Clinical and economic characteristics of emergency department visits due to acetaminophen toxicity in the USA

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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 USA from 2006 to 2010.

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

Setting: Non-federal, non-rehabilitation, community EDs in the USA.

Participants: Inclusion criteria included any listed diagnosis identifying poisoning by aromatic analgesics paracetamol/APAP or associated supplementary code. Generalised 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 on patient, hospital and clinical characteristics.

Results: Across the 625.2 million ED visits in the USA from 2006 to 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. Overall, the incidence proportion was 27.10 per 100 000, exceeding 70 per 100 000 at age 2 years and ages 16–18 years. The total national bill was $1.06 billion per year (US$ 2014), and predominantly involved females (65.5%) and intentional self-harm (58.4%), which were notably higher within the 12–20 years age category (female12–20 years=74.8%, intentional self-harm12–20 years=71.4%). Behavioural 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=1351). 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 US from 2006 to 2010, with incidence proportions peaking at age 2 years and ages 16–18 years. After controlling for numerous factors, no consistent change was observed over the 5-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 on an estimated 130 million emergency department visits per year within the USA to report national estimates of case incidence and to provide assessments of clinical and economic outcomes.
- No specific categorisation existed to classify cases as being unsupervised ingestions or therapeutic misadventures (eg, overuse, medication errors); as per the type of acetaminophen (APAP) product consumed (eg, single-agent, combination products, tablets, liquid); and according to the amount ingested or serum levels observed.
- The use of N-acetyl cysteine or gastric decontamination was also not consistently captured within the data set, nor was a designation of acute liver injury directly attributable to APAP toxicity.

INTRODUCTION

As one of the most frequently used analgesics and antipyretics worldwide, acetaminophen (APAP) is a common single or combination agent among the numerous over-the-counter 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 US poison centre data indicate that APAP combinations were associated with the fourth highest number of fatalities compared with other medications in 2012, with APAP overdose being the principal cause of toxic drug ingestion that ultimately contributed to 39% of all acute liver failures.2,3 Hepatotoxicity is a well-recognised 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
Overall, previous studies have suggested that APAP overdoses leads annually to 56,000–78,000 emergency department (ED) visits, 26,000–34,000 hospitalisations, and an estimated 500 deaths.\textsuperscript{5–8}

The US Food and Drug Administration (FDA) has issued several updates in recent years involving APAP to increase the safety and limit the toxicity associated with the use of this medication, presented in figure 1.\textsuperscript{9–13}

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 USA from 2006 to 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 on patient, hospital and clinical characteristics.

\section*{METHODS}

This cross-sectional, retrospective investigation utilised 2006–2010 Nationwide Emergency Department Sample (NEDS) from the Agency for Healthcare Research and Quality (AHRQ).\textsuperscript{14} These data comprise nationally representative case presentations across hospital-based EDs within the non-federal, non-rehabilitation, community facilities and generalising, overall, to approximately 130 million ED visits that occur in the USA per year.\textsuperscript{14} Given the fully de-identified and anonymised data, this research is classified as exempt via human participants protection.\textsuperscript{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, Ninth edition, Clinical Manifestations (ICD-9-CM) codes identifying poisoning by aromatic analgesics paracetamol/APAP (ie, 965.4) or associated supplementary code (ie, E850.4: accidental poisoning by aromatic analgesics paracetamol/APAP).\textsuperscript{5–8} Previous research has addressed the challenges faced regarding the sensitivity and specificity of utilising diagnosis or supplementary codes to identify APAP toxicity-related cases, suggesting that the use of these aforementioned codes remains a valid approach.\textsuperscript{15} All ages were investigated and stratified according to the following age categories: (A) 0–11; (B) 12–20; (C) 21–64; and (D) ≥65 years.

\begin{itemize}
  \item An updated warning label concerning acetaminophen use and alcohol consumption was issued to limit the possibility of hepatotoxicity.\textsuperscript{9,11,13}
  \item An additional recommendation to place more comprehensive hepatotoxicity warnings on all acetaminophen products was issued.\textsuperscript{9,11,13}
  \item Acetaminophen labelling was changed to highlight acetaminophen within combination products. Further, warnings were placed on all prescription acetaminophen products indicating the risk of liver injury and the possibility of a rare but serious hypersensitivity reaction when acetaminophen is used.\textsuperscript{9,10}
  \item The amount of acetaminophen in children’s liquid medications was standardised by manufactures to 160 mg/5 mL, and concentrated infant drops were discontinued.\textsuperscript{12}
  \item Another warning was issued that highlighted the association of acetaminophen with fatal skin reactions.\textsuperscript{9,10} In 2014, in response to the increasing number of cases of acetaminophen toxicity, the U.S. Food and Drug Administration limited the amount of acetaminophen found in prescription combination products to 325 mg per tablet or capsule.\textsuperscript{1}
\end{itemize}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{US Food and Drug Administration sequence of updates concerning acetaminophen.}
\end{figure}
Clinical outcomes assessed were admission to an inpatient setting from the ED, mortality and requirement of invasive mechanical ventilation (ie, 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 analysed involved inflation-adjusted charges (US$ 2014) and inpatient length of stay. Independent predictor variables analysed were patient demographics (ie, 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 comprising 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.67 

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 analysed via a logistic regression. Generalised linear models were used to analyse inflation-adjusted charges and inpatient length of stay, specified by a γ 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 OR in a logistic regression; an exponentiated β value (exp(b)) in a γ regression; and an incidence ratio in a negative binomial regression.21 Therein, estimated coefficients may be interpreted as suggesting a reduced likelihood (<1.00) or no difference in likelihood (=1.00) or an increased likelihood (>1.00).

The Simes22 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. Inherently controlling for multiple comparisons by definition, the multinomial regression of disposition from the ED used an α level of 0.05 for significance and established treat-and-release cases as the baseline comparator. Owing 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 V.9.2 (Cary, North Carolina, USA) and STATA SE V.12.1 (College Station, Texas, USA).

RESULTS

Across the 625.2 million ED visits in the USA from 2006 to 2010, APAP-related toxicity was observed in 411 881 ED visits, with peaks occurring at approximately ages 0–5, 15–20 and 35–45 years (figure 2). Overall, the incidence proportion of APAP toxicity-related ED visits according to age per 100 000 per US population was 27.10, and by age category: 17.29 for ages 0–11 years; 63.17 for ages 12–20 years; 27.77 for ages 21–64 years; and 8.18 for ages 65 years and over. Reflecting in figure 3, peak incidence proportions exceeding 70 per 100 000 US population were observed at age 2 years (78.39 per 100 000) and ages 16–18 years (76.16, 77.52 and 74.00 per 100 000, respectively). Inpatient admissions averaged 12.46 per 100 000 US population, being

Figure 2 Overall number of acetaminphen (APAP) toxicity-related emergency department (ED) cases according to age, 2006–2010.
lowest for age group <12 years (0.50 per 100 000) and highest for cases from age group 12–20 years (23.34 per 100 000); peaks were noted at ages 18 (33.55 per 100 000) and 19 years (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 of inpatient lengths of stay, and these involved intentional self-harm (58.4%). Within the 12–20 years age category, cases were markedly female (74.8%) and involved intentional self-harm (71.4%). Among the APAP-related cases presenting to the ED, 45.4% resulted in direct inpatient admissions, 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 US population. Those treated-and-released directly in the ED, 45.4% resulted in direct inpatient admissions, 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 US population. Those treated-and-released directly in the ED, 45.4% resulted in direct inpatient admissions, 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 US population. Those treated-and-released directly in the ED involved chronic pulmonary disease, coagulopathy, and fluid and electrolyte disorders were significant predictors among cases aged ≥65 years (p<0.05). Intentional self-harm was also associated with over a 3× increase odds of admission across all age categories ≥12 years (p<0.05); was almost perfectly predictive of mortality cases among those 12–20 years of age; and was associated with a 8.57× (p<0.001) for those aged ≥65 years.

Comorbidities of liver disease, coagulopathy, fluid and electrolyte disorders, and weight loss/cachexia were associated with statistical significance (p<0.05), and large relative risks for both admission and mortality across age groups (sample size permitting for analysis). Specifically among paediatric cases <12 years of age, other neurological disorders, fluid and electrolyte disorders, and blood or deficiency anaemia were significantly associated with increased admissions (p<0.05). Across other age categories while considering admissions alone, comorbid conditions of valvular disease, peripheral vascular disorders, hypertension with complications, other neurological disorders, obesity, deficiency or other anaemia, 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 was observed consistently across the age categories.

The requirement of invasive mechanical ventilation (table 3) indicated that chronic pulmonary disease, coagulopathy, and fluid and electrolyte disorders were significant predictors among cases aged ≥12 years (p<0.028). Intentional self-harm was associated with a 1.49× higher odds among those aged 21–64 years, and a 2.42× higher odds among cases aged ≥65 years (p<0.028). Other neurological disorders, blood loss or...
| Table 1 | Descriptive statistics of ED cases associated with APAP toxicity according to age category in the USA, 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±SD) | 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 | ≤0.1% | 26.4% | 10.0% | 88.3% | 9.5% |
| Medicare | 48.9% | 51.5% | 35.1% | 7.8% | 39.7% |
| Medicaid | 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% | 26.6% | 34.5% | 28.2% | 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 tumour | ≤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% |

Continued
| Function                          | 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) |
|----------------------------------|-----------------------------------|----------------------------|----------------------------|-----------------------------------|--------------------|
| 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 anaemia | ≤0.1%                             | 1.5%                       | 4.3%                       | 12.3%                             | 3.4%               |
| Alcohol abuse                    | ≤0.1%                             | 5.7%                       | 19.8%                      | 6.6%                              | 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 (US$2014) (mean±SD) | $1343±3162 | $7884±13 034 | $15 624±31 404 | $28 631±50 515 | $12 766±28 414 |
| Annual: total national bill (US$ 2014) (mean±SD) | $11.45 million | $168.28 million | $789.11 million | $91.00 million | $1059.86 million |
| 2006–2010: total national bill (US$ 2014) (mean±SD) | $0.06 billion | $0.84 billion | $3.95 billion | $0.46 billion | $5.30 billion |
| Inpatient length of stay (mean±SD) | 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* | 17.29              | 63.17                      | 27.77                      | 8.18                              | 27.10              |
| Inpatient admissions per 100 000 persons per year* | 0.50                | 23.34                      | 15.50                      | 5.68                              | 12.46              |

*Base US populations for 2006–2010 obtained from the Centers for Disease Control and Prevention, National Vital Statistics System, Vintage 2012 bridged-race postcensus US resident population estimates.

APAP, acetaminophen; ED, emergency department; PUD, peptic ulcer disease.
## Table 2

| Patient characteristics | Admission (RRR, 95th CI) | Mortality (RRR, 95th CI) | Admission (RRR, 95th CI) | Mortality (RRR, 95th CI) | Admission (RRR, 95th CI) | Mortality (RRR, 95th CI) |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Age                     | 1.11** (1.03 to 1.19)   | 1.09*** (1.06 to 1.11)  | 1.49* (1.01 to 2.19)    | 1.01*** (1.01 to 1.02)  | 1.05*** (1.04 to 1.06)  | 1.00 (0.99 to 1.01)     |
|                         |                         |                         |                         |                         |                         |                         |
| Female sex              | 1.01 (0.77 to 1.33)     | 0.97 (0.89 to 1.06)     | 1.94 (0.28 to 13.60)    | 0.90*** (0.85 to 0.95)  | 0.96 (0.76 to 1.22)     | 1.24 (0.99 to 1.56)     |
|                         |                         |                         |                         |                         |                         |                         |
| Payer (vs commercial insurance) |                |                         |                         |                         |                         |                         |
| Medicare                | –                       | 0.54* (0.30 to 0.97)    |                         | 0.83** (0.75 to 0.92)   | 0.87 (0.59 to 1.28)     | 1.17 (0.49 to 2.78)     |
| Medicaid                | 0.62** (0.45 to 0.86)   | 0.97 (0.87 to 1.07)     | 0.42 (0.09 to 1.85)     | 1.02 (0.94 to 1.11)     | 0.90 (0.64 to 1.27)     | 0.64 (0.25 to 1.69)     |
| Other                   | 0.58* (0.37 to 0.92)    | 0.86* (0.76 to 0.98)    | 0.32 (0.07 to 1.46)     | 0.90* (0.83 to 0.98)    | 0.87 (0.62 to 1.22)     | 0.31* (0.10 to 0.93)    |
| Income quartile (vs lowest) |                |                         |                         |                         |                         |                         |
| 2nd quartile            | 1.12 (0.79 to 1.59)     | 1.13* (1.00 to 1.27)    | 2.50 (0.21 to 29.40)    | 1.05 (0.97 to 1.14)     | 0.93 (0.67 to 1.28)     | 0.84 (0.61 to 1.14)     |
| 3rd quartile            | 0.75 (0.48 to 1.16)     | 1.15* (1.02 to 1.29)    | 13.40* (1.59 to 113.21) | 1.08 (0.98 to 1.20)     | 1.21 (0.86 to 1.69)     | 1.08 (0.75 to 1.54)     |
| 4th quartile            | 0.90 (0.58 to 1.39)     | 1.24** (1.07 to 1.43)   |                         | 1.26** (1.13 to 1.41)   | 1.20 (0.83 to 1.73)     | 1.18 (0.83 to 1.69)     |
| Rural residence          | 2.26* (1.19 to 4.30)    | 1.30* (1.06 to 1.60)    | 0.82 (0.18 to 3.78)     | 1.24** (1.07 to 1.44)   | 1.21 (0.72 to 2.03)     | 1.36 (0.76 to 2.43)     |
| Clinical characteristics |                       |                         |                         |                         |                         |                         |
| Congestive heart failure| –                       |                         |                         |                         |                         |                         |
| Valvular disease         | –                       | 3.94* (1.15 to 13.50)   |                         | 4.47*** (2.70 to 7.40)  | 2.06 (0.60 to 7.01)     | 3.64** (1.67 to 7.92)   |
| Pulmonary circulation disorders |                |                         |                         |                         |                         |                         |
| Peripheral             | –                       |                         |                         |                         |                         |                         |
| Hypertension with complications |                | 2.46*** (1.53 to 3.96)  |                         | 2.27** (1.32 to 3.92)   | 1.66 (0.59 to 4.68)     | 5.74*** (2.32 to 14.21) |
| Paralysis               | –                       | 1.54 (0.31 to 7.54)     |                         | 3.28** (1.90 to 5.65)   | 11.47*** (4.84 to 27.23)| 1.75 (0.57 to 5.38)     |
| Other neurological disorders |                | 3.14*** (2.40 to 4.12)  | 50.97*** (10.75 to 241.71) | 2.19*** (1.95 to 2.47)  | 2.21*** (1.55 to 3.15)  | 1.97*** (1.40 to 2.78)  |
| Chronic pulmonary disease|                  | 1.94 (0.95 to 3.96)     | 2.35*** (1.93 to 2.86)  | 2.01*** (1.78 to 2.28)  | 1.29 (0.83 to 2.00)     | 3.21*** (2.27 to 4.54)  |
| Diabetes with complications |                | 0.97 (0.58 to 1.64)     |                         | 4.52*** (2.55 to 8.01)  | 3.57* (1.01 to 12.64)   | 2.34 (0.62 to 8.88)     |
| Hypothyroidism           | –                       | 1.04 (0.58 to 1.85)     |                         | 2.67** (2.16 to 3.31)   | 1.52 (0.77 to 2.99)     | 2.15*** (1.43 to 3.24)  |
| Renal failure            | –                       | 2.11 (0.24 to 18.52)    |                         | 2.39** (1.51 to 3.80)   | 3.16* (1.38 to 7.25)    | 0.50 (0.22 to 1.12)     |
| Liver disease            | –                       | 2.98* (1.03 to 8.64)    |                         | 12.13*** (5.98 to 24.60) | 47.89*** (21.53 to 106.52) | Omitted^6       |
| HIV/AIDS                | –                       | –                       |                         | 2.18 (0.82 to 5.83)     | 6.86* (1.35 to 34.92)   | –                       |

Continued
### Table 2

Continued

| 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)     |
| Lymphoma                         |                             |                             |                                 |
| –                                | –                           | 1.43 (0.60 to 3.43)         | 4.24 (0.69 to 25.95)            |
| Metastatic cancer                |                             |                             |                                 |
| –                                | –                           | 6.08*** (2.22 to 16.67)     | 30.32*** (8.35 to 110.18)       |
| Solid tumour                     |                             |                             |                                 |
| –                                | –                           | 5.77** (2.13 to 15.59)      | 2.41 (0.98 to 5.91)             |
| Rheumatoid arthritis/collagen    |                             |                             |                                 |
| –                                | –                           | 3.18 (0.78 to 13.04)        | 1.76 (0.29 to 10.55)            |
| Vascular disease                 |                             |                             |                                 |
| Coagulopathy                     |                             |                             |                                 |
| –                                | –                           | 3.60*** (1.68 to 7.50)      | 19.01** (2.50 to 144.65)        |
| Obesity                          |                             |                             |                                 |
| –                                | –                           | 7.70*** (5.09 to 11.87)     | 28.39*** (17.45 to 468.08)      |
| Weight loss                      |                             |                             |                                 |
| –                                | –                           | 1.70*** (1.66 to 1.76)      | 1.10 (0.17 to 6.74)             |
| Fluid and electrolyte disorders  |                             |                             |                                 |
| –                                | –                           | 1.70*** (1.66 to 1.76)      | 1.10 (0.17 to 6.74)             |
| Blood loss or deficiency         |                             |                             |                                 |
| Anaemia                          |                             |                             |                                 |
| –                                | –                           | 1.70*** (1.66 to 1.76)      | 1.10 (0.17 to 6.74)             |
| Alcohol abuse                    |                             |                             |                                 |
| –                                | –                           | 2.32*** (1.94 to 2.77)      | 2.96*** (1.76 to 4.95)          |
| Drug abuse                       |                             |                             |                                 |
| –                                | –                           | 2.37*** (1.27 to 2.59)      | 1.70 (0.60 to 5.44)             |
| Psychoses                        |                             |                             |                                 |
| –                                | –                           | 1.75*** (1.62 to 1.89)      | 1.95*** (1.44 to 2.64)          |
| Depression                       |                             |                             |                                 |
| –                                | –                           | 1.75*** (1.62 to 1.89)      | 1.95*** (1.44 to 2.64)          |
| Intentional self-harm            |                             |                             |                                 |
| –                                | –                           | 3.03*** (2.81 to 3.26)      | 4.89*** (3.59 to 6.64)          |
| Calendar year                    |                             |                             |                                 |
| 2007 (vs 2006)                   |                             |                             |                                 |
| 0.78 (0.48 to 1.28)              |                             | 0.92 (0.80 to 1.06)         | 0.99 (0.88 to 1.11)             |
| 2008 (vs 2006)                   |                             | 0.88 (0.72 to 0.98)         | 0.87 (0.77 to 1.00)             |
| 2009 (vs 2006)                   |                             | 0.88 (0.74 to 1.03)         | 0.83 (0.73 to 0.95)             |
| 2010 (vs 2006)                   |                             | 0.88 (0.74 to 1.03)         | 0.83 (0.73 to 0.95)             |

Omitted\(^a\), variable omitted due to near-perfect association with survival (ie, OR<0.01).

Omitted\(^b\), variable omitted due to near-perfect association with mortality (ie, RRR>10 000).

\(^*\)Statistically significant at p<0.05.

\(^**\)Statistically significant at p<0.01.

\(^***\)Statistically significant at p<0.001.

–, Variable omitted due to small sample size (n<0.1%); APAP, acetaminophen; ED, emergency department; RRR, relative risk ratio.
| 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 | Invasive mechanical ventilation | Invasive mechanical ventilation | Invasive mechanical ventilation |
| (OR, 95th CI)                   | (OR, 95th CI)                | (OR, 95th CI)               | (OR, 95th CI)                    |
| Patient characteristics        |                             |                             |                                  |
| Age                             | 1.26* (1.16 to 1.36)        | 1.03* (1.02 to 1.03)        | 0.96* (0.95 to 0.98)             |
| Female sex                      | 0.46* (0.35 to 0.60)        | 0.85* (0.78 to 0.92)        | 1.12 (0.84 to 1.50)              |
| Payer (vs commercial insurance) |                             |                             |                                  |
| Medicare                        | 0.62 (0.15 to 2.58)         | 0.82* (0.72 to 0.95)        | 1.03 (0.37 to 2.84)              |
| Medicaid                        | 0.92 (0.67 to 1.28)         | 1.05 (0.94 to 1.17)         | 1.52 (0.52 to 4.45)              |
| Other                           | 1.01 (0.71 to 1.43)         | 0.78* (0.70 to 0.87)        | 0.46 (0.12 to 1.79)              |
| Income quartile (vs lowest)     |                             |                             |                                  |
| 2nd quartile                    | 0.92 (0.63 to 1.35)         | 1.10 (0.99 to 1.23)         | 1.12 (0.76 to 1.65)              |
| 3rd quartile                    | 0.92 (0.62 to 1.37)         | 1.23* (1.08 to 1.39)        | 1.01 (0.69 to 1.48)              |
| 4th quartile                    | 0.92 (0.61 to 1.40)         | 1.08 (0.95 to 1.24)         | 0.91 (0.58 to 1.41)              |
| Rural residence                 | 1.96 (0.97 to 3.99)         | 1.25 (1.01 to 1.55)         | 1.07 (0.55 to 2.10)              |
| Hospital characteristics        |                             |                             |                                  |
| Rural location                  | 0.38* (0.16 to 0.91)        | 0.61* (0.47 to 0.77)        | 0.57 (0.26 to 1.26)              |
| Teaching facility               | 1.51* (1.12 to 2.03)        | 1.10 (0.98 to 1.22)         | 1.27 (0.95 to 1.71)              |
| Region (vs Northeast)           |                             |                             |                                  |
| Midwest                         | 0.79 (0.53 to 1.18)         | 0.87 (0.75 to 1.01)         | 0.88 (0.56 to 1.36)              |
| South                           | 0.77 (0.51 to 1.17)         | 0.99 (0.86 to 1.15)         | 0.90 (0.59 to 1.36)              |
| West                            | 0.72 (0.45 to 1.13)         | 0.94 (0.81 to 1.08)         | 0.90 (0.57 to 1.42)              |
| Clinical characteristics        |                             |                             |                                  |
| Congestive heart failure        |                             | 1.61* (1.17 to 2.21)        | 1.39 (0.86 to 2.25)              |
| Valvular disease                |                             | 1.12 (0.78 to 1.62)         | 0.77 (0.35 to 1.73)              |
| Pulmonary circulation disorders |                             | 2.66* (1.46 to 4.86)        | 0.83 (0.27 to 2.53)              |
| Peripheral vascular disorders   |                             | 1.25 (0.70 to 2.21)         | 1.06 (0.56 to 2.02)              |
| Hypertension with complications |                             | 2.48* (1.11 to 5.56)        | 0.86 (0.54 to 1.36)              |
| Paralysis                       |                             | 1.95* (1.29 to 2.94)        | 0.26 (0.03 to 2.25)              |
| Other neurological disorders    |                             | 1.88* (1.66 to 2.13)        | 1.10 (0.76 to 1.60)              |
| Chronic pulmonary disease       |                             | 1.75* (1.26 to 2.44)        |                                  |
| Diabetes with complications     |                             | 0.91 (0.56 to 1.46)         | 0.62 (0.21 to 1.79)              |
| Hypothyroidism                  |                             | 0.91 (0.75 to 1.11)         | 0.56 (0.35 to 0.89)              |
| Renal failure                   |                             | 1.25 (0.82 to 1.92)         | 0.42 (0.19 to 0.94)              |
| Liver disease                   |                             | 2.23* (1.77 to 2.81)        | 2.47* (1.17 to 5.21)             |
| AIDS                            |                             | 2.11* (1.23 to 3.60)        |                                  |
| Lymphoma                        |                             | 1.93 (0.84 to 4.40)         |                                  |
| Metastatic cancer               |                             | 1.68 (0.79 to 3.59)         | 0.47 (0.09 to 2.47)              |
| Solid tumour                    |                             | 0.68 (0.32 to 1.44)         | 0.27 (0.06 to 1.22)              |
| Rheumatoid arthritis/ collagen vascular disease | 1.59* (1.18 to 2.14) | 0.48 (0.18 to 1.25) |
| Coagulopathy                    |                             | 2.58* (1.13 to 5.89)        | 2.17* (1.27 to 3.70)             |
| Obesity                         |                             | 0.98 (0.29 to 3.29)         | 0.49 (0.17 to 1.35)              |
| Weight loss/cachexia            |                             | 1.90* (1.43 to 2.53)        | 1.92* (1.13 to 3.28)             |
| Fluid and electrolyte disorders |                             | 5.84* (4.26 to 8.00)        | 2.26* (1.71 to 3.00)             |
| Blood loss or deficiency anaemia|                             | 2.07* (1.33 to 3.97)        | 1.15 (0.79 to 1.67)              |

Continued
Among psychoses were associated with increased odds (p<0.028) of requiring invasive mechanical ventilation within the 12–20 years age category. Several factors had near-perfect associations with invasive mechanical ventilation within the 12–20 years age group. Notably, over time, no consistent change in odds of requiring 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 years; HIV/AIDS was significant in the 21–64 years 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 anaemia; 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 USA from 2006 to 2010, assessing the independent associations between outcomes of inpatient admission, mortality, required use of invasive mechanical ventilation, charges and lengths of stay based on 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 the summing up to a national bill of $1.06 billion per year (US$ 2014). Some 37.2% cases 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=1351), though representing an overall change from 27.15 to 25.78 visits per 100 000 US population annually.

Comparatively, Nourjah et al estimated that attributable APAP overdoses from 1993 to 1999 were lower than aforementioned findings, with approximately 56 000 ED visits, 26 000 hospitalisations and 458 deaths per year; Li and Martin also reported a decrease in rates from 2001 to 2007 to slightly less than 45 000 ED visits per year. From 1993 to 1999, Li and Martin found a lower number of ED visits, at 21.03 visits per 100 000 persons per year and decreasing to 15.21 from 2000 to 2007. It is critical to note that Nourjah et al and Li and Martin utilised 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; however, unintentional poisonings appeared to be similar across various data sources.

Manthripragada et al presented results illustrating differences present within nationally representative studies, in which the number of APAP toxicity-associated ED visits may be potentially underestimated by perhaps one-third to one-half. More closely parallel to the present study, Budnitz et al reported 78 414 annual ED visits associated with APAP overdoses from 2005 to 2006 using data from the National Electronic Injury Surveillance System (NEISS), while Manthripragada et al found an age-adjusted rate of 13.9 hospitalisations per 100 000 US population from 2000 to

### Table 3

| Calendar year | 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) |
| Alcohol abuse | – | 1.90* (1.34 to 2.71) | 1.26* (1.16 to 1.37) | 0.78 (0.47 to 1.29) |
| Drug abuse    | – | 1.50* (1.10 to 2.04) | 1.16* (1.06 to 1.27) | 0.62 (0.32 to 1.18) |
| Psychoses     | – | 1.62* (1.12 to 2.35) | 1.51* (1.37 to 1.67) | 1.28 (0.91 to 1.80) |
| Depression    | – | 1.10 (0.81 to 1.49) | 1.04 (0.95 to 1.14) | 0.87 (0.61 to 1.23) |
| Intentional self-harm | – | 1.34 (0.96 to 1.87) | 1.49* (1.35 to 1.63) | 2.42* (1.80 to 3.25) |

Omitted A, variable omitted due to near-perfect association with no requirement of intubation (ie, OR<0.01).

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

*– , Variable omitted due to small sample size (n<0.1%); APAP, acetaminophen; ED, emergency department.
### 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), 95% CI)         | Charges (exp(b), 95% CI)     | Charges (exp(b), 95% CI)     | Charges (exp(b), 95% CI)         |
| Patient characteristics          |                              |                             |                                  |
| Age                              | 1.04* (1.01 to 1.07)         | 1.03 (0.99 to 1.07)         | 1.05* (1.04 to 1.06)             | 0.99 (0.98 to 1.01) |
| Female sex                       | 0.94 (0.86 to 1.02)          | 1.07 (0.88 to 1.31)         | 0.97 (0.93 to 1.01)              | 1.00 (0.95 to 1.05) |
| Payer (vs commercial)            |                              |                              |                                  |                      |
| Medicare                         |                              | 0.93 (0.65 to 1.33)         | 1.55 (0.90 to 2.65)              | 0.98 (0.94 to 1.03)  |
| Medicaid                         | 0.81* (0.71 to 0.92)         | 0.96 (0.79 to 1.16)         | 0.92* (0.87 to 0.96)             | 0.98* (0.93 to 0.98) |
| Other                            | 0.89 (0.71 to 1.05)          | 1.08 (0.75 to 1.55)         | 0.87* (0.82 to 0.92)             | 0.97* (0.92 to 0.98) |
| Income quartile (vs lowest)      |                              |                              |                                  |                      |
| 2nd quartile                     | 1.06 (0.95 to 1.18)          | 1.27 (0.97 to 1.66)         | 1.04 (0.98 to 1.10)              | 1.05 (0.99 to 1.11)  |
| 3rd quartile                     | 1.06 (0.88 to 1.28)          | 1.33 (0.95 to 1.88)         | 1.03 (0.97 to 1.10)              | 1.05 (0.98 to 1.12)  |
| 4th quartile                     | 0.95 (0.79 to 1.14)          | 1.28 (0.97 to 1.68)         | 1.03 (0.95 to 1.12)              | 1.00 (0.93 to 1.07)  |
| Rural residence                  | 1.19* (0.97 to 1.45)         | 1.12 (0.71 to 1.75)         | 1.00 (0.92 to 1.08)              | 0.96 (0.86 to 1.07)  |
| Hospital characteristics         |                              |                              |                                  |                      |
| Rural location                   | 0.68* (0.55 to 0.87)         | 0.86 (0.52 to 1.43)         | 0.73* (0.66 to 0.81)             | 0.80* (0.71 to 0.91)  |
| Teaching facility                | 1.28* (1.10 to 1.49)         | 1.23 (0.98 to 1.54)         | 1.14* (1.06 to 1.24)             | 1.03 (0.96 to 1.10)  |
| Region (vs Northeast)            |                              |                              |                                  |                      |
| Midwest                          | 0.74* (0.64 to 0.87)         | 0.72* (0.55 to 0.95)        | 0.78* (0.71 to 0.86)             | 0.82* (0.76 to 0.90)  |
| South                            | 0.89 (0.76 to 1.05)          | 0.91 (0.68 to 1.23)         | 0.88* (0.79 to 0.98)             | 0.91* (0.85 to 0.97)  |
| West                             | 0.35* (0.27 to 0.45)         | 0.71* (0.54 to 0.95)        | 0.64* (0.57 to 0.73)             | 0.76* (0.71 to 0.82)  |
| Clinical characteristics         |                              |                              |                                  |                      |
| Congestive heart failure         |                              |                              |                                  |                      |
| Valvular disease                 |                              |                              |                                  |                      |
| Pulmonary circulation            |                              |                              |                                  |                      |
| Hypertension with complications  |                              |                              |                                  |                      |
| Paralysis                        | 1.51* (1.28 to 1.79)         | 1.35* (1.17 to 1.56)        | 1.43* (1.19 to 1.71)             | 1.23* (1.05 to 1.45)  |
| Other neurological disorders     |                              |                              |                                  |                      |
| Chronic pulmonary disease        | 0.98 (0.80 to 1.20)          | 0.81 (0.61 to 1.08)         | 1.18* (1.11 to 1.26)             | 0.97 (0.91 to 1.04)  |
| Diabetes with complications      |                              |                              |                                  |                      |
| Hypothyroidism                   | 1.02 (0.86 to 1.20)          | 0.90 (0.74 to 1.11)         | 1.27* (1.11 to 1.45)             | 1.07 (0.95 to 1.22)  |
| Renal failure                    | 1.31 (1.00 to 1.72)          | 1.39* (1.08 to 1.79)        | 1.23* (1.15 to 1.31)             | 1.01 (0.94 to 1.08)  |
| Liver disease                    | 1.41 (0.84 to 2.37)          | 0.88 (0.51 to 1.51)         | 1.43* (1.23 to 1.67)             | 1.16 (1.00 to 1.33)  |
| HIV/AIDS                         | 1.76* (1.30 to 2.39)         | 1.53* (1.15 to 2.03)        | 2.00* (1.80 to 2.23)             | 1.52* (1.39 to 1.67)  |
| Lymphoma                         |                              |                              | 2.34* (1.66 to 3.31)             | 1.52* (1.19 to 1.95)  |
| Metastatic cancer                |                              |                              |                                  |                      |
| Solid tumour                     |                              |                              | 1.23 (0.97 to 1.56)              | 1.12 (0.92 to 1.36)  |
| Rheumatoid arthritis/            |                              |                              | 1.02 (0.84 to 1.24)              | 0.88 (0.72 to 1.08)  |
| collagen vascular disease        |                              |                              |                                  |                      |
| Coagulopathy                     |                              |                              | 1.64* (1.16 to 2.31)             | 1.48* (1.07 to 2.03)  |
| Obesity                          |                              |                              | 1.95* (1.84 to 2.08)             | 1.82* (1.76 to 1.88)  |
| Weight loss/cachexia             |                              |                              |                                  |                      |
| Fluid and electrolyte disorders  |                              |                              |                                  |                      |
| Glucose                          | 3.04* (2.46 to 3.78)         | 1.98* (1.63 to 2.41)        | 2.08* (1.91 to 2.26)             | 1.48* (1.39 to 1.59)  |
| Paralysis                        | 1.58* (1.40 to 1.79)         | 1.14 (1.01 to 1.28)         | 1.39* (1.31 to 1.48)             | 1.11 (1.01 to 1.22)  |
| Weight loss/cachexia             |                              |                              | 1.99* (1.63 to 2.42)             | 1.83* (1.58 to 2.13)  |
| Fluid and electrolyte disorders  |                              |                              | 1.16* (1.13 to 1.20)             | 1.81* (1.62 to 2.02)  |

Continued
Table 4

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.27 (1.17 to 1.37) | 1.11 (1.00 to 1.23) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.01 (0.84 to 1.22) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.07 (0.89 to 1.28) |

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

### Blood loss or deficiency

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.22 (1.12 to 1.33) | 1.12 (1.00 to 1.26) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.07 (0.90 to 1.25) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.08 (0.90 to 1.30) |

### Anaemia

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.22 (1.12 to 1.33) | 1.12 (1.00 to 1.26) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.07 (0.90 to 1.25) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.08 (0.90 to 1.30) |

### Alcohol abuse

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.22 (1.12 to 1.33) | 1.12 (1.00 to 1.26) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.07 (0.90 to 1.25) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.08 (0.90 to 1.30) |

### Drug abuse

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.22 (1.12 to 1.33) | 1.12 (1.00 to 1.26) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.07 (0.90 to 1.25) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.08 (0.90 to 1.30) |

### Depression

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.22 (1.12 to 1.33) | 1.12 (1.00 to 1.26) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.07 (0.90 to 1.25) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.08 (0.90 to 1.30) |

### Intentional self-harm

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.22 (1.12 to 1.33) | 1.12 (1.00 to 1.26) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.07 (0.90 to 1.25) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.08 (0.90 to 1.30) |

### Invasive mechanical ventilation

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 11 years and below (N=42 623) | 1.22 (1.12 to 1.33) | 1.12 (1.00 to 1.26) |
| 12–20 years (N=106 725) | 1.20 (1.10 to 1.31) | 1.07 (0.90 to 1.25) |
| 21 years and above (N=246 640) | 1.27 (1.14 to 1.33) | 1.08 (0.90 to 1.30) |

### Year

| Age | Charges (exp(b)) | LoS (IR, 95th CI) |
|-----|------------------|------------------|
| 2008 (vs 2006) | 1.04 (0.84 to 1.28) | 1.03 (0.81 to 1.30) |
| 2009 (vs 2006) | 1.05 (0.86 to 1.27) | 1.04 (0.82 to 1.31) |
| 2010 (vs 2006) | 1.16 (0.97 to 1.39) | 1.07 (0.88 to 1.30) |

*Statistically significant below the computed Simes (1986) p value for charges (p<0.036) and LoS (p<0.024).

2006. Also consistent with the current work, a decrease in the number of ED visits or hospitalisations 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 US 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 to 2 and 15–22 years, peaking at over 70 per 100 000 specifically at age 2 years and ages 16–18 years. Broader surveillance figures suggest that age-adjusted overall non-fatal injuries relating to poisoning of any type was 36.14 per 100 000 in 2013, though the crude rate for ages 1–2 years is 12.27 per 100 000 and is 35.79 per 100 000 for ages 15–22 years.23 Prior investigations suggest a substantially large number of APAP toxicity-related ED visits occur among young children, adolescents and young adults; Li and Martin6 reported 72.42 visits per 100 000 for cases under 5 years of age, 61.91 per 100 000 for ages 15–17 years and 40.92 per 100 000 for ages 18–24 years.7 24 25 Budnitz et al7 found that 13.4% of APAP overdose ED visits were attributed to unsupervised ingestions by children aged 5 years and under, a finding which has been observed across other work.26–28 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 26

A majority of cases in the current work involved the female sex (65.5%) and intentional self-harm (58.4%): these were highest in the 12–20 years age category: 74.8% female and 71.4% intentional self-harm. Similar to Li and Bradly (2011), behavioural 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 ≥12 years within the multivariable analyses.8 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 al7 reported that 69.8% of ED visits involving APAP overdoses from 2006 to 2007 were associated with self-directed violence, peaking among those between 15 and 24 years of age, with 75% ultimately resulting in either psychiatric or inpatient hospitalisations. Surveillance data also suggest that one-quarter of all ED cases for intentional poisoning involve APAP.23 Budnitz et al7 also noted that females had the highest rates of intentional self-harm, especially as adolescents or young adults. 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. Importantly, Manthripragada et al emphasised 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 (ie, E-codes) or differences in hospital reporting requirements.

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. Li and Martin (2011) reported a 8.62× 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 2× higher relative risk of admission (age categories ≥12 years), a 1.75× higher relative risk of mortality (ages 21–64 years), over 1.19× higher charges (age categories ≥12 years), and 1.26× or greater odds of invasive mechanical ventilation (ages 12–20 and 21–64 years). Paediatric admission cases of age <12 years were associated with other neurological disorders, fluid and electrolyte disorders, and blood loss or deficiency anaemia; Budnitz et al reported that most of the unsupervised ingestions of APAP were observed among children aged <6 years, typically treated-and-released from the ED setting via gastric decontamination or N-acetyl cysteine (NAS) treatment.

Although findings from this study provide updated information concerning the burden of APAP-related ED visits in the USA, some important study limitations exist. While similar coding algorithms were used, as in other retrospective studies, to identify APAP-toxicity cases, no specific categorisation was present that may have classified cases as being unsupervised ingestions or therapeutic misadventures (eg, overuse, medication errors); as per the type of APAP product consumed (eg, single-agent, combination products, tablets, liquid), and according to the estimated amount ingested or serum levels observed. In this context, Budnitz et al 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 overingestion from multiple source products. The use of NAS or gastric decontamination was also not consistently captured within the data set, nor was a designation of acute liver injury directly attributable to APAP toxicity. Generalisations of findings beyond acute care settings are not appropriate to estimate the prevalence of APAP poisoning in the USA, as cases presenting to poison centres or within ambulatory practices are not captured. At the time of this study’s initiation, the 2006–2010 time frame reflected the entirety of HCUP NEDS data; the complex process of collecting, integrating, validating and distributing data of this nature typically takes 2 years. 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 on consumer perceptions, attitudes, beliefs, knowledge and health literacy.

**CONCLUSION**

This nationally representative study of ED visits in the USA highlights a substantial public health impact of APAP toxicity-related cases from 2006 to 2010. Overall, 82 376 cases per year were observed, summing up to a national bill of $1.06 billion. The ED visit average rate across all ages was 27.10 ED visits per 100 000 US population, exceeding 70 per 100 000 for age 2 years and ages 16–18 years. After controlling for numerous factors, no consistent temporal change was observed during the 5-year time horizon concerning outcomes of admission, mortality, invasive mechanical ventilation, charges or length of stay.

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