5.89)	4.46 (0.91,21.85)	4.44*** (4.00,4.93)	1.42 (1.00,2.03)	6.41*** (3.88,10.57)	6.46 (0.84,49.84)
Depression	--	--	1.71***	3.46	1.75***	1.10	1.95***	1.88

			(1.55,1.88)	(0.94,12.70)	(1.62,1.89)	(0.82,1.48)	(1.44,2.64)	(0.79,4.49)
Intentional Self-Harm	--	--	3.40*** (3.07,3.77)	omitted[B]	3.03*** (2.81,3.26)	1.69*** (1.30,2.21)	4.89*** (3.59,6.64)	8.57*** (3.97,18.49)
CALENDAR YEAR								
2007 (vs. 2006)	0.78 (0.48,1.28)	--	0.92 (0.80,1.06)	0.95 (0.17,5.34)	0.99 (0.88,1.11)	1.01 (0.69,1.49)	1.29 (0.92,1.81)	1.97 (0.39,9.87)
2008 (vs. 2006)	0.79 (0.49,1.26)	--	0.79** (0.68,0.92)	0.65 (0.07,5.73)	0.82** (0.72,0.94)	0.82 (0.56,1.21)	0.94 (0.67,1.32)	3.13 (0.96,10.19)
2009 (vs. 2006)	0.67 (0.40,1.11)	--	0.84* (0.72,0.98)	0.30 (0.03,3.17)	0.87 (0.77,1.00)	0.58* (0.38,0.88)	0.79 (0.55,1.13)	2.23 (0.65,7.64)
2010 (vs. 2006)	0.74 (0.45,1.22)	--	0.88 (0.74,1.03)	0.56 (0.06,5.18)	0.83** (0.73,0.95)	0.78 (0.53,1.13)	1.03 (0.74,1.45)	2.57 (0.72,9.18)

ED: emergency department; RRR = relative risk ratio
omitted[A] = variable omitted due to near-perfect association with survival (i.e., OR <0.01)
omitted[B] = variable omitted due to near-perfect association with mortality (i.e., RRR>10000)
'- -' = variable omitted due to small sample size (n≤0.1%)
*** statistically significant at p<0.001
** statistically significant at p<0.01
* statistically significant at p<0.05

TABLE 3. Invasive Mechanical Ventilation among APAP-Toxicity-Related Cases Presenting to the ED According to Age Category, 2006-2010.

	Age 11 Years and Below (N = 42,623)	**Age 12-20 Years** (N = 106,725)	**Age 21-64 Years** (N = 246,640)	**Age 65 Years and Above** (N = 15,893)
	Invasive Mechanical Ventilation [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]
PATIENT CHARACTERISTICS				
Age	--	1.26* (1.16,1.36)	1.03* (1.02,1.03)	0.96* (0.95,0.98)
Female Sex	--	0.46* (0.35,0.60)	0.85* (0.78,0.92)	1.12 (0.84,1.50)
Payer (vs. Commercial Insurance) Medicare	--	0.62 (0.15,2.58)	0.82* (0.72,0.95)	1.03 (0.37,2.84)
Medicaid	--	0.92 (0.67,1.28)	1.05 (0.94,1.17)	1.52 (0.52,4.45)
Other	--	1.01 (0.71,1.43)	0.78* (0.70,0.87)	0.46 (0.12,1.79)
Income Quartile (vs. Lowest) 2nd Quartile	--	0.92 (0.63,1.35)	1.10 (0.99,1.23)	1.12 (0.76,1.65)
3rd Quartile	--	0.92 (0.62,1.37)	1.23* (1.08,1.39)	1.01 (0.69,1.48)
4th Quartile	--	0.92 (0.61,1.40)	1.08 (0.95,1.24)	0.91 (0.58,1.41)
Rural Residence	--	1.96 (0.97,3.99)	1.25 (1.01,1.55)	1.07 (0.55,2.10)
HOSPITAL CHARACTERISTICS				
Rural Location	--	0.38* (0.16,0.91)	0.61* (0.47,0.77)	0.57 (0.26,1.26)
Teaching Facility	--	1.51* (1.12,2.03)	1.10 (0.98,1.22)	1.27 (0.95,1.71)
Region (vs. Northeast) Midwest	--	0.79 (0.53,1.18)	0.87 (0.75,1.01)	0.88 (0.56,1.36)
South	--	0.77 (0.51,1.17)	0.99 (0.86,1.15)	0.90 (0.59,1.36)
West	--	0.72 (0.45,1.13)	0.94 (0.81,1.08)	0.90 (0.57,1.42)
CLINICAL CHARACTERISTICS				
Congestive Heart Failure	--	--	1.61* (1.17,2.21)	1.39 (0.86,2.25)
Valvular Disease	--	8.31* (1.91,36.10)	1.12 (0.78,1.62)	0.77 (0.35,1.73)

Pulmonary Circulation Disorders	--	--	2.66* (1.46,4.86)	0.83 (0.27,2.53)
Peripheral Vascular Disorders	--	--	1.25 (0.70,2.21)	1.06 (0.56,2.02)
Hypertension with Complications	--	2.48* (1.11,5.56)	0.86 (0.54,1.36)	2.01 (0.91,4.45)
Paralysis	--	omitted[A]	1.95* (1.29,2.94)	0.26 (0.03,2.25)
Other Neurological Disorders	--	7.11* (5.00,10.11)	1.88* (1.66,2.13)	1.10 (0.76,1.60)
Chronic Pulmonary Disease	--	1.79* (1.09,2.92)	1.34* (1.18,1.51)	1.75* (1.26,2.44)
Diabetes with Complications	--	0.79 (0.13,4.81)	0.91 (0.56,1.46)	0.62 (0.21,1.79)
Hypothyroidism	--	0.87 (0.25,3.09)	0.91 (0.75,1.11)	0.56* (0.35,0.89)
Renal Failure	--	1.78 (0.18,17.95)	1.25 (0.82,1.92)	0.42 (0.19,0.94)
Liver Disease	--	2.49 (0.44,14.03)	2.23* (1.77,2.81)	2.47* (1.17,5.21)
AIDS	--	--	2.11* (1.23,3.60)	--
Lymphoma	--	--	1.93 (0.84,4.40)	--
Metastatic Cancer	--	--	1.68 (0.79,3.59)	0.47 (0.09,2.47)
Solid Tumor	--	--	0.68 (0.32,1.44)	0.27 (0.06,1.22)
Rheumatoid Arthritis/Collagen Vascular Disease	--	omitted[A]	1.59* (1.18,2.14)	0.48 (0.18,1.25)
Coagulopathy	--	2.58* (1.13,5.89)	2.48* (2.10,2.94)	2.17* (1.27,3.70)
Obesity	--	0.98 (0.29,3.29)	1.11 (0.91,1.36)	0.49 (0.17,1.35)
Weight Loss/Cachexia	--	--	1.90* (1.43,2.53)	1.92* (1.13,3.28)
Fluid and Electrolyte Disorders	--	5.84* (4.26,8.00)	4.08* (3.75,4.43)	2.26* (1.71,3.00)
Blood Loss or Deficiency Anemia	--	2.07* (1.33,3.97)	1.36* (1.17,1.58)	1.15 (0.79,1.67)
Alcohol Abuse	--	1.90* (1.34,2.71)	1.26* (1.16,1.37)	0.78 (0.47,1.29)
Drug Abuse	--	1.50* (1.10,2.04)	1.16* (1.06,1.27)	0.62 (0.32,1.18)
Psychoses	--	1.62* (1.12,2.35)	1.51* (1.37,1.67)	1.28 (0.91,1.80)

Depression	--	1.10 (0.81,1.49)	1.04 (0.95,1.14)	0.87 (0.61,1.23)
Intentional Self-Harm	--	1.34 (0.96,1.87)	1.49* (1.35,1.63)	2.42* (1.80,3.25)
CALENDAR YEAR				
2007 (vs. 2006)	--	0.99 (0.64,1.55)	0.99 (0.86,1.14)	1.02 (0.63,1.67)
2008 (vs. 2006)	--	0.98 (0.64,1.51)	1.05 (0.92,1.20)	0.81 (0.53,1.25)
2009 (vs. 2006)	--	0.94 (0.60,1.48)	0.92 (0.81,1.05)	1.07 (0.69,1.65)
2010 (vs. 2006)	--	0.96 (0.63,1.46)	0.95 (0.83,1.10)	1.12 (0.73,1.71)

OR = odds ratio; CI = confidence interval

omitted[A] = variable omitted due to near-perfect association with no requirement of intubation (i.e., OR <0.01)

'- -' = variable omitted due to small sample size (n≤0.1%)

* Statistically significant below the computed Simes (1986) false discovery rate p-value (p<0.036)

TABLE 4. Total Charges and Inpatient Length of Stay among APAP-Toxicity-Related Cases Presenting to the ED According to Age Category, 2006-2010.

	Age 11 Years and Below (N = 42,623)		Age 12-20 Years (N = 106,725)		Age 21-64 Years (N = 246,640)		Age 65 Years and Above (N = 15,893)	
	Charges [*exp(b)*,95th CI]	**LoS** [*IR*,95th CI]	**Charges** [*exp*(b),95th CI]	**LoS** [*IR*,95th CI]	**Charges** [*exp(b)*,95th CI]	**LoS** [*IR*,95th CI]	**Charges** [*exp(b)*,95th CI]	**LoS** [*IR*,95th CI]
PATIENT CHARACTERISTICS								
Age	1.04* (1.01,1.07)	1.03 (0.99,1.07)	1.05* (1.04,1.06)	0.99 (0.98,1.01)	1.01* (1.01,1.01)	1.01* (1.01,1.01)	1.00 (1.00,1.01)	1.01 (1.00,1.01)
Female Sex	0.94 (0.86,1.02)	1.07 (0.88,1.31)	0.97 (0.93,1.01)	1.00 (0.95,1.05)	0.96* (0.93,0.98)	0.97* (0.94,0.99)	0.91 (0.83,1.01)	0.94 (0.85,1.03)
Payer (vs. Commercial) Medicare	--	--	0.93 (0.65,1.33)	1.55 (0.90,2.65)	0.98 (0.94,1.03)	1.01 (0.96,1.06)	1.14 (0.83,1.56)	1.18 (0.81,1.72)
Medicaid	0.81* (0.71,0.92)	0.96 (0.79,1.16)	0.92* (0.87,0.96)	0.94* (0.89,0.98)	0.96* (0.93,0.98)	0.86* (0.83,0.91)	0.92 (0.65,1.31)	1.12 (0.74,1.69)
Other	0.89 (0.71,1.05)	1.08 (0.75,1.55)	0.87* (0.82,0.92)	0.92* (0.87,0.98)	0.97 (0.94,1.01)	0.94* (0.90,0.98)	0.56* (0.36,0.86)	0.93 (0.58,1.49)
Income Quartile (vs. Lowest) 2nd Quartile	1.06 (0.95,1.18)	1.27 (0.97,1.66)	1.04 (0.98,1.10)	1.05 (0.99,1.11)	1.01 (0.97,1.04)	0.99 (0.95,1.02)	0.98 (0.86,1.11)	0.99 (0.88,1.12)
3rd Quartile	1.06 (0.88,1.28)	1.33 (0.95,1.88)	1.03 (0.97,1.10)	1.05 (0.98,1.12)	1.01 (0.96,1.06)	1.00 (0.95,1.05)	0.99 (0.87,1.14)	0.92 (0.81,1.04)
4th Quartile	0.95 (0.79,1.14)	1.28 (0.97,1.68)	1.03 (0.95,1.12)	1.00 (0.93,1.07)	1.09* (1.02,1.17)	0.99 (0.94,1.04)	1.13 (0.96,1.33)	0.95 (0.85,1.09)
Rural Residence	1.19 (0.97,1.45)	1.12 (0.71,1.75)	1.00 (0.92,1.08)	0.96 (0.86,1.07)	1.03 (0.96,1.10)	1.01 (0.94,1.09)	0.93 (0.75,1.14)	1.06 (0.88,1.27)
HOSPITAL CHARACTERISTICS								
Rural Location	0.68* (0.55,0.87)	0.86 (0.52,1.43)	0.73* (0.66,0.81)	0.80* (0.71,0.91)	0.66* (0.60,0.72)	0.76* (0.69,0.83)	0.52* (0.42,0.66)	0.67* (0.54,0.82)
Teaching Facility	1.28* (1.10,1.49)	1.23 (0.98,1.54)	1.14* (1.06,1.24)	1.03 (0.96,1.10)	1.06 (0.99,1.13)	1.09* (1.05,1.15)	0.95 (0.84,1.07)	1.02 (0.93,1.13)
Region (vs. Northeast) Midwest	0.74* (0.64,0.87)	0.72* (0.55,0.95)	0.78* (0.71,0.86)	0.83* (0.76,0.90)	0.71* (0.65,0.78)	0.79* (0.73,0.85)	0.72* (0.61,0.85)	0.74* (0.66,0.83)
South	0.89 (0.76,1.05)	0.91 (0.68,1.23)	0.88* (0.79,0.98)	0.91* (0.85,0.97)	0.87* (0.79,0.97)	0.90* (0.85,0.96)	0.88 (0.75,1.04)	0.85* (0.75,0.96)
West	0.35* (0.27,0.45)	0.71* (0.54,0.95)	0.64* (0.57,0.73)	0.76* (0.71,0.82)	0.78* (0.70,0.86)	0.82* (0.77,0.87)	0.85 (0.71,1.02)	0.74* (0.65,0.83)
CLINICAL CHARACTERISTICS								
Congestive Heart Failure	--	--	--	--	1.52* (1.30,1.78)	1.31* (1.14,1.50)	1.39* (1.23,1.59)	1.25* (1.12,1.40)
Valvular Disease	--	--	1.36 (0.94,1.96)	0.99 (0.68,1.44)	1.42* (1.23,1.63)	1.06 (0.95,1.18)	1.56* (1.26,1.94)	1.08 (0.91,1.29)
Pulmonary Circulation Disorders	--	--	--	--	1.90* (1.45,2.47)	1.45* (1.19,1.77)	1.27 (0.89,1.81)	1.10 (0.79,1.54)

Peripheral Vascular Disorders	--	--	--	--	1.81* (1.47,2.23)	1.40* (1.12,1.74)	1.18 (0.98,1.42)	1.01 (0.85,1.19)
Hypertension with Complications	--	--	1.51* (1.28,1.79)	1.35* (1.17,1.56)	1.43* (1.19,1.71)	1.23* (1.05,1.45)	1.50* (1.23,1.84)	1.17 (0.99,1.37)
Paralysis	--	--	1.79 (1.03,3.09)	1.02 (0.70,1.48)	1.60* (1.32,1.94)	1.39* (1.19,1.63)	1.94* (1.12,3.36)	2.24 (1.08,4.62)
Other Neurological Disorders	7.00* (2.80,17.49)	1.41 (1.02,1.96)	1.61* (1.45,1.78)	1.05 (0.94,1.17)	1.29* (1.24,1.34)	1.00 (0.97,1.04)	1.15* (1.03,1.29)	1.01 (0.90,1.13)
Chronic Pulmonary Disease	0.98 (0.80,1.20)	0.81 (0.61,1.08)	1.18* (1.11,1.26)	0.97 (0.91,1.04)	1.20* (1.15,1.26)	1.02 (0.98,1.07)	1.37* (1.23,1.52)	1.03 (0.94,1.12)
Diabetes with Complications	--	--	1.02 (0.86,1.20)	0.90 (0.74,1.11)	1.27* (1.11,1.45)	1.07 (0.95,1.22)	1.60 (0.97,2.66)	1.07 (0.79,1.46)
Hypothyroidism	--	--	1.31 (1.00,1.72)	1.39* (1.08,1.79)	1.23* (1.15,1.31)	1.01 (0.94,1.08)	1.12 (1.00,1.25)	0.89 (0.81,0.99)
Renal Failure	--	--	1.41 (0.84,2.37)	0.88 (0.51,1.51)	1.43* (1.23,1.67)	1.16 (1.00,1.33)	1.03 (0.82,1.29)	0.99 (0.80,1.22)
Liver Disease	--	--	1.76* (1.30,2.39)	1.53* (1.15,2.03)	2.00* (1.80,2.23)	1.52* (1.39,1.67)	2.34* (1.66,3.31)	1.52* (1.19,1.95)
HIV/AIDS	--	--	--	--	1.56* (1.18,2.06)	1.30* (1.12,1.52)	--	--
Lymphoma	--	--	--	--	1.16 (0.86,1.57)	1.02 (0.78,1.34)	--	--
Metastatic Cancer	--	--	--	--	1.64* (1.16,2.31)	1.48* (1.07,2.03)	1.38 (0.89,2.15)	1.06 (0.64,1.76)
Solid Tumor	--	--	--	--	1.23 (0.97,1.56)	1.12 (0.92,1.36)	1.02 (0.84,1.24)	0.88 (0.72,1.08)
Rheumatoid Arthritis/Collagen Vascular Disease	--	--	0.71 (0.38,1.32)	0.84 (0.41,1.72)	1.34* (1.21,1.49)	1.12 (1.00,1.25)	1.33* (1.07,1.64)	1.02 (0.83,1.25)
Coagulopathy	--	--	3.04* (2.46,3.78)	1.98* (1.63,2.41)	2.08* (1.91,2.26)	1.48* (1.39,1.59)	1.54* (1.26,1.89)	1.12 (0.92,1.36)
Obesity	--	--	1.58* (1.40,1.79)	1.14 (1.01,1.28)	1.39* (1.31,1.48)	1.11 (1.01,1.22)	1.18 (0.96,1.44)	0.95 (0.76,1.20)
Weight Loss/Cachexia	--	--	--	--	1.99* (1.63,2.42)	1.83* (1.58,2.13)	1.68* (1.32,2.16)	1.58* (1.31,1.89)
Fluid and Electrolyte Disorders	6.46* (3.26,12.81)	1.93* (1.34,2.80)	1.95* (1.84,2.08)	1.04 (0.99,1.09)	1.82* (1.76,1.88)	1.16* (1.13,1.20)	1.81* (1.62,2.02)	1.18* (1.08,1.28)
Blood Loss or Deficiency Anemia	3.02* (1.67,5.47)	1.28 (0.74,2.19)	1.67* (1.43,1.94)	1.20* (1.07,1.36)	1.64* (1.55,1.74)	1.27* (1.17,1.37)	1.40* (1.23,1.59)	1.11 (1.00,1.23)
Alcohol Abuse	--	--	1.23* (1.14,1.31)	1.01 (0.95,1.08)	1.24* (1.21,1.27)	0.98 (0.95,1.01)	1.19* (1.06,1.34)	1.01 (0.88,1.15)
Drug Abuse	--	--	1.19* (1.13,1.20)	1.11* (1.05,1.19)	1.30* (1.26,1.34)	1.11* (1.08,1.15)	1.16 (0.99,1.36)	1.09 (0.95,1.24)
Psychoses	--	--	1.65* (1.57,1.74)	1.01 (0.95,1.08)	1.50* (1.46,1.55)	1.02 (0.98,1.07)	1.50* (1.33,1.70)	1.27* (1.13,1.43)
Depression	--	--	1.27* (1.22,1.33)	0.87* (0.83,0.92)	1.19* (1.16,1.23)	0.84* (0.82,0.87)	1.22* (1.10,1.35)	0.90* (0.83,0.98)

Intentional Self-Harm	--	--	1.40* (1.33,1.49)	1.16* (1.09,1.23)	1.17* (1.13,1.21)	1.09* (1.05,1.13)	1.16* (1.06,1.28)	1.02 (0.94,1.11)
Invasive Mechanical Ventilation	--	--	3.21* (2.84,3.63)	1.60* (1.41,1.82)	3.37* (3.20,3.55)	1.57* (1.50,1.64)	1.39* (1.23,1.59)	1.57* (1.39,1.78)
CALENDAR YEAR								
2007 (vs. 2006)	0.95 (0.80,1.13)	1.12 (0.85,1.47)	0.99 (0.91,1.08)	1.02 (0.95,1.09)	1.04 (0.98,1.10)	1.03 (0.98,1.08)	1.06 (0.90,1.24)	1.01 (0.87,1.17)
2008 (vs. 2006)	1.04 (0.84,1.28)	0.91 (0.68,1.23)	0.99 (0.91,1.08)	0.99 (0.92,1.07)	1.03 (0.97,1.09)	1.03 (0.98,1.07)	1.02 (0.87,1.20)	0.97 (0.85,1.10)
2009 (vs. 2006)	1.01 (0.84,1.22)	0.91 (0.69,1.22)	1.04 (0.96,1.13)	1.01 (0.94,1.09)	1.06 (1.00,1.12)	0.98 (0.93,1.03)	0.97 (0.83,1.12)	0.90 (0.79,1.02)
2010 (vs. 2006)	1.16 (0.97,1.39)	0.89 (0.69,1.15)	1.08 (1.00,1.18)	0.96 (0.90,1.03)	1.07* (1.01,1.14)	0.97 (0.93,1.02)	1.09 (0.93,1.27)	0.94 (0.83,1.07)

exp(b)= exponentiated beta coefficient; IR = incidence ratio; LoS = length of stay; CI = confidence interval

'- -' = variable omitted due to small sample size (n≤0.1%)

* Statistically significant below the computed Simes (1986) false discovery rate p-value for charges (p<0.036) and length of stay (p<0.024)

Figure 1. U.S. Food and Drug Administration Sequence of Updates concerning Acetaminophen

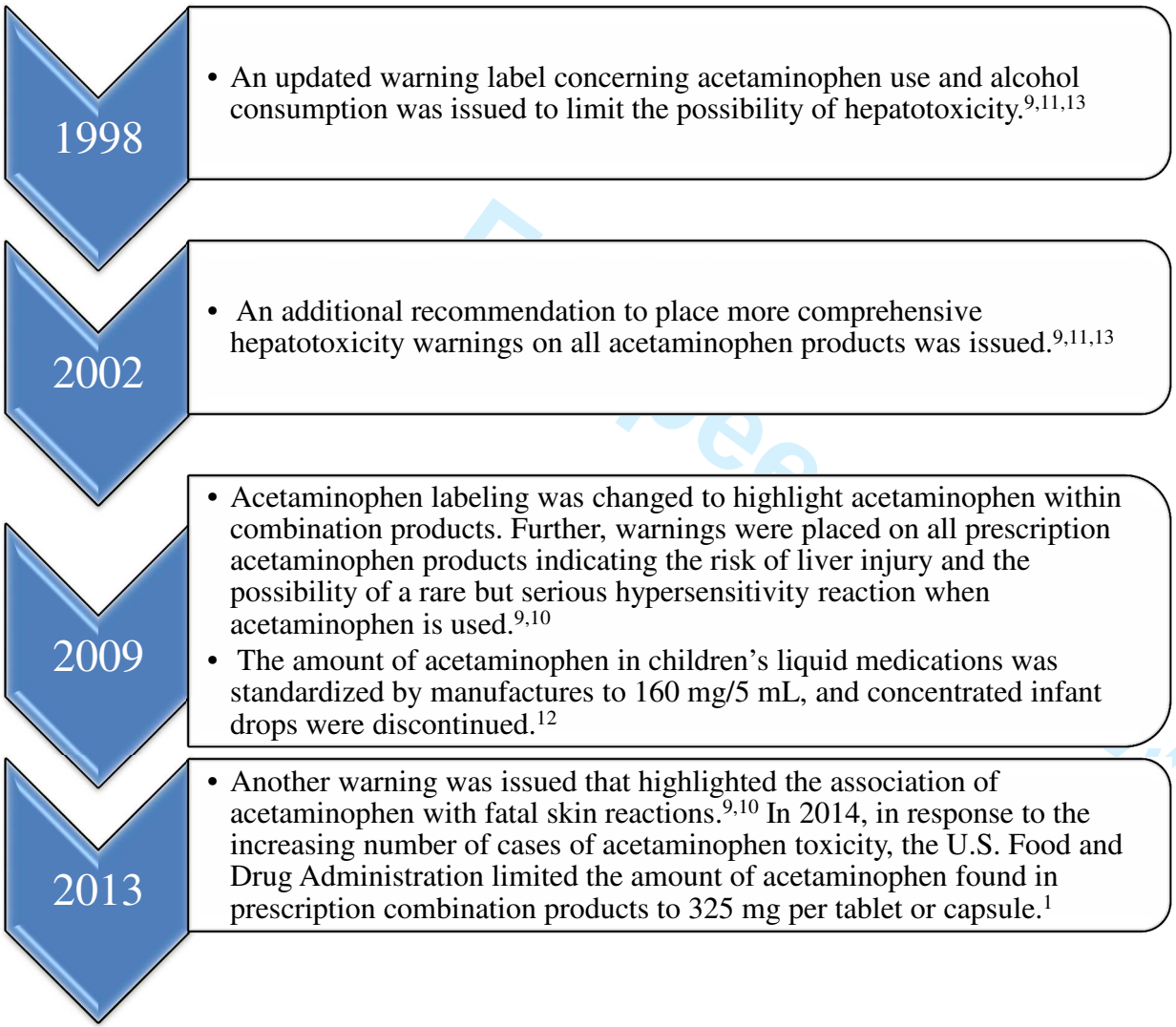


Figure 2. Overall Number of APAP toxicity-related ED Cases According to Age, 2006-2010.

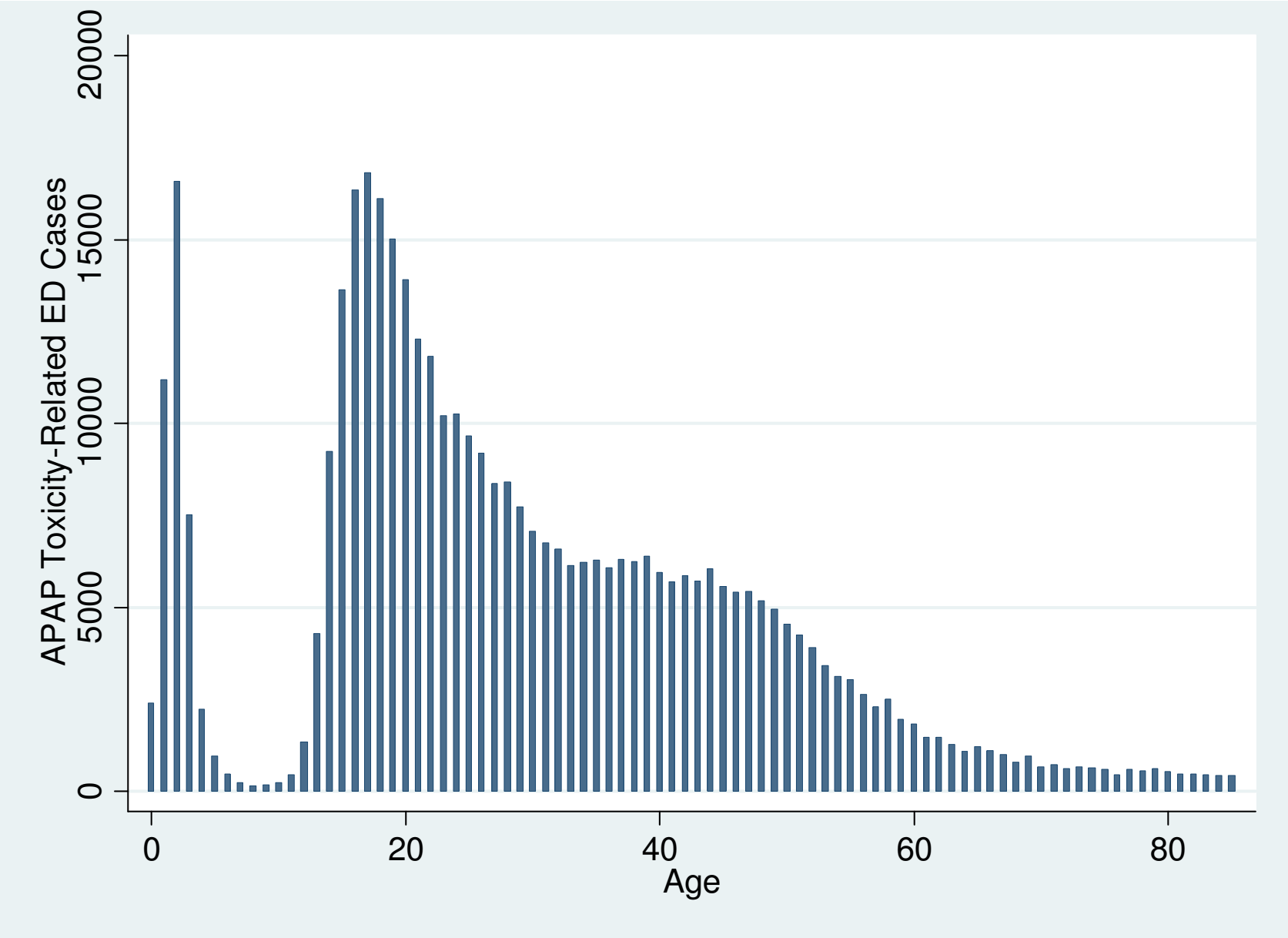
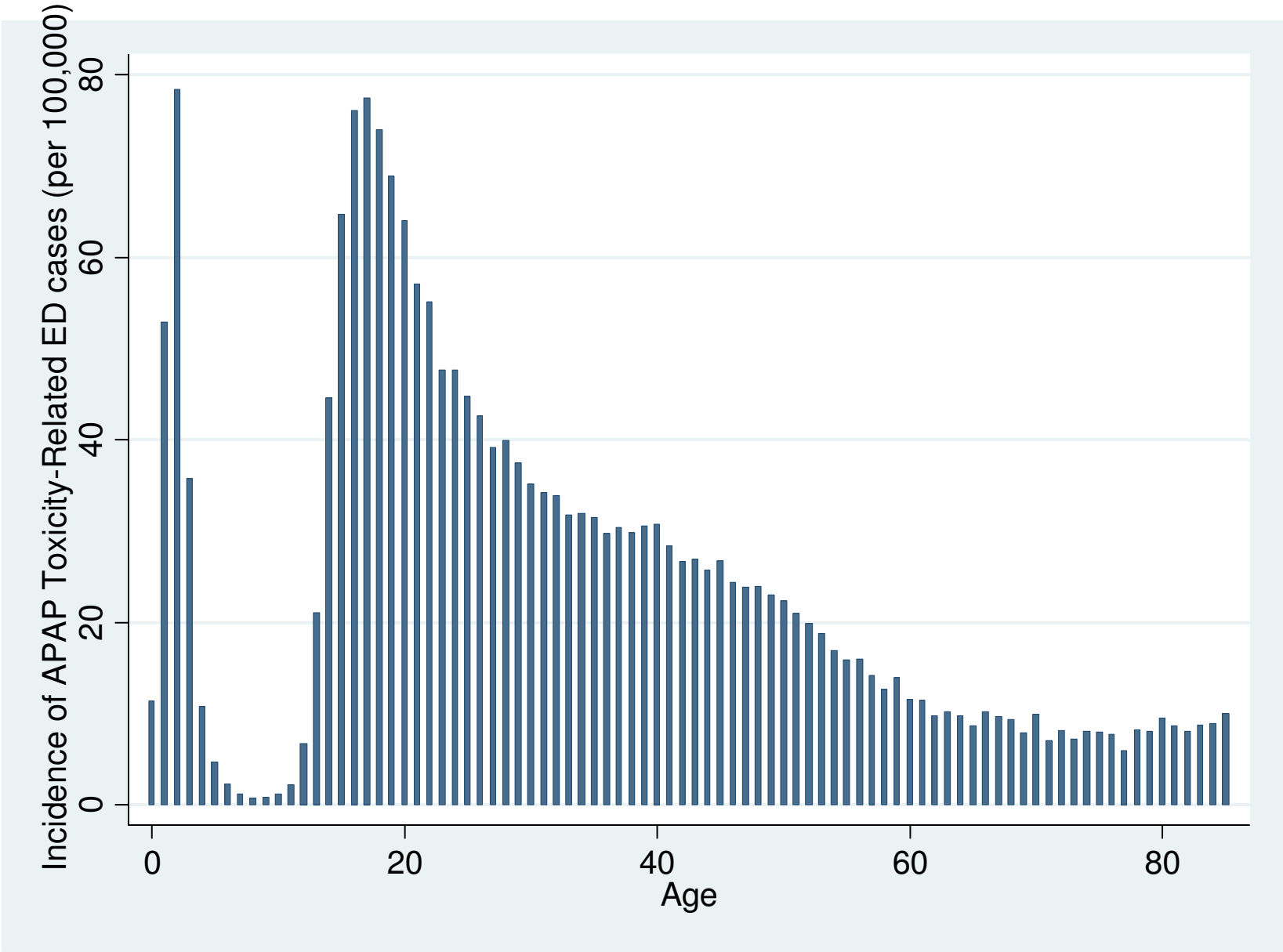
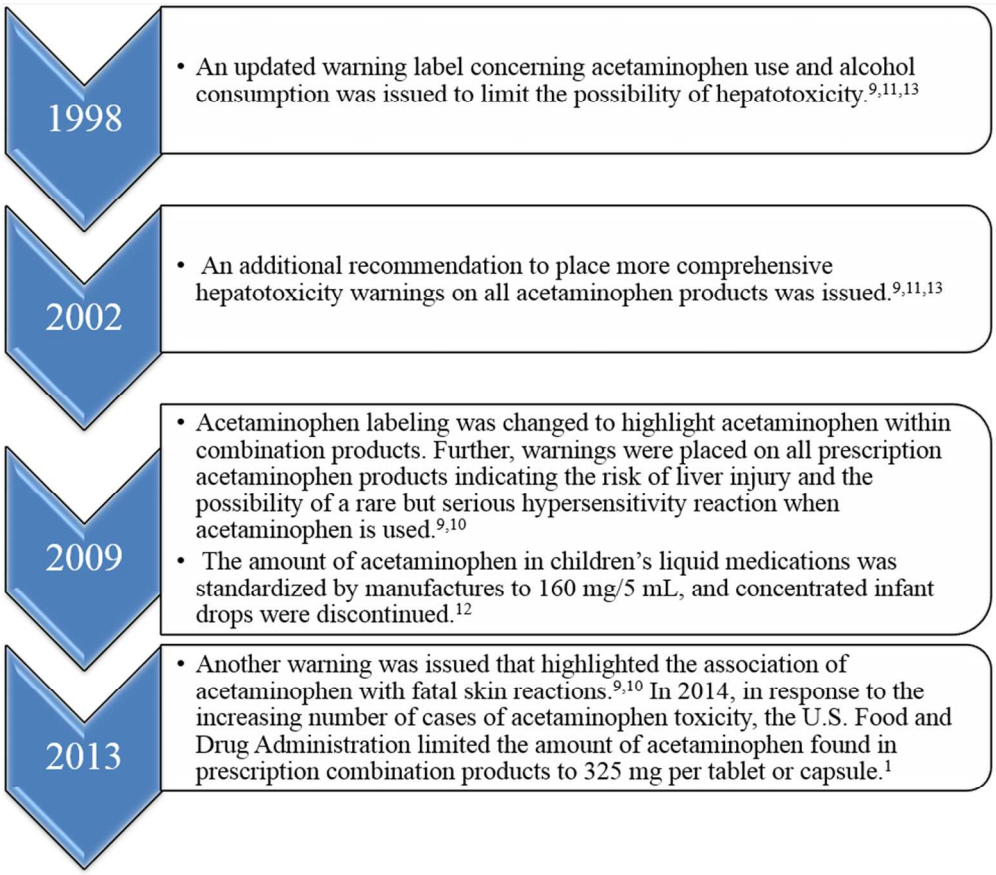


Figure 3. Age-Adjusted of APAP toxicity-related ED Cases per 100,000 U.S. Population, 2006-2010.[A]



[A] Base U.S. populations for 2006-2010 obtained from the Centers for Disease Control and Prevention, National Vital Statistics System, Vintage 2012 bridged-race post-census U.S. resident population estimates



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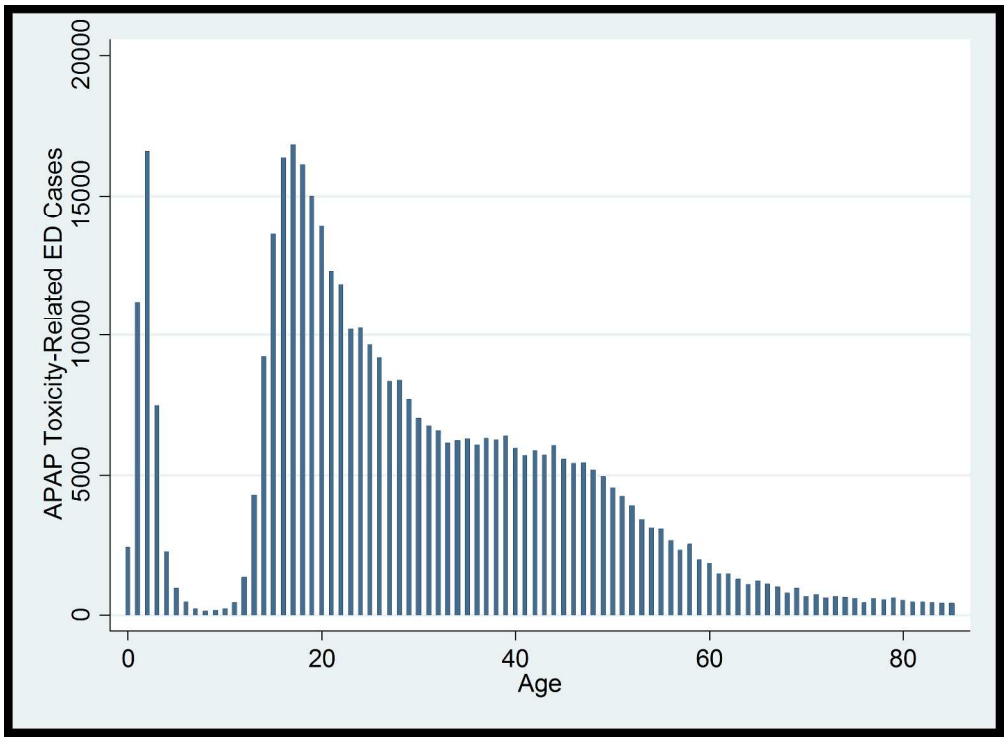

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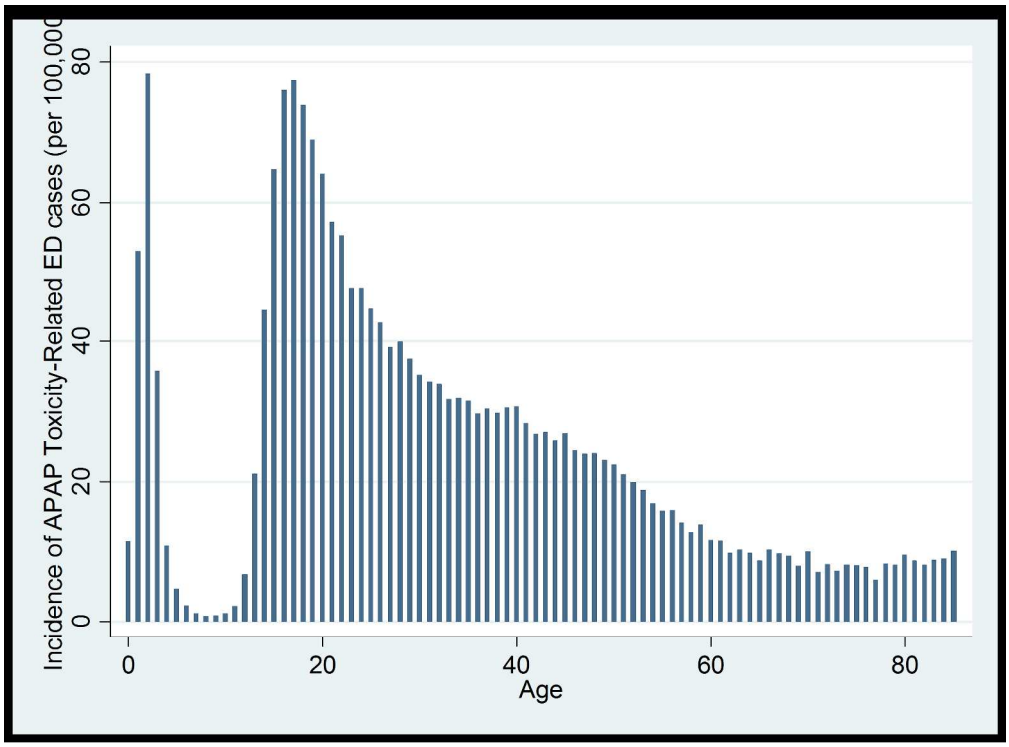

890x655mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	None conducted
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7; Tables 1-4
		(b) Give reasons for non-participation at each stage	6-7; Tables 1-4
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-4
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 (descriptives); Table 2-4 (multivariable analysis)
		(*b*) Report category boundaries when continuous variables were categorized	6-7; Tables 1-4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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CLINICAL AND ECONOMIC CHARACTERISTICS OF EMERGENCY DEPARTMENT VISITS DUE TO ACETAMINOPHEN TOXICITY IN THE UNITED STATES

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CLINICAL AND ECONOMIC CHARACTERISTICS OF EMERGENCY DEPARTMENT VISITS DUE TO ACETAMINOPHEN TOXICITY IN THE UNITED STATES

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Preliminary findings of this study were presented as a plenary presentation at The Western States Conference for Pharmacy Residents, Fellows, Preceptors and Sponsors, May 21-24, 2012, Pacific Grove, California, USA, and as a poster at the American Society of Health-System Pharmacists ASHP Summer Meeting and Exhibition, May 31-June 4, 2014, Las Vegas, Nevada, USA.

ABSTRACT

Objectives: To estimate the number of acetaminophen (APAP) toxicity-related emergency department (ED) visits and to assess their associated clinical and economic burden in the U.S. from 2006-2010.

Design: Cross-sectional, retrospective, large-scale database study.

Setting: Non-federal, non-rehabilitation, community emergency departments in the U.S.

Participants: Inclusion criteria included any-listed diagnosis identifying poisoning by aromatic analgesics paracetamol/acetaminophen or associated supplementary code. Generalized linear models were used to investigate the association between outcomes of inpatient admission, mortality, requirement of invasive mechanical ventilation, charges, and inpatient lengths of stay based upon patient, hospital, and clinical characteristics.

Results: Across the 625.2 million ED visits in the U.S. from 2006-2010, 411,811 APAP-related toxicity ED visits were observed, with 45.5% resulting in inpatient admission, 4.7% requiring invasive mechanical ventilation, and 0.6% involving death. The incidence proportion was 27.10 per 100,000 U.S. population overall, exceeding 70 per 100,000 at age 2 and ages 16-18. The

total national bill was $1.06 billion per year (USD 2014), and predominantly involved females (65.5%) and intentional self-harm (58.4%), which were notably higher within the 12-20 age category (female$_{12\text{-}20\ years}$=74.8%, intentional self-harm$_{12\text{-}20\ years}$=71.4%). Behavioral and mental health comorbidities were relatively common and associated with an increased relative risk of admission and likelihood of charges almost entirely across all age categories of ≥12 years within the multivariable analyses. The number of ED visits did not appreciably change over time, decreasing by <2% from 2006 to 2010 (n=1,351). Multivariable results also suggested no consistent change in outcomes across the study's time horizon.

Conclusions: A substantial public health impact of APAP toxicity-related cases was observed in the U.S. from 2006-2010, with incidence proportions peaking at age 2 and ages 16-18. After controlling for numerous factors, no consistent change was observed over the five-year time horizon concerning outcomes of admission, mortality, invasive mechanical ventilation, charges, or length of stay.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study draws upon an estimated 130 million ED visits per year within the U.S. to report national estimates of case incidence and to provide assessments of clinical and economic outcomes.
- No specific categorization existed to classify cases as being unsupervised ingestions or therapeutic misadventures (e.g., overuse, medication errors), the type of APAP product consumed (e.g., single-agent, combination products, tablets, liquid), and the amount ingested or serum levels observed.

- The use of n-acetyl cysteine (NAS) or gastric decontamination was also not consistently captured within the dataset, nor was a designation of acute liver injury directly attributable to acetaminophen (APAP) toxicity.

INTRODUCTION

As one of the most frequently-used analgesic and antipyretics worldwide, acetaminophen (APAP) is a common single or combination agent within numerous over-the-counter (OTC) and prescription products.[1] Though considered generally safe at approved doses, APAP has a known and established toxicity pattern at higher doses.[2] Of all pharmaceuticals involved in human overdoses, analgesics are considered the most frequently involved.[2] U.S. poison center data indicate that APAP combinations were associated with the fourth highest number of fatalities compared to other medications in 2012, with APAP overdose being principal cause of toxic drug ingestion that ultimately contributed to 39% of all acute liver failures.[2,3] Hepatotoxicity is a well-recognized adverse event associated with APAP overdose that may result in liver failure and death.[4] The percentage of APAP-induced acute liver failure cases increased from 28% in 1998 to 51% in 2003, establishing this medication as the most common cause of acute liver failure in the U.S.[4] Overall, previous studies have suggested that APAP overdoses leads annually to 56,000-78,000 emergency department (ED) visits, 26,000-34,000 hospitalizations, and an estimated 500 deaths.[5-8]

The U.S. Food and Drug Administration (FDA) has issued several updates in recent years involving APAP to increase the safety and limit the toxicity associated with use of the medication, presented in Figure 1.[9-13]

<FIGURE 1>

Given the aforementioned, the overall purpose of this investigation was to estimate the number of APAP toxicity-related ED visits and to assess their associated clinical and economic burden in the U.S. from 2006-2010. More specifically, the objectives were to assess the relationships between outcomes of inpatient admission, mortality, requirement of invasive mechanical ventilation, charges, and inpatient lengths of stay based upon patient, hospital, and clinical characteristics.

METHODS

This cross-sectional, retrospective investigation utilized 2006-2010 Nationwide Emergency Department Sample (NEDS) from the Agency for Healthcare Research and Quality (AHRQ).[14] These data comprise nationally-representative case presentations across hospital-based EDs within non-federal, non-rehabilitation, community facilities and generalizing, overall, to approximately 130 million ED visits that occur in the U.S. per year.[14] Given the fully de-identified and anonymized, this research is classified as exempt via human subjects protection.[14]

Consistent with previous research, ED visits involving APAP toxicity were identified based on the inclusion criteria of any-listed diagnosis according to International Classification of Disease, 9th edition, Clinical Manifestations (ICD-9-CM) codes identifying poisoning by aromatic analgesics paracetamol/acetaminophen (i.e., 965.4) or associated supplementary code (i.e., E850.4: accidental poisoning by aromatic analgesics paracetamol/acetaminophen).[5-8,15,16] Previous research has addressed the challenges in the sensitivity and specificity of utilizing diagnosis or supplementary codes to identify acetaminophen toxicity-related cases, suggesting that the use of these aforementioned codes remains a valid approach.[15] All ages were investigated and stratified according to the following age categories: A) 0-11 years; B) 12-20 years; C) 21-64 years; and ≥65 years.

Clinical outcomes assessed were admission to an inpatient setting from the ED, mortality, and requirement of invasive mechanical ventilation (i.e., as a proxy for acute respiratory distress syndrome and supportive care measures associated with APAP toxicity disease progression or acute liver failure).[17,18] Economic outcomes analyzed involved inflation-adjusted charges (USD 2014) and inpatient length of stay. Independent predictor variables analyzed were patient demographics (i.e., age category, sex, income quartile, age, primary payer, rural location defined by communities ≤50,000 residents), ED and hospital characteristics (geographic region, urban/rural location, teaching status), clinical case-mix disease severity measured via Elixhauser comorbidities (a validated case-mix risk severity measure comprised of 30 disease states), designation of intentional self-harm, and year (2006-2010).[14,19] Notably, if any given Elixhauser comorbidity was observed in <0. 1% of cases within any age category, it was omitted to allow for appropriate statistical inference; peptic ulcer disease with bleeding was consistently observed to be <0. 1% of cases and summarily removed from the study.[6,7]

Multivariable analyses for outcomes of admission to an inpatient setting from the ED and mortality were conducted using a multinomial logit regression, specifying treat-and-release ED cases as a baseline comparator.[20,21] The requirement of invasive mechanical ventilation was analyzed via a logistic regression. Generalized linear models were used to analyze inflation-adjusted charges and inpatient length of stay, specified by a gamma distribution with log link and negative binomial distribution with log link, respectively.[21] Accordingly, results may be interpreted generally as relative risk measures, superficially as: a relative risk ratio (RRR) in a multinomial regression; an odds ratio (OR) in a logistic regression; an exponentiated beta value (exp(b)) in a gamma regression; and an incidence ratio (IR) in a negative binomial regression.[21]

Therein, estimated coefficients may be interpreted as suggesting a reduced likelihood (<1.00), suggesting no difference in likelihood (=1.00), and suggesting an increased likelihood (>1.00).

The Simes (1986) procedure to control for false discovery rates was used to control for multiple comparisons across age categories within the analysis of invasive mechanical ventilation, charges, and length of stay, yielding critical p-values for significance of 0.028, 0.036, and 0.024, respectively.[22] Inherently controlling for multiple comparisons by definition, the multinomial regression of disposition from the ED used an alpha level of 0.05 for significance and established treat-and-release cases as the baseline comparator. Due to the complex nature of sampling employed by the NEDS, Taylor-series weighting procedures were incorporated to yield national estimates.[14] All analyses were conducted using SAS 9.2 (Cary, North Carolina) and STATA SE 12.1 (College Station, Texas).

RESULTS

Across the 625.2 million ED visits in the U.S. from 2006-2010, APAP-related toxicity was observed among 411,881 ED visits, with peaks occurring at approximately ages 0-5, 15-20, and 35-45 years (Figure 2). The incidence proportion of APAP toxicity-related ED visits according to age per 100,000 per U.S. population was 27.10 overall and, by age category: 17.29 for ages 0-11; 63.17 for ages 12-20; 27.77 for ages 21-64; and 8.18 for ages 65 and over. Reflected in Figure 3, peak incidence proportions exceeding 70 per 100,000 U.S. population were observed at age 2 (78.39 per 100,000) and ages 16-18 (76.16, 77.52, and 74.00 per 100,000, respectively). Inpatient admissions averaged 12.46 per 100,000 US population, lowest among <12 years (0.50 per 100,000) and highest within cases from 12-20 (23.34 per 100,000); peaks were noted at ages 18 (33.55 per 100,000) and 19 (31.07 per 100,000).

<FIGURE 2>

<FIGURE 3>

In general, cases involved females (65.5%) averaging 29.3 (±17.6) years of age with 3.1 (±4.4) days for inpatient lengths of stay, and involved intentional self-harm (58.4%). Within the 12-20 age category, cases were markedly female (74.8%) and involving intentional self-harm (71.4%). Among the APAP-related cases presenting to the ED, 45.4% resulted in direct inpatient admission, highest in percentage terms among cases age ≥65 years (66.0%) even though this age category constituted an age-adjusted 5.68 admissions per 100,000 U.S. population. Those treated-and-released directly in the ED involved 37.4% of cases, particularly characteristic among cases <12 years (92.7%). The most common Elixhauser comorbidities observed were depression (25.0%), drug abuse (15.6%), psychoses (15.3%), alcohol abuse (13.7%), and fluid and electrolyte disorders (13.6%); no Elixhauser comorbidities were noted among 38.0%. Inpatient mortality was low (0.6%), and the requirement of invasive mechanical ventilation was 4.7%. The total national bill across the five-year time horizon was $5.30 billion (USD 2014), equating to $12,766 (±28414) per case. The full descriptive statistics appear in Table 1.

<TABLE 1>

Multivariable Analysis: Inpatient Admission, Mortality, Invasive Mechanical Ventilation

Results of the multinomial logit regression of patient disposition from the ED (Table 2) indicated that numerous patient, hospital, and clinical characteristics were associated with an increased likelihood of admission or death. After statistically controlling for numerous factors, rural patient residence suggested a significant ($p<0.05$) increased relative risk of admission among the 0-11, 12-20, and 21-64 year-old categories ($RRR_{0-11}=2.26$, $RRR_{12-20}=1.30$, $RRR_{21-64}=1.24$). Intentional self-harm was also associated with over a 3x increase odds of admission across all age categories ≥12 years ($p<0.05$), was almost perfectively predictive of mortality

cases among those 12-20 years of age, and was associated with a 8.57x ($p<0.001$) for those ≥65 years.

<TABLE 2>

Comorbidities of liver disease, coagulopathy, fluid and electrolyte disorders, and weight loss/cachexia were associated with significant ($p<0.05$) and large relative risks for both admission and mortality across age groups (sample size permitting for analysis). Specifically among pediatric cases <12 years, other neurological disorders, fluid and electrolyte disorders, and blood or deficiency anemia were significantly associated with increased admission ($p<0.05$). Across other age categories concerning admissions alone, comorbid conditions of valvular disease, peripheral vascular disorders, hypertension with complications, other neurological disorders, obesity, deficiency or other anemia, alcohol abuse, psychoses, and depression were significantly associated with an increased relative risk across all age groups ($p<0.05$). Over time, no sustained decrease in admissions or mortality were observed consistently across age categories over time.

The requirement of invasive mechanical ventilation (Table 3) indicated that chronic pulmonary disease, coagulopathy, and fluid and electrolyte disorders were significant predictors among cases ≥12 years ($p<0.028$). Intentional self-harm was associated with a 1.49x higher odds among those aged 21-64 years, and a 2.42x higher odds among cases ≥65 years ($p<0.028$). Other neurological disorders, blood loss or deficiency anemia, alcohol abuse, drug abuse, and psychoses were associated with an increased odds ($p<0.028$) among 12-20 and 21-64 age groups. Several factors had near-perfect associations with invasive mechanical ventilation within the 12-20 age group. Notably, over time, no consistent change in odds of invasive mechanical ventilation across years was observed from 2006.

<TABLE 3>

Multivariable Analysis: Charges, Length of Stay

The multivariable analysis of charges and length of stay (Table 4) indicated varying associations with these economic outcomes. Suggestive of greater intensities of care required across all age categories, consistently significant increased charges and lengths of stay were associated with liver disease ($p<0.036$ for charges, $p<0.024$ for length of stay), while weight loss/cachexia and coagulopathy were significant across age groups 21-64 and ≥65 and HIV/AIDS was significant in the 21-64 age category. Increased charges alone were associated with intentional self-harm and most Elixhauser comorbidities: heart failure; hypertension with complications; other neurological disorders; coagulopathy; fluid and electrolyte disorders; blood loss or deficiency anemia; alcohol abuse; psychoses; and depression ($p<0.036$). No consistent change across age categories was noted over time for either charges or length of stay.

<TABLE 4>

DISCUSSION

This investigation examined nationally-representative cases of APAP toxicity-associated ED visits in the U.S. from 2006-2010, assessing the independent associations between outcomes of inpatient admission, mortality, required use of invasive mechanical ventilation, charges, and lengths of stay based upon several patient, clinical, and hospital characteristics. Overall, 411,881 ED visits were observed (82,376 per year), equating to 27.10 ED visits per 100,000 US population annually and summing to a national bill of $1.06 billion per year (USD 2014). Some 37.2% were treated-and-released directly from the ED (30,783 per year), 45.5% were admitted to the inpatient setting (37,877 per year), and 0.6% involved death (484 per year). The number of ED presentations did not appreciably change over time, decreasing by <2% from 2006 to 2010

(n=1,351), though representing a change from 27.15 to 25.78 visits per 100,000 U.S. population annually overall.

Comparatively, Nouraj et al. (2006) estimated that attributable APAP overdoses from 1993-1999 were lower than aforementioned findings, with approximately 56,000 ED visits, 26,000 hospitalizations, and 458 deaths per year, wherein Li and Martin (2011) also reported a decrease in rates from 2001-2007 to slightly less than 45,000 ED visits per year.[5,8] From 1993-1999, Li and Martin (2011) found a lower number of ED visits, at 21.03 visits per 100,000 persons per year and decreasing to 15.21 from 2000-2007.[8] It is critical to note that Nouraj et al. (2006) and Li and Martin (2011) utilized different national data than the present study, data that have explicitly been identified with a discrepancy in the number of cases associated with intentional APAP overdose-related visits, though unintentional poisonings appeared to be similar across various data sources.[5-8] Manthripragada et al. (2011) presented results illustrating differences present within nationally-representative studies, wherein the number of APAP toxicity-associated ED visits may be potentially underestimated perhaps by one-third to one-half.[6] More closely paralleling the present study, Budnitz et al. (2011) reported 78,414 annual ED visits associated with APAP overdoses from 2005-2006 using data from the National Electronic Injury Surveillance System (NEISS), while Manthripragada et al. (2011) found an age-adjusted rate of 13.9 hospitalizations per 100,000 U.S. population from 2000-2006.[6,7] Also consistent with the current work, a decrease in the number of ED visits or hospitalizations over time relating to APAP overdose was not observed.[6]

The average age in the present study was 29.3 years, with 60.0% of ED visits occurring across the 21-64 year age group. Though constituting 16.2% and 11.1% of the U.S. population, some 10.3% and 25.9% of cases, respectively, involved persons 0-11 and 12-20 years of age.

Furthermore, ED presentations exceeding 50 visits per 100,000 persons per year were noted from ages 1-2 and 15-22, peaking at over 70 per 100,000 specifically at age 2 and ages 16-18. Broader surveillance figures suggest that age-adjusted overall nonfatal injuries relating to poisoning of any type was 36.14 per 100,000 in 2013, though the crude rate for ages 1-2 is 12.27 per 100,000 and is 35.79 per 100,000 for ages 15-22.[23] Prior investigations suggest a substantially large number of APAP toxicity-related ED visits occur among young children, adolescents, and young adults; Li and Martin (2011) reported 72.42 visits per 100,000 for cases under 5 years, 61.91 per 100,000 for ages 15-17, and 40.92 per 100,000 for ages 18-24.[7,8,24,25] Budnitz et al. (2011), found that 13.4% of APAP overdose ED visits were attributed to unsupervised ingestions by children 5 years of age and under, a finding which has been observed across other work.[7,26,27,28] Others have found higher risks for APAP toxicity-related ED visits due, in part, to single-ingredient unintentional overdose or high use of APAP products.[24,25,28]

A majority of cases in the current work involved female sex (65.5%) and intentional self-harm (58.4%), highest in the 12-20 year age category at 74.8% female and 71.4% intentional self-harm. Similar to Li and Bradly (2011), behavioral and mental health comorbidities were common and represented the largest proportions of Elixhauser comorbidities including depression (25.0%), psychoses (15.3%), drug abuse (15.6%), and alcohol abuse (13.7%). Notably, these comorbid conditions were also associated with increased relative risk of admission and likelihood of charges almost entirely across all age categories of ≥12 years within the multivariable analyses. Over most age categories ≥12 years, intentional self-harm was generally associated with increased odds of admission, mortality, requirement of invasive mechanical ventilation, charges, and length of stay. Budnitz et al. (2011) reported that 69.8% of ED visits involving APAP overdoses from 2006-2007 were associated with self-directed

violence, peaking among those between 15-24 years of age, with 75% ultimately resulting in either psychiatric or inpatient hospitalizations.[7] Surveillance data also suggest that one-quarter of all ED cases for intentional poisoning involve APAP.[23] Budnitz et al. (2011) also noted that females had the highest rates of intentional self-harm, especially as adolescents or young adults.[7] It has been noted in prior work that suicide attempts via toxic medication ingestion is more frequently observed among adolescents and often associated with impulsivity, of which toxic APAP ingestion has been classified.[7,29,30,31] Importantly, Manthripragada et al. (2011) emphasized that discerning whether self-harm was intentional versus accidental remains challenging to ascertain via secondary data, potentially resulting in the misclassification of cases involving non-accidental poisoning via supplementary ICD-9 codes (i.e., E-codes) or differences in hospital reporting requirements.[6,32,33]

Results of the multivariable analysis indicated that rural patient residence (municipalities ≤50,000 persons) was associated with a higher odds of admission across age categories <65 years. Among age categories ≥12 years, an increased relative risk of admission and mortality was associated with liver disease, coagulopathy, fluid and electrolyte disorders, and weight loss/cachexia. With some exceptions, increased odds of invasive mechanical ventilation, charges, and lengths of stay were also observed with these comorbidities as well. As Li and Martin (2011) reported a 8.62x higher odds of ED visits attributed to APAP toxicity with alcohol abuse or dependence ($p<0.001$), findings from the current work also suggest over a 2x higher relative risk of admission (age categories ≥12 years), a 1.75x higher relative risk of mortality (ages 21-64), over 1.19x higher charges (age categories ≥12 years), and 1.26x or greater odds of invasive mechanical ventilation (ages 12-20 and 21-64). Pediatric admissions <12 years were associated with other neurological disorders, fluid and electrolyte disorders, and blood loss or

deficiency anemia; Budnitz et al. (2011) reported that most of the unsupervised ingestions of APAP were observed among children <6 years, typically treated-and-released from the ED setting via gastric decontamination or n-acetyl cysteine (NAS) treatment.[7]

Although findings from this study provide updated information concerning the burden of APAP-related ED visits in the U.S., some important study limitations exist. While similar coding algorithms were used as other retrospective studies to identify APAP-toxicity cases, no specific categorization was present that may have classified cases as being unsupervised ingestions or therapeutic misadventures (e.g., overuse, medication errors), the type of APAP product consumed (e.g., single-agent, combination products, tablets, liquid), and the estimated amount ingested or serum levels observed.[5-8,15,16] In this context, Budnitz et al. (2011) reported that 13.4% of APAP toxicity-related ED visits were attributed to unsupervised ingestions and 16.7% involved therapeutic misadventures, with slightly over half involving overuse of agents versus dosage confusion or APAP over-ingestion from multiple source products.[7] The use of NAS or gastric decontamination was also not consistently captured within the dataset, nor was a designation of acute liver injury directly attributable to APAP toxicity.[6,7] Generalizations of findings beyond acute care settings are not appropriate to estimate the prevalence of APAP poisoning in the U.S., as cases presenting to poison centers or within ambulatory practices are not captured. At the time of this study's initiation, the 2006-2010 the time frame reflected the entirety of HCUP NEDS data; the complex process of collecting, integrating, validating, and distributing data of this nature typically takes two years.[14] As such, given the time horizon of this study and available data, continued work is warranted to study the impact of more recent APAP dose limitations established by the FDA in addition to studies focusing directly upon consumer perceptions, attitudes, beliefs, knowledge, and health literacy.[9-13,34-45]

CONCLUSION

This nationally-representative study of ED visits in the U.S. highlights a substantial public health impact of APAP toxicity-related cases from 2006-2010. Overall, 82,376 cases per year were observed, summing to a national bill of $1.06 billion. The ED visit average rate across all ages was 27.10 ED visits per 100,000 U.S. population, exceeding 70 per 100,000 age 2 and ages 16-18. After controlling for numerous factors, no consistent temporal change was observed during the five-year time horizon concerning outcomes of admission, mortality, invasive mechanical ventilation, charges, or length of stay.

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CONTRIBUTIONS

AA and GHS conducted the initial planning of this investigation. AA, LK, and GHS were involved in formalizing and executing the study methodology, analysis, interpretation of results, and drafting and revisions of the manuscript. GHS was involved in the acquisition of data and overall study supervision.

COMPETING INTEREST STATEMENTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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TABLE 1. Descriptive Statistics of ED Cases Associated with APAP Toxicity According to Age Category in the U.S., 2006-2010.

	Age 11 Years and Below (N = 42,623)	Age 12-20 Years (N = 106,725)	Age 21-64 Years (N = 246,640)	Age 65 Years and Above (N = 15,893)	Overall (N = 411,881)
PATIENT CHARACTERISTICS					
Age (mean ± standard deviation)	2.2 ±1.7	16.9 ±2.1	36.4 ±11.4	75.2 ±7.9	29.3 ±17.6
Female Sex	48.3%	74.8%	64.4%	68.0%	65.5%
Payer, Commercial Insurance	38.1%	26.4%	20.4%	1.6%	23.1%
Medicare	≤0.1%	0.2%	10.0%	88.3%	9.5%
Medicaid	48.9%	51.5%	35.1%	7.8%	39.7%
Other	12.8%	21.8%	34.5%	2.3%	27.7%
Income Quartile, Lowest	24.3%	23.2%	28.1%	24.4%	26.3%
2nd Quartile	28.3%	27.5%	28.5%	27.0%	28.2%
3rd Quartile	25.5%	25.6%	24.5%	25.4%	24.9%
4th Quartile	21.9%	23.8%	18.9%	23.3%	20.6%
Rural Residence	19.6%	16.7%	17.1%	17.9%	17.3%
HOSPITAL CHARACTERISTICS					
Region, Northeast	14.4%	16.2%	15.6%	16.4%	15.6%
Midwest	25.6%	18.2%	26.4%	21.0%	26.6%
South	32.1%	30.0%	34.7%	34.5%	33.2%
West	18.1%	25.6%	23.3%	28.2%	24.5%
Rural Facility	18.5%	15.3%	15.3%	16.2%	15.6%
Teaching Facility	38.9%	39.9%	39.5%	35.7%	39.4%
CLINICAL CHARACTERISTICS					
Congestive Heart Failure	≤0.1%	≤0.1%	0.7%	8.8%	0.8%
Valvular Disease	≤0.1%	≤0.1%	0.6%	3.3%	0.5%
Pulmonary Circulation Disorders	≤0.1%	≤0.1%	0.2%	1.4%	0.2%
Peripheral Vascular Disorders	≤0.1%	≤0.1%	0.3%	3.8%	0.3%
Hypertension with Complications	≤0.1%	≤0.1%	0.7%	7.6%	0.7%
Paralysis	≤0.1%	≤0.1%	0.4%	1.5%	0.3%
Other Neurological Disorders	0.3%	2.2%	7.4%	14.6%	5.6%
Chronic Pulmonary Disease	2.0%	4.9%	7.8%	19.2%	6.9%
Diabetes with Complications	≤0.1%	≤0.1%	0.5%	2.0%	0.4%

Hypothyroidism	≤0.1%	0.5%	2.9%	11.9%	2.3%
Renal Failure	≤0.1%	≤0.1%	0.8%	7.3%	0.8%
Liver Disease	≤0.1%	0.2%	2.2%	1.7%	1.4%
HIV/AIDS	≤0.1%	≤0.1%	0.2%	≤0.1%	≤0.1%
PUD, excluding bleeding	≤0.1%	≤0.1%	≤0.1%	≤0.1%	≤0.1%
Lymphoma	≤0.1%	≤0.1%	≤0.1%	≤0.1%	≤0.1%
Metastatic Cancer	≤0.1%	≤0.1%	≤0.1%	1.0%	0.2%
Solid Tumor	≤0.1%	≤0.1%	0.3%	2.1%	0.2%
Rheumatoid Arthritis/Collagen Vascular Disease	≤0.1%	≤0.1%	0.9%	3.1%	0.7%
Coagulopathy	≤0.1%	0.5%	2.3%	4.2%	1.7%
Obesity	≤0.1%	1.2%	3.3%	2.4%	2.4%
Weight Loss/Cachexia	≤0.1%	≤0.1%	0.8%	3.2%	0.6%
Fluid and Electrolyte Disorders	0.7%	8.1%	17.2%	29.4%	13.6%
Blood Loss or Deficiency Anemia	≤0.1%	1.5%	4.3%	12.3%	3.4%
Alcohol Abuse	≤0.1%	5.7%	19.8%	8.6%	13.7%
Drug Abuse	≤0.1%	12.1%	20.3%	6.3%	15.6%
Psychoses	≤0.1%	11.2%	19.8%	13.3%	15.3%
Depression	≤0.1%	27.4%	28.4%	22.6%	25.0%
No Elixhauser Comorbidities Present	96.4%	47.0%	25.7%	12.6%	38.0%
Intentional Self-Harm	≤0.1%	71.4%	64.2%	34.9%	58.4%
CALENDAR YEAR					
2006	18.1%	21.1%	19.5%	17.5%	19.7%
2007	21.0%	20.5%	19.6%	17.0%	19.9%
2008	21.8%	21.1%	20.6%	20.1%	20.8%
2009	20.8%	19.7%	20.4%	21.8%	20.3%

2010	18.3%	17.6%	20.0%	23.6%	19.3%
OUTCOMES					
Disposition, treat and release	92.7%	38.4%	28.1%	23.8%	37.4%
Transfer	2.5%	22.4%	14.0%	6.3%	14.7%
Admission	2.9%	37.0%	55.1%	66.0%	45.4%
Death	≤0.1%	≤0.1%	0.7%	3.4%	0.6%
Other	1.9%	2.2%	1.9%	0.5%	1.9%
Average ED and Inpatient Charge (USD 2014) (mean ± standard deviation)	$1,343 ±3162	$7,884 ±13034	$15,824 ±31404	$28,631 ±50515	$12,766 ±28414
Annual: Total National Bill (USD 2014) (mean ± standard deviation)	$11.45 million	$168.28 million	$789.11 million	$91.00 million	$1,059.86 million
2006-2010: Total National Bill (USD 2014) (mean ± standard deviation)	$0.06 billion	$0.84 billion	$3.95 billion	$0.46 billion	$5.30 billion
Inpatient Length of Stay (mean ± standard deviation)	1.8±1.8	2.3±2.2	3.2±4.5	4.9±6.9	3.1±4.4
Invasive Mechanical Ventilation	≤0.1%	1.2%	6.8%	8.6%	4.7%
ED Visits per 100,000 persons per year[A]	17.29	63.17	27.77	8.18	27.10
Inpatient Admissions per 100,000 persons per year[A]	0.50	23.34	15.50	5.68	12.46

ED: emergency department; APAP: acetaminpophen

[A] Base U.S. populations for 2006-2010 obtained from the Centers for Disease Control and Prevention, National Vital Statistics System, Vintage 2012 bridged-race post-census U.S. resident population estimates

TABLE 2. Patient Disposition of Admission or Mortality versus Treat-and-Release from APAP-Toxicity-Related Presentation to the ED, 2006-2010.

	Age 11 Years and Below (N = 42,623)		Age 12-20 Years (N = 106,725)		Age 21-64 Years (N = 246,640)		Age 65 Years and Above (N = 15,893)	
	Admission [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]	**Admission** [*RRR*,95th CI]	**Mortality** [*RRR*,95th CI]
PATIENT CHARACTERISTICS								
Age	1.11** (1.03,1.19)	--	1.09*** (1.06,1.11)	1.49* (1.01,2.19)	1.01*** (1.01,1.02)	1.05*** (1.04,1.06)	1.00 (0.99,1.01)	1.09** (1.03,1.14)
Female Sex	1.01 (0.77,1.33)	--	0.97 (0.89,1.06)	1.94 (0.28,13.60)	0.90*** (0.85,0.95)	0.96 (0.76,1.22)	1.24 (0.99,1.56)	0.54 (0.25,1.15)
Payer (vs. Commercial Insurance) Medicare	--	--	0.54* (0.30,0.97)	omitted[A]	0.83** (0.75,0.92)	0.87 (0.59,1.28)	1.17 (0.49,2.78)	0.12** (0.03,0.55)
Medicaid	0.62** (0.45,0.86)	--	0.97 (0.87,1.07)	0.42 (0.09,1.85)	1.02 (0.94,1.11)	0.90 (0.64,1.27)	0.64 (0.25,1.69)	0.04** (0.01,0.28)
Other	0.58* (0.37,0.92)	--	0.86* (0.76,0.98)	0.32 (0.07,1.46)	0.90* (0.83,0.98)	0.87 (0.62,1.22)	0.31* (0.10,0.93)	omitted[A]
Income Quartile (vs. Lowest) 2nd Quartile	1.12 (0.79,1.59)	--	1.13* (1.00,1.27)	2.50 (0.21,29.40)	1.05 (0.97,1.14)	0.93 (0.67,1.28)	0.84 (0.61,1.14)	0.23* (0.07,0.74)
3rd Quartile	0.75 (0.48,1.16)	--	1.15* (1.02,1.29)	13.40* (1.59,113.21)	1.08 (0.98,1.20)	1.21 (0.86,1.69)	1.08 (0.75,1.54)	1.03 (0.32,3.24)
4th Quartile	0.90 (0.58,1.39)	--	1.24** (1.07,1.43)	omitted[A]	1.26*** (1.13,1.41)	1.20 (0.83,1.73)	1.18 (0.83,1.69)	1.76 (0.64,4.85)
Rural Residence	2.26* (1.19,4.30)	--	1.30* (1.06,1.60)	0.82 (0.18,3.78)	1.24** (1.07,1.44)	1.21 (0.72,2.03)	1.36 (0.76,2.43)	1.88 (0.44,7.97)
HOSPITAL CHARACTERISTICS								
Rural Location	0.53 (0.26,1.12)	--	0.79* (0.62,0.99)	1.48 (0.15,14.19)	0.67*** (0.56,0.80)	0.42** (0.21,0.81)	0.63 (0.35,1.14)	1.27 (0.34,4.68)
Teaching Facility	3.13*** (2.17,4.50)	--	1.55*** (1.35,1.79)	5.08 (0.82,31.72)	0.98* (0.86,1.12)	1.04 (0.79,1.37)	1.31* (1.03,1.68)	1.58 (0.68,3.66)
Region (vs. Northeast) Midwest	0.72 (0.47,1.12)	--	0.96 (0.81,1.14)	1.18 (0.11,13.16)	0.87 (0.72,1.04)	0.59* (0.40,0.90)	0.63* (0.44,0.90)	0.48 (0.16,1.45)
South	0.79 (0.51,1.22)	--	0.85 (0.72,1.02)	1.92 (0.17,21.10)	0.86 (0.72,0.99)	0.79 (0.55,1.14)	0.85 (0.61,1.18)	0.36* (0.14,0.92)
West	0.65 (0.39,1.08)	--	0.62*** (0.52,0.74)	0.39 (0.01,12.73)	0.51*** (0.43,0.59)	0.52** (0.35,0.77)	0.54** (0.38,0.77)	0.26* (0.08,0.82)
CLINICAL CHARACTERISTICS								
Congestive Heart Failure	--	--	--	--	1.48 (0.95,2.31)	1.67 (0.80,3.49)	3.36*** (2.01,5.63)	1.64 (0.55,4.87)
Valvular Disease	--	--	3.94* (1.15,13.50)	omitted[A]	4.47*** (2.70,7.40)	2.06 (0.60,7.01)	3.64** (1.67,7.92)	3.55 (0.51,24.58)
Pulmonary Circulation Disorders	--	--	--	--	2.35*	8.50**	3.70	omitted[A]

					(1.03,5.40)	(2.54,28.43)	(0.39,35.40)	
Peripheral Vascular Disorders	--	--	--	--	3.15*** (1.55,6.37)	2.64 (0.59,11.89)	2.88** (1.32,6.28)	5.77 (0.96,34.48)
Hypertension with Complications	--	--	2.46*** (1.53,3.96)	omitted[A]	2.27** (1.32,3.92)	1.66 (0.59,4.68)	5.74*** (2.32,14.21)	0.66 (0.06,6.75)
Paralysis	--	--	1.54 (0.31,7.54)	omitted[A]	3.28*** (1.90,5.65)	11.47*** (4.84,27.23)	1.75 (0.57,5.38)	1.20 (0.14,10.13)
Other Neurological Disorders	24.83*** (10.48,58.83)	--	3.14*** (2.40,4.12)	50.97*** (10.75,241.71)	2.19*** (1.95,2.47)	2.21*** (1.55,3.15)	1.97*** (1.40,2.78)	1.48 (0.67,3.27)
Chronic Pulmonary Disease	1.94 (0.95,3.96)	--	2.35*** (1.93,2.86)	omitted[A]	2.01*** (1.78,2.28)	1.29 (0.83,2.00)	3.21*** (2.27,4.54)	5.16** (1.75,15.25)
Diabetes with Complications	--	--	0.97 (0.58,1.64)	omitted[A]	4.52*** (2.55,8.01)	3.57* (1.01,12.64)	2.34 (0.62,8.88)	16.60 (0.12,225.36)
Hypothyroidism	--	--	1.04 (0.58,1.85)	omitted[A]	2.67*** (2.16,3.31)	1.52 (0.77,2.99)	2.15*** (1.43,3.24)	2.17 (0.75,6.33)
Renal Failure	--	--	2.11 (0.24,18.52)	omitted[A]	2.39*** (1.51,3.80)	3.16** (1.38,7.25)	0.50 (0.22,1.12)	1.06 (0.13,8.44)
Liver Disease	--	--	2.98* (1.03,8.64)	omitted[B]	12.13*** (5.98,24.60)	47.89*** (21.53,106.52)	omitted[B]	omitted[B]
HIV/AIDS	--	--	--	--	2.18 (0.82,5.83)	6.86* (1.35,34.92)	--	--
Lymphoma	--	--	--	--	1.43 (0.60,3.43)	4.24 (0.69,25.95)	--	--
Metastatic Cancer	--	--	--	--	6.08*** (2.22,16.67)	30.32*** (8.35,110.18)	3.18 (0.78,13.04)	1.76 (0.29,10.55)
Solid Tumor	--	--	--	--	1.97* (1.09,3.55)	5.77** (2.13,15.59)	2.41 (0.98,5.91	5.46 (0.94,31.63)
Rheumatoid Arthritis/Collagen Vascular Disease	--	--	0.80 (0.21,3.07)	omitted[A]	2.66*** (1.89,3.76)	2.28 (0.95,5.43)	3.32* (1.24,8.90)	omitted[A]
Coagulopathy	--	--	21.75*** (7.70,61.42)	178.62*** (10.96,291.11)	16.06*** (9.70,26.57)	72.42*** (39.91,131.40)	omitted[B]	omitted[B]
Obesity	--	--	6.29*** (3.95,10.01)	omitted[A]	4.96*** (3.32,6.27)	5.55*** (3.08,10.02)	5.43** (1.68,17.54)	0.10 (0.01,1.37)
Weight Loss	--	--	--	--	20.51*** (7.35,57.18)	25.74*** (7.64,86.71)	19.01** (2.50,144.65)	283.59*** (17.45,468.08)
Fluid and Electrolyte Disorders	20.75*** (9.22,46.70)	--	6.78*** (5.70,8.07)	8.91** (2.48,31.96)	7.97*** (7.09,8.96)	28.45*** (21.84,37.07)	9.77*** (6.85,13.92)	56.28*** (22.19,142.71)
Blood Loss or Deficiency Anemia	13.27** (2.65,66.38)	--	4.17*** (2.83,6.15)	omitted[A]	4.46*** (3.64,5.46)	3.34*** (2.22,5.04)	2.64*** (1.72,4.04)	0.15 (0.01,4.35)
Alcohol Abuse	--	--	2.32*** (1.94,2.77)	1.16 (0.09,14.53)	2.53*** (2.33,2.75)	1.75*** (1.34,2.29)	2.96*** (1.76,4.95)	3.27 (0.71,15.09)
Drug Abuse	--	--	2.02*** (1.77,2.30)	3.02 (0.59,15.37)	2.37*** (2.17,2.59)	1.58** (1.17,2.13)	1.71 (0.96,3.04)	0.59 (0.06,5.44)
Psychoses	--	--	5.13*** (4.48,5.89)	4.46 (0.91,21.85)	4.44*** (4.00,4.93)	1.42 (1.00,2.03)	6.41*** (3.88,10.57)	6.46 (0.84,49.84)
Depression	--	--	1.71***	3.46	1.75***	1.10	1.95***	1.88

			(1.55,1.88)	(0.94,12.70)	(1.62,1.89)	(0.82,1.48)	(1.44,2.64)	(0.79,4.49)
Intentional Self-Harm	--	--	3.40*** (3.07,3.77)	omitted[B]	3.03*** (2.81,3.26)	1.69*** (1.30,2.21)	4.89*** (3.59,6.64)	8.57*** (3.97,18.49)
CALENDAR YEAR								
2007 (vs. 2006)	0.78 (0.48,1.28)	--	0.92 (0.80,1.06)	0.95 (0.17,5.34)	0.99 (0.88,1.11)	1.01 (0.69,1.49)	1.29 (0.92,1.81)	1.97 (0.39,9.87)
2008 (vs. 2006)	0.79 (0.49,1.26)	--	0.79** (0.68,0.92)	0.65 (0.07,5.73)	0.82** (0.72,0.94)	0.82 (0.56,1.21)	0.94 (0.67,1.32)	3.13 (0.96,10.19)
2009 (vs. 2006)	0.67 (0.40,1.11)	--	0.84* (0.72,0.98)	0.30 (0.03,3.17)	0.87 (0.77,1.00)	0.58* (0.38,0.88)	0.79 (0.55,1.13)	2.23 (0.65,7.64)
2010 (vs. 2006)	0.74 (0.45,1.22)	--	0.88 (0.74,1.03)	0.56 (0.06,5.18)	0.83** (0.73,0.95)	0.78 (0.53,1.13)	1.03 (0.74,1.45)	2.57 (0.72,9.18)

ED: emergency department; RRR = relative risk ratio
omitted[A] = variable omitted due to near-perfect association with survival (i.e., OR <0.01)
omitted[B] = variable omitted due to near-perfect association with mortality (i.e., RRR>10000)
'- -' = variable omitted due to small sample size (n≤0.1%)
*** statistically significant at p<0.001
** statistically significant at p<0.01
* statistically significant at p<0.05

TABLE 3. Invasive Mechanical Ventilation among APAP-Toxicity-Related Cases Presenting to the ED According to Age Category, 2006-2010.

	Age 11 Years and Below (N = 42,623)	**Age 12-20 Years** (N = 106,725)	**Age 21-64 Years** (N = 246,640)	**Age 65 Years and Above** (N = 15,893)
	Invasive Mechanical Ventilation [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]	**Invasive Mechanical Ventilation** [*OR*,95th CI]
PATIENT CHARACTERISTICS				
Age	--	1.26* (1.16,1.36)	1.03* (1.02,1.03)	0.96* (0.95,0.98)
Female Sex	--	0.46* (0.35,0.60)	0.85* (0.78,0.92)	1.12 (0.84,1.50)
Payer (vs. Commercial Insurance) Medicare	--	0.62 (0.15,2.58)	0.82* (0.72,0.95)	1.03 (0.37,2.84)
Medicaid	--	0.92 (0.67,1.28)	1.05 (0.94,1.17)	1.52 (0.52,4.45)
Other	--	1.01 (0.71,1.43)	0.78* (0.70,0.87)	0.46 (0.12,1.79)
Income Quartile (vs. Lowest) 2nd Quartile	--	0.92 (0.63,1.35)	1.10 (0.99,1.23)	1.12 (0.76,1.65)
3rd Quartile	--	0.92 (0.62,1.37)	1.23* (1.08,1.39)	1.01 (0.69,1.48)
4th Quartile	--	0.92 (0.61,1.40)	1.08 (0.95,1.24)	0.91 (0.58,1.41)
Rural Residence	--	1.96 (0.97,3.99)	1.25 (1.01,1.55)	1.07 (0.55,2.10)
HOSPITAL CHARACTERISTICS				
Rural Location	--	0.38* (0.16,0.91)	0.61* (0.47,0.77)	0.57 (0.26,1.26)
Teaching Facility	--	1.51* (1.12,2.03)	1.10 (0.98,1.22)	1.27 (0.95,1.71)
Region (vs. Northeast) Midwest	--	0.79 (0.53,1.18)	0.87 (0.75,1.01)	0.88 (0.56,1.36)
South	--	0.77 (0.51,1.17)	0.99 (0.86,1.15)	0.90 (0.59,1.36)
West	--	0.72 (0.45,1.13)	0.94 (0.81,1.08)	0.90 (0.57,1.42)
CLINICAL CHARACTERISTICS				
Congestive Heart Failure	--	--	1.61* (1.17,2.21)	1.39 (0.86,2.25)
Valvular Disease	--	8.31* (1.91,36.10)	1.12 (0.78,1.62)	0.77 (0.35,1.73)

Pulmonary Circulation Disorders	--	--	2.66* (1.46,4.86)	0.83 (0.27,2.53)
Peripheral Vascular Disorders	--	--	1.25 (0.70,2.21)	1.06 (0.56,2.02)
Hypertension with Complications	--	2.48* (1.11,5.56)	0.86 (0.54,1.36)	2.01 (0.91,4.45)
Paralysis	--	omitted[A]	1.95* (1.29,2.94)	0.26 (0.03,2.25)
Other Neurological Disorders	--	7.11* (5.00,10.11)	1.88* (1.66,2.13)	1.10 (0.76,1.60)
Chronic Pulmonary Disease	--	1.79* (1.09,2.92)	1.34* (1.18,1.51)	1.75* (1.26,2.44)
Diabetes with Complications	--	0.79 (0.13,4.81)	0.91 (0.56,1.46)	0.62 (0.21,1.79)
Hypothyroidism	--	0.87 (0.25,3.09)	0.91 (0.75,1.11)	0.56* (0.35,0.89)
Renal Failure	--	1.78 (0.18,17.95)	1.25 (0.82,1.92)	0.42 (0.19,0.94)
Liver Disease	--	2.49 (0.44,14.03)	2.23* (1.77,2.81)	2.47* (1.17,5.21)
AIDS	--	--	2.11* (1.23,3.60)	--
Lymphoma	--	--	1.93 (0.84,4.40)	--
Metastatic Cancer	--	--	1.68 (0.79,3.59)	0.47 (0.09,2.47)
Solid Tumor	--	--	0.68 (0.32,1.44)	0.27 (0.06,1.22)
Rheumatoid Arthritis/Collagen Vascular Disease	--	omitted[A]	1.59* (1.18,2.14)	0.48 (0.18,1.25)
Coagulopathy	--	2.58* (1.13,5.89)	2.48* (2.10,2.94)	2.17* (1.27,3.70)
Obesity	--	0.98 (0.29,3.29)	1.11 (0.91,1.36)	0.49 (0.17,1.35)
Weight Loss/Cachexia	--	--	1.90* (1.43,2.53)	1.92* (1.13,3.28)
Fluid and Electrolyte Disorders	--	5.84* (4.26,8.00)	4.08* (3.75,4.43)	2.26* (1.71,3.00)
Blood Loss or Deficiency Anemia	--	2.07* (1.33,3.97)	1.36* (1.17,1.58)	1.15 (0.79,1.67)
Alcohol Abuse	--	1.90* (1.34,2.71)	1.26* (1.16,1.37)	0.78 (0.47,1.29)
Drug Abuse	--	1.50* (1.10,2.04)	1.16* (1.06,1.27)	0.62 (0.32,1.18)
Psychoses	--	1.62* (1.12,2.35)	1.51* (1.37,1.67)	1.28 (0.91,1.80)

Depression	--	1.10 (0.81,1.49)	1.04 (0.95,1.14)	0.87 (0.61,1.23)
Intentional Self-Harm	--	1.34 (0.96,1.87)	1.49* (1.35,1.63)	2.42* (1.80,3.25)
CALENDAR YEAR				
2007 (vs. 2006)	--	0.99 (0.64,1.55)	0.99 (0.86,1.14)	1.02 (0.63,1.67)
2008 (vs. 2006)	--	0.98 (0.64,1.51)	1.05 (0.92,1.20)	0.81 (0.53,1.25)
2009 (vs. 2006)	--	0.94 (0.60,1.48)	0.92 (0.81,1.05)	1.07 (0.69,1.65)
2010 (vs. 2006)	--	0.96 (0.63,1.46)	0.95 (0.83,1.10)	1.12 (0.73,1.71)

OR = odds ratio; CI = confidence interval

omitted[A] = variable omitted due to near-perfect association with no requirement of intubation (i.e., OR <0.01)

'- -' = variable omitted due to small sample size (n≤0.1%)

* Statistically significant below the computed Simes (1986) false discovery rate p-value (p<0.036)

TABLE 4. Total Charges and Inpatient Length of Stay among APAP-Toxicity-Related Cases Presenting to the ED According to Age Category, 2006-2010.

	Age 11 Years and Below (N = 42,623)		Age 12-20 Years (N = 106,725)		Age 21-64 Years (N = 246,640)		Age 65 Years and Above (N = 15,893)	
	Charges [*exp(b)*,95th CI]	**LoS** [*IR*,95th CI]	**Charges** [*exp*(b),95th CI]	**LoS** [*IR*,95th CI]	**Charges** [*exp(b)*,95th CI]	**LoS** [*IR*,95th CI]	**Charges** [*exp(b)*,95th CI]	**LoS** [*IR*,95th CI]
PATIENT CHARACTERISTICS								
Age	1.04* (1.01,1.07)	1.03 (0.99,1.07)	1.05* (1.04,1.06)	0.99 (0.98,1.01)	1.01* (1.01,1.01)	1.01* (1.01,1.01)	1.00 (1.00,1.01)	1.01 (1.00,1.01)
Female Sex	0.94 (0.86,1.02)	1.07 (0.88,1.31)	0.97 (0.93,1.01)	1.00 (0.95,1.05)	0.96* (0.93,0.98)	0.97* (0.94,0.99)	0.91 (0.83,1.01)	0.94 (0.85,1.03)
Payer (vs. Commercial) Medicare	--	--	0.93 (0.65,1.33)	1.55 (0.90,2.65)	0.98 (0.94,1.03)	1.01 (0.96,1.06)	1.14 (0.83,1.56)	1.18 (0.81,1.72)
Medicaid	0.81* (0.71,0.92)	0.96 (0.79,1.16)	0.92* (0.87,0.96)	0.94* (0.89,0.98)	0.96* (0.93,0.98)	0.86* (0.83,0.91)	0.92 (0.65,1.31)	1.12 (0.74,1.69)
Other	0.89 (0.71,1.05)	1.08 (0.75,1.55)	0.87* (0.82,0.92)	0.92* (0.87,0.98)	0.97 (0.94,1.01)	0.94* (0.90,0.98)	0.56* (0.36,0.86)	0.93 (0.58,1.49)
Income Quartile (vs. Lowest) 2nd Quartile	1.06 (0.95,1.18)	1.27 (0.97,1.66)	1.04 (0.98,1.10)	1.05 (0.99,1.11)	1.01 (0.97,1.04)	0.99 (0.95,1.02)	0.98 (0.86,1.11)	0.99 (0.88,1.12)
3rd Quartile	1.06 (0.88,1.28)	1.33 (0.95,1.88)	1.03 (0.97,1.10)	1.05 (0.98,1.12)	1.01 (0.96,1.06)	1.00 (0.95,1.05)	0.99 (0.87,1.14)	0.92 (0.81,1.04)
4th Quartile	0.95 (0.79,1.14)	1.28 (0.97,1.68)	1.03 (0.95,1.12)	1.00 (0.93,1.07)	1.09* (1.02,1.17)	0.99 (0.94,1.04)	1.13 (0.96,1.33)	0.95 (0.85,1.09)
Rural Residence	1.19 (0.97,1.45)	1.12 (0.71,1.75)	1.00 (0.92,1.08)	0.96 (0.86,1.07)	1.03 (0.96,1.10)	1.01 (0.94,1.09)	0.93 (0.75,1.14)	1.06 (0.88,1.27)
HOSPITAL CHARACTERISTICS								
Rural Location	0.68* (0.55,0.87)	0.86 (0.52,1.43)	0.73* (0.66,0.81)	0.80* (0.71,0.91)	0.66* (0.60,0.72)	0.76* (0.69,0.83)	0.52* (0.42,0.66)	0.67* (0.54,0.82)
Teaching Facility	1.28* (1.10,1.49)	1.23 (0.98,1.54)	1.14* (1.06,1.24)	1.03 (0.96,1.10)	1.06 (0.99,1.13)	1.09* (1.05,1.15)	0.95 (0.84,1.07)	1.02 (0.93,1.13)
Region (vs. Northeast) Midwest	0.74* (0.64,0.87)	0.72* (0.55,0.95)	0.78* (0.71,0.86)	0.83* (0.76,0.90)	0.71* (0.65,0.78)	0.79* (0.73,0.85)	0.72* (0.61,0.85)	0.74* (0.66,0.83)
South	0.89 (0.76,1.05)	0.91 (0.68,1.23)	0.88* (0.79,0.98)	0.91* (0.85,0.97)	0.87* (0.79,0.97)	0.90* (0.85,0.96)	0.88 (0.75,1.04)	0.85* (0.75,0.96)
West	0.35* (0.27,0.45)	0.71* (0.54,0.95)	0.64* (0.57,0.73)	0.76* (0.71,0.82)	0.78* (0.70,0.86)	0.82* (0.77,0.87)	0.85 (0.71,1.02)	0.74* (0.65,0.83)
CLINICAL CHARACTERISTICS								
Congestive Heart Failure	--	--	--	--	1.52* (1.30,1.78)	1.31* (1.14,1.50)	1.39* (1.23,1.59)	1.25* (1.12,1.40)
Valvular Disease	--	--	1.36 (0.94,1.96)	0.99 (0.68,1.44)	1.42* (1.23,1.63)	1.06 (0.95,1.18)	1.56* (1.26,1.94)	1.08 (0.91,1.29)
Pulmonary Circulation Disorders	--	--	--	--	1.90* (1.45,2.47)	1.45* (1.19,1.77)	1.27 (0.89,1.81)	1.10 (0.79,1.54)

Peripheral Vascular Disorders	--	--	--	--	1.81* (1.47,2.23)	1.40* (1.12,1.74)	1.18 (0.98,1.42)	1.01 (0.85,1.19)
Hypertension with Complications	--	--	1.51* (1.28,1.79)	1.35* (1.17,1.56)	1.43* (1.19,1.71)	1.23* (1.05,1.45)	1.50* (1.23,1.84)	1.17 (0.99,1.37)
Paralysis	--	--	1.79 (1.03,3.09)	1.02 (0.70,1.48)	1.60* (1.32,1.94)	1.39* (1.19,1.63)	1.94* (1.12,3.36)	2.24 (1.08,4.62)
Other Neurological Disorders	7.00* (2.80,17.49)	1.41 (1.02,1.96)	1.61* (1.45,1.78)	1.05 (0.94,1.17)	1.29* (1.24,1.34)	1.00 (0.97,1.04)	1.15* (1.03,1.29)	1.01 (0.90,1.13)
Chronic Pulmonary Disease	0.98 (0.80,1.20)	0.81 (0.61,1.08)	1.18* (1.11,1.26)	0.97 (0.91,1.04)	1.20* (1.15,1.26)	1.02 (0.98,1.07)	1.37* (1.23,1.52)	1.03 (0.94,1.12)
Diabetes with Complications	--	--	1.02 (0.86,1.20)	0.90 (0.74,1.11)	1.27* (1.11,1.45)	1.07 (0.95,1.22)	1.60 (0.97,2.66)	1.07 (0.79,1.46)
Hypothyroidism	--	--	1.31 (1.00,1.72)	1.39* (1.08,1.79)	1.23* (1.15,1.31)	1.01 (0.94,1.08)	1.12 (1.00,1.25)	0.89 (0.81,0.99)
Renal Failure	--	--	1.41 (0.84,2.37)	0.88 (0.51,1.51)	1.43* (1.23,1.67)	1.16 (1.00,1.33)	1.03 (0.82,1.29)	0.99 (0.80,1.22)
Liver Disease	--	--	1.76* (1.30,2.39)	1.53* (1.15,2.03)	2.00* (1.80,2.23)	1.52* (1.39,1.67)	2.34* (1.66,3.31)	1.52* (1.19,1.95)
HIV/AIDS	--	--	--	--	1.56* (1.18,2.06)	1.30* (1.12,1.52)	--	--
Lymphoma	--	--	--	--	1.16 (0.86,1.57)	1.02 (0.78,1.34)	--	--
Metastatic Cancer	--	--	--	--	1.64* (1.16,2.31)	1.48* (1.07,2.03)	1.38 (0.89,2.15)	1.06 (0.64,1.76)
Solid Tumor	--	--	--	--	1.23 (0.97,1.56)	1.12 (0.92,1.36)	1.02 (0.84,1.24)	0.88 (0.72,1.08)
Rheumatoid Arthritis/Collagen Vascular Disease	--	--	0.71 (0.38,1.32)	0.84 (0.41,1.72)	1.34* (1.21,1.49)	1.12 (1.00,1.25)	1.33* (1.07,1.64)	1.02 (0.83,1.25)
Coagulopathy	--	--	3.04* (2.46,3.78)	1.98* (1.63,2.41)	2.08* (1.91,2.26)	1.48* (1.39,1.59)	1.54* (1.26,1.89)	1.12 (0.92,1.36)
Obesity	--	--	1.58* (1.40,1.79)	1.14 (1.01,1.28)	1.39* (1.31,1.48)	1.11 (1.01,1.22)	1.18 (0.96,1.44)	0.95 (0.76,1.20)
Weight Loss/Cachexia	--	--	--	--	1.99* (1.63,2.42)	1.83* (1.58,2.13)	1.68* (1.32,2.16)	1.58* (1.31,1.89)
Fluid and Electrolyte Disorders	6.46* (3.26,12.81)	1.93* (1.34,2.80)	1.95* (1.84,2.08)	1.04 (0.99,1.09)	1.82* (1.76,1.88)	1.16* (1.13,1.20)	1.81* (1.62,2.02)	1.18* (1.08,1.28)
Blood Loss or Deficiency Anemia	3.02* (1.67,5.47)	1.28 (0.74,2.19)	1.67* (1.43,1.94)	1.20* (1.07,1.36)	1.64* (1.55,1.74)	1.27* (1.17,1.37)	1.40* (1.23,1.59)	1.11 (1.00,1.23)
Alcohol Abuse	--	--	1.23* (1.14,1.31)	1.01 (0.95,1.08)	1.24* (1.21,1.27)	0.98 (0.95,1.01)	1.19* (1.06,1.34)	1.01 (0.88,1.15)
Drug Abuse	--	--	1.19* (1.13,1.20)	1.11* (1.05,1.19)	1.30* (1.26,1.34)	1.11* (1.08,1.15)	1.16 (0.99,1.36)	1.09 (0.95,1.24)
Psychoses	--	--	1.65* (1.57,1.74)	1.01 (0.95,1.08)	1.50* (1.46,1.55)	1.02 (0.98,1.07)	1.50* (1.33,1.70)	1.27* (1.13,1.43)
Depression	--	--	1.27* (1.22,1.33)	0.87* (0.83,0.92)	1.19* (1.16,1.23)	0.84* (0.82,0.87)	1.22* (1.10,1.35)	0.90* (0.83,0.98)

Intentional Self-Harm	--	--	1.40* (1.33,1.49)	1.16* (1.09,1.23)	1.17* (1.13,1.21)	1.09* (1.05,1.13)	1.16* (1.06,1.28)	1.02 (0.94,1.11)
Invasive Mechanical Ventilation	--	--	3.21* (2.84,3.63)	1.60* (1.41,1.82)	3.37* (3.20,3.55)	1.57* (1.50,1.64)	1.39* (1.23,1.59)	1.57* (1.39,1.78)
CALENDAR YEAR								
2007 (vs. 2006)	0.95 (0.80,1.13)	1.12 (0.85,1.47)	0.99 (0.91,1.08)	1.02 (0.95,1.09)	1.04 (0.98,1.10)	1.03 (0.98,1.08)	1.06 (0.90,1.24)	1.01 (0.87,1.17)
2008 (vs. 2006)	1.04 (0.84,1.28)	0.91 (0.68,1.23)	0.99 (0.91,1.08)	0.99 (0.92,1.07)	1.03 (0.97,1.09)	1.03 (0.98,1.07)	1.02 (0.87,1.20)	0.97 (0.85,1.10)
2009 (vs. 2006)	1.01 (0.84,1.22)	0.91 (0.69,1.22)	1.04 (0.96,1.13)	1.01 (0.94,1.09)	1.06 (1.00,1.12)	0.98 (0.93,1.03)	0.97 (0.83,1.12)	0.90 (0.79,1.02)
2010 (vs. 2006)	1.16 (0.97,1.39)	0.89 (0.69,1.15)	1.08 (1.00,1.18)	0.96 (0.90,1.03)	1.07* (1.01,1.14)	0.97 (0.93,1.02)	1.09 (0.93,1.27)	0.94 (0.83,1.07)

exp(b)= exponentiated beta coefficient; IR = incidence ratio; LoS = length of stay; CI = confidence interval

'- -' = variable omitted due to small sample size (n≤0.1%)

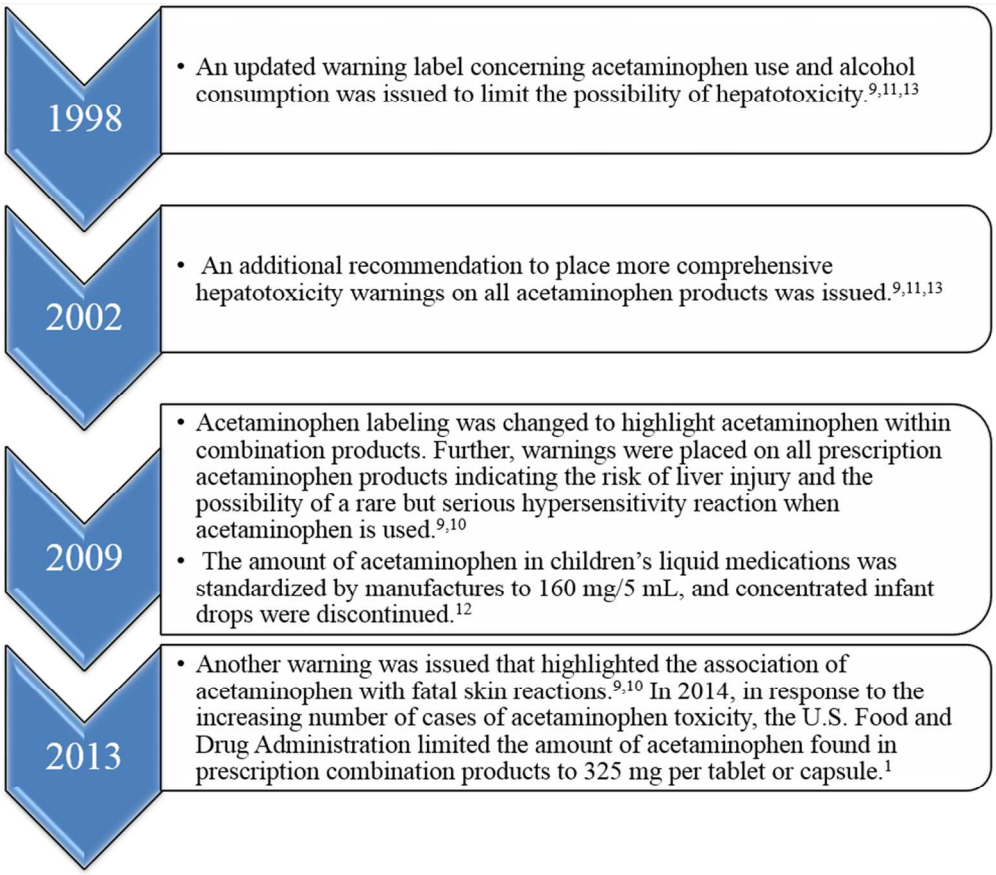
* Statistically significant below the computed Simes (1986) false discovery rate p-value for charges (p<0.036) and length of stay (p<0.024)

Figure 1. U.S. Food and Drug Administration Sequence of Updates concerning Acetaminophen

Figure 2. Overall Number of APAP toxicity-related ED Cases According to Age, 2006-2010.

Figure 3. Age-Adjusted of APAP toxicity-related ED Cases per 100,000 U.S. Population, 2006-2010.[A]

[A] Base U.S. populations for 2006-2010 obtained from the Centers for Disease Control and Prevention, National Vital Statistics System, Vintage 2012 bridged-race post-census U.S. resident population estimates



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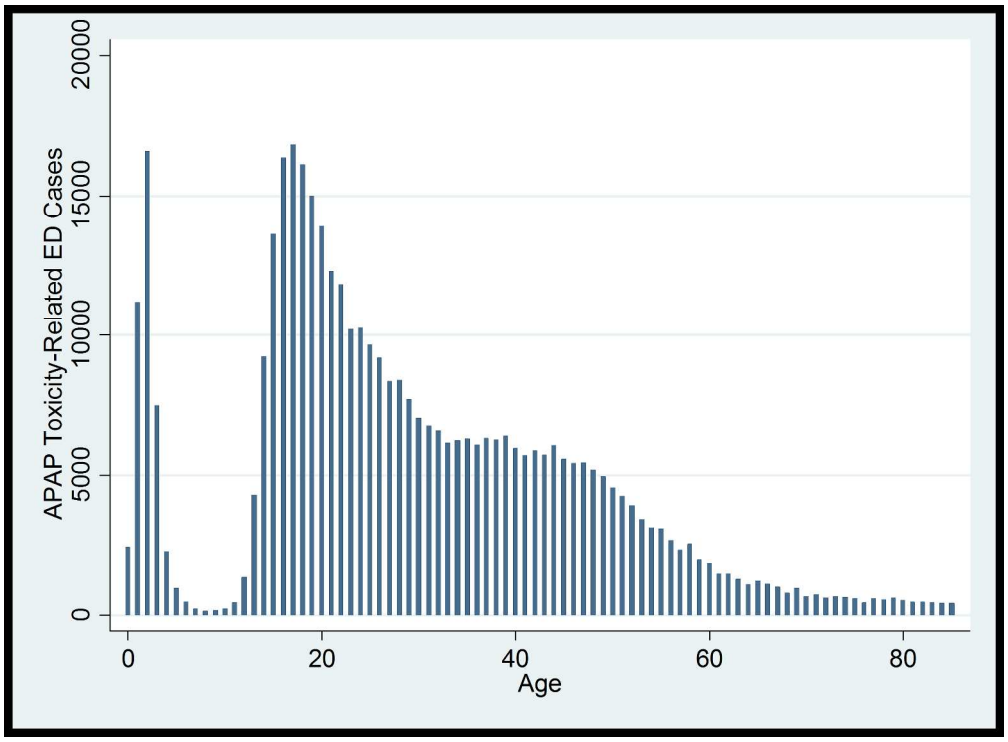

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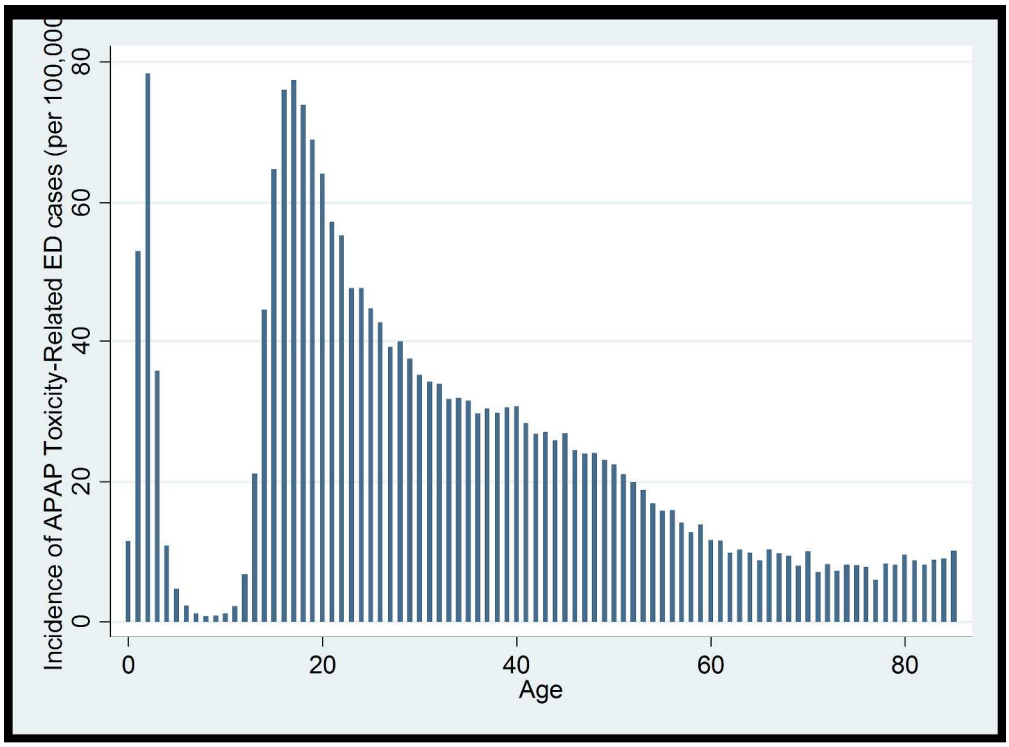

890x655mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	None conducted
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7; Tables 1-4
		(b) Give reasons for non-participation at each stage	6-7; Tables 1-4
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-4
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 (descriptives); Table 2-4 (multivariable analysis)
		(*b*) Report category boundaries when continuous variables were categorized	6-7; Tables 1-4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.