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CHARACTERIZATION AND ECONOMIC BURDEN ASSOCIATED WITH PEDIATRIC OPIOID EXPOSURES AND POISONINGS

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Dedication

This research is dedicated to my mother – Radha Patel.

"Mummy, I hope you are looking from heaven and feeling proud. I love you and how I wish I could share this success with you!"

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List of Abbreviations

AAPCC	American Association of Poison Control Centers
ADE/ADR	Adverse drug event/Adverse drug reaction
AHRQ	Agency for Healthcare Research and Quality
APR-DRG	All Patients Refined Diagnosis Related Group
AMA	Against medical advice
APAP	Acetaminophen
APS	American Pain Society
AOR	Adjusted odds ratio
AIC	Akaike Information Criterion
ASA	Acetylsalicylic acid
BLS	Bureau of Labor Statistics
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPI	Consumer Price Index
CPT	Current Procedural Terminology
CCR	Cost-to-charge ratios
CCS	Clinical Classification Software
CMS	Centers for Medicare & Medicaid Services
CNC	Cough and cold products

CVS	Cardiovascular
DAWN	Drug Abuse Warning Network
DRG	Diagnosis Related Group
DPV	Daily production value
ECI	Employment Cost Index
ED	Emergency department
FSMB	Federation of State Medical Board
GAO	Government Accountability Office
GI	Gastrointestinal
GLM	Generalized linear model
GLMM	Generalized linear mixed model
HCRU	Health care resources use
HCUP	Healthcare Cost and Utilization Project
HCF	Health care facility
HH/FHH	Household/Family household
IOM	Institute of Medicine
ICD	International Classification of Diseases, 9th Revision, Clinical Modification
IRB	Institutional review board
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
KID	Kids' Inpatient Database
LOS	Length of stay
MCMC	Markov chain Monte Carlo

MCOD	Multiple Cause-of-Death
MPFS	Medicare Physician Fee Schedule
NPDS	National Poison Data System
NVSS	National Vital Statistics System
NSDUH	National Survey on Drug Use and Health
NEDS	Nationwide Emergency Department Sample
NEISS	National Electronic Injury Surveillance System
NHAMCS	National Hospital Ambulatory Medical Care Survey
NIS	Nationwide Inpatient Sample
NSAIDS	Nonsteroidal anti-inflammatory drugs
OLS	Ordinary Least Squares
OTC	Over-the-counter
PC	Poison Center
PICU	Pediatric Intensive Care Unit
PVFP	Present value of expected future productivity
QIC	Quasi-likelihood criteria
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
Rx	Prescription
SES	Socioeconomic status
SPI	Specialists in poison information
SD	Standard deviation
SE	Standard error
SNF	Skilled nursing facility

T/E & R	Treated, evaluated and released
USD	United States dollar
WHO	World Health Organization
ZIP	Zone Improvement Plan

Abstract

CHARACTERIZATION AND ECONOMIC BURDEN ASSOCIATED WITH PEDIATRIC OPIOID EXPOSURES AND POISONINGS

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Introduction

Drug exposures and poisonings in children continue to be an important public health concern. Among different drugs involved in pediatric exposures and poisonings, opioids are an important class due to their increased medical and nonmedical use. The main objectives of this study were: 1) to examine the prevalence and characteristics of opioid exposures, 2) to estimate the economic costs associated with opioid poisonings, and 3) to examine the characteristics associated with opioid poisoning-related health care resource use (HCRU) and costs in children.

Methods

Data from the National Poison Data System from January 1, 2010 to December 31, 2014 were utilized to identify opioid exposures and poisonings in children <18 years. Standardized prevalence

rates were calculated. Opioid exposures were characterized based on sociodemographic and clinical factors.

Economic costs were estimated using the 2012 Nationwide Emergency Department Sample, Kids' Inpatient Database, Multiple Cause-of-Death file and other published sources, applying a societal perspective. Direct costs included costs associated with ED visits, hospitalizations and ambulance transports. Indirect cost were estimated using the human capital method and included productivity costs due to caregivers' absenteeism and premature mortality among children.

Results

There were a total of 83,418 pediatric opioid exposures over the 5-year period and nearly half of them resulted in poisoning. The epidemiology of opioid exposures differed considerably by age. Opioid exposures were more prevalent and mainly accidental in young children. Exposures in adolescents were more likely to be intentional and severe.

The total economic costs of pediatric opioid poisonings in the United States were calculated at $230.8 million in 2012. Total direct costs were estimated to be over $21.1 million, the majority resulting from opioid poisoning-related ED visits and inpatients stays. Total productivity costs were calculated at $209.7 million, and 98.6% of these costs were attributed to opioid poisoning-related mortality.

Conclusions

Opioid exposures and poisonings in children continue to occur and impose an economic burden on the society. Development of targeted age-specific prevention efforts is warranted. Quantified

HCRU and costs associated with pediatric opioid poisonings can help decision-makers to understand the economic trade-offs in planning interventions.

Chapter 1: Introduction

Opioids and their therapeutic uses

Opioids are any natural, semi-synthetic or synthetic substances that bind to the opioid receptors in the body. The three classical opioid receptors, mu, kappa and delta are found in the brain, spinal cord, gastrointestinal tract, and other organs in the body. Opioids are broadly classified as agonist, partial agonist or antagonist, depending on their strength of interaction and the ability to bind at the receptors to produce a response. Opioid agonists exhibit their effect by binding to the opioid receptors and activating them. Opioid antagonists bind to the opioid receptors without stimulating them. These agents do not produce any functional effect and simultaneously block the receptors to prevent an agonist from producing an effect. Partial agonists have a mixed agonist-antagonist effect. They show agonist properties by exhibiting some functional effects when used in low doses or in combination with a strong agonist, but at high doses they may exhibit an antagonist effect. Morphine, codeine, oxycodone, hydrocodone and fentanyl are examples of opioid agonists, buprenorphine is a partial agonist-antagonist, and naloxone is an opioid antagonist. These opioids also differ in their potency and plasma half-life. Opioid formulations are further classified as short- or long-acting depending of their duration of action.[1–3] Opioids are widely used for their analgesic properties to relieve pain (opioid analgesics) although some opioids are used in antidiarrheal or antitussive preparations.

Opioid analgesics and pain

Opioid analgesics are a mainstay of treatment for moderate-to-severe cancer pain as well as acute and chronic non-cancer pain. A survey by the Stanford University Medical Center reported that more than half of the adults in the United States lived with chronic or recurrent pain in 2005.[4,5] In 2009, the Institute of Medicine (IOM) pain report indicated that at least 116 million American adults are affected by one or more common chronic pain conditions such as low back pain, arthritis pain, and neuropathic pain.[6] This high prevalence of pain, coupled with expanded clinical guidelines, has resulted in an increase in the number of opioid analgesic prescriptions over the past decade.

In l998, Federation of State Medical Board (FSMB) released model guidelines for use of opioid analgesics for treatment of pain which reassured physicians that no disciplinary action will be taken based on quantity and amount of opioids prescribed as long as there was a good cause for making such treatment decision.[7] Around the same time, the American Pain Society (APS) pushed for the concept of "pain as the fifth vital sign" i.e., in addition to the four vital signs examined during a routine physical (temperature, heart rate, blood pressure and breathing), the examining clinician should also assess patient's pain.[8] This, followed by the implementation of new pain management standards by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 2000, led to an increase of pain awareness and management in inpatient and outpatient settings, with the idea of "patient's right to pain relief".[9] These initiatives were in parallel to small clinician groups' efforts to destigmatize use of opioid analgesics for pain treatment and patient advocacy group campaigns against undertreatment of pain. These movements conjoined with the release of new prescription opioid analgesics and the aggressive marketing by pharmaceutical manufacturers, resulted in the "opioid epidemic" of our generation.[10,11]

Rise in the use of opioid analgesics

The number of opioid analgesic prescriptions per 100 persons rose from 61.9 in 2000 to 83.7 in 2009 and this increase was more apparent for stronger opioids.[12,13] The sales of opioid analgesics in 2010 were four times that in 1999, with 710 mg per person of opioid analgesics sold in the United States.[14] There were 259 million prescriptions written for opioid analgesics in 2012 alone, which the Centers for Disease Control and Prevention (CDC) noted "*is enough for every American adult to have a bottle*".[15] The rise in the use of prescription opioid analgesics is a global problem, but it is distinct in the United States since American adults are reported to consume more than 80% of the world's opioid supply, and opioids such as hydrocodone have been one of the top prescribed drugs nationally.[16–18]

Opioid analgesics side-effects and concerns

Constipation, sedation, nausea and vomiting are some common side-effects associated with the use of opioid analgesics. Opioid-induced respiratory depression is reported in patients starting on high doses of opioids or using them in combination with psychoactive drugs such as benzodiazepines or alcohol. Additionally, opioid analgesics are associated with the risk of aberrant drug-related behavior and high abuse liability. This includes potential for misuse or nonmedical use, abuse, dependence and addiction. Diversion is also a major concern with the use of opioid analgesics.[19,20] The definitions of these terms are presented in Table 1.[21]

Table 1: Terminology and definition

Terminology	Definition
Aberrant drug-related behavior[a]	A constellation of behaviors that have grown to be recognized by clinicians as potentially indicative of prescription opioid abuse.
Abuse[b]	Persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice.
Addiction[b]	Repeated use of a psychoactive substance or substances, to the extent that the user is periodically or chronically intoxicated, shows a compulsion to take the preferred substance, has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain psychoactive substances by almost any means.
Diversion[a]	The intentional removal of a medication from legitimate distribution and dispensing channels.
Dependence[b]	The experience of impaired control over drug use.
Misuse[b]	Use of a substance for a purpose not consistent with legal or medical guidelines, as in the nonmedical use of prescription medications.
Nonmedical use[b]	Use of a prescription drug, whether obtained by prescription or otherwise, other than in the manner or for the time period prescribed, or by a person for whom the drug was not prescribed.
Overdose[b]	Use of any drug in such an amount that acute adverse physical or mental effects are produced.

[a]Tufts Health Care Institute expert panel definition
[b]World Health Organization (WHO) definition

The number of persons aged 12 or older that had used opioid analgesics for nonmedical purposes for the first time in the past year increased by 41% from 1998 to 2008. Consumption of prescription opioid analgesics for nonmedical reasons was second to marijuana and more frequent than cocaine or heroin, even in youths aged 12 to 17 years. The National Survey on Drug Use and Health (NSDUH) reported that 4.9 million people 12 years or older were current nonmedical users of prescription opioid analgesics in 2012. Of these, 2.1 million people were reported to have a substance use disorder, defined as substance abuse or dependence, related to prescription opioid

analgesics.[22] Another investigation suggested that the prevalence rate of aberrant drug related behavior ranged from 5% to 24%, and that of abuse ranged from 18% to 41% among patients treated with chronic opioids.[16] Majority of nonmedical use related to opioids involves opioid analgesics. However, recent reports have suggested that adults with a history of opioid abuse or addition are using combination opioid products such as antidiarrheals for nonmedical purposes due to low cost and easy accessibility of these drugs compared to opioid analgesics.[23]

The wide accessibility of opioid analgesics and parallel surge in their nonmedical use has resulted in an increased number of opioid overdoses and poisonings.[14] The dramatic rise in opioid analgesics such as hydrocodone and oxycodone is reported to be significantly associated with an increase in drug-related emergency department (ED) visits.[24] There were nearly 366,181 ED visits involving nonmedical use of opioid analgesics in 2011, an increase of 117% from 2005.[25] Recently, the CDC reported approximately 1.5 times more drug overdose deaths compared to deaths from car crashes. Opioids were involved in 61% of these drug overdose deaths.[26] Owing to this ubiquitous use of opioids in the community, much research in the past decade has focused on opioid overdoses, especially fatal overdoses, due to nonmedical use and abuse among adults. Few studies have examined the simultaneous rise in unintentional opioid exposures and poisonings in young children.

Opioid exposures and poisonings in children

Exposure is defined as, "*an actual or suspected contact with any substance that has been ingested, inhaled, absorbed, applied to, or injected into the body*".[27] Poisoning is, "*a state of major disturbance of consciousness level, vital functions, and behavior following the administration in excessive dosage (deliberately or accidentally) of a psychoactive substance*".[28] Although the two

terms are used interchangeably in the literature, poisoning may indicate more severe exposure. Exposure and poisoning can be intentional (or deliberate) or unintentional (or accidental) in nature, and can occur in the intended or unintended recipient of the drug.

Unintentional exposure and poisoning due to accidental ingestions by young children is an important public health concern. The CDC reports that over 300 children less than 20 years of age are treated in the ED every day and at least two children die due to medicinal or nonmedicinal poisonings.[29] Research over the past decade shows that majority of these childhood poisonings are due to medicinal drugs. Although child fatalities related to unintentional drug poisonings have decreased in the late 2000s, the number of pediatric unintentional drug exposures and poisonings reported to poison centers (PCs) and the associated morbidity i.e., rates of ED visits and hospital admissions, and rates of injury (moderate or major medical outcome) have risen.[30,31] PCs receive about 500,000 calls annually for drug ingestions among children less than 6 years of age.[32] Each year, there are over 70,000 ED visits related to unintentional drug exposures and poisonings involving children, with peak incidence among 1-2 year olds. [33,34] In fact a 2009 study reported that drug poisonings had sent 1 of every 150 two-year olds to the ED, majority due to accidental exposures.[35,36] From 2005 to 2009, ED visits due to unintentional drug poisonings were highest among children less than 15 years of age, compared to any other age group in Rhode Island alone.[37]

Among different drugs involved in pediatric exposures and poisonings, opioids are an important class not only due to their increased legitimate use but also due to a rise in their nonmedical use. The 30th Annual Report of the American Association of Poison Control Centers' (AAPCC) noted that over 60% of drug exposure calls in 2012 involved children less than 20 years of age. Analgesics, specifically opioids, were reported to be the most common substance involved in these exposure calls.[32] The increase in opioid exposures among children is significantly associated with

an increase in adults' opioid prescriptions.[38,39] This association was seen for opioid analgesics used for pain treatments, such as hydrocodone, oxycodone, and morphine, as well as for agents used for opioid addiction treatment such as buprenorphine and methadone.[38–40] In the state of Utah alone, the annual number of patients filling buprenorphine prescriptions increased by over 444-fold, from 22 in 2002 to 9,793 in 2011. At the same time, the total number of buprenorphine exposures rose by 13-fold, and 39% of these exposures were among children aged 5 years or under.[41] While in Indiana, adolescent opioid exposure cases reported to the PC almost doubled and the medical complications (moderate or major medical outcome, or death) resulting from these exposures more than doubled, following the release of 2000 JCAHO pain initiative. The increase in the number of exposures among adolescents was significant for hydrocodone and methadone. The number of deaths per adolescent opioid cases with medical complications rose by 11% between the two time periods i.e., the period before (1994 to 2000) and after (2001 to 2007) the release of JCAHO pain management standards.[42] At a national level, there were over 10,000 intentional opioid exposures among adolescents recorded in the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) system from 2007 to 2009. Hydrocodone, oxycodone and tramadol were the most frequently misused opioids by these children.[43]

Opioid exposures in children are high-risk due to the high toxicity associated with these drugs, even for combination opioids such as acetaminophen combinations. Ingestion of a single tablet of opioids such as buprenorphine and methadone can be fatal in young children.[38,39,44] Opioid exposures and poisonings in children are unique because they constitute a majority of accidental exposures, especially among children 12 years or younger, as opposed to poisonings in adults. Morbidity and mortality related to these opioid exposures and poisonings in children is preventable.

Clinical presentation of opioid exposures and poisonings in children

Opioid poisonings in children can result in serious symptoms or complications including respiratory disorders such as apnea, respiratory failure, and respiratory depression; psychiatric or nervous system disorders such as agitation, seizures, and coma; and cardiac disorders such as tachycardia, bradycardia and cardiac arrest.[39,44] Presentation of opioid poisonings in children can differ from that in adults. Opioid poisonings in children can have delayed onset of symptoms, and severe and prolonged toxic effects. ED or hospital admission is recommended for young children with exposure to any long-acting opioid formulations; exposure to fentanyl, methadone or any buprenorphine formulations; or exposure to a high amount of any opioid. Treatment with naloxone is recommended in children with for respiratory depression following an opioid exposure, particularly methadone or buprenorphine exposures. [44,45]

Chapter 2: Literature Review and Conceptual Framework

2.1: Literature Review

A comprehensive literature search of MEDLINE through PubMed and Google Scholar was performed. The search strategy combined multiple search terms and MeSH terms to retrieve relevant articles including, "Analgesics, Opioid"; "Poisoning", "Drug overdose" or "Opioid-related disorders"; "Infant", "Child" or "Adolescent"; and "Cost and cost analysis", "Emergency treatment" or "Economic burden". A manual search of the cited references in the originally retrieved articles was also conducted to identify additional research articles. The research articles were not reviewed if they were published in non-English language, if the research was based outside the United States, or if the article was published prior to 2000.

A total of 19 studies were identified for full-text review. Table 2 summarizes 16 studies that examined prevalence and characteristics related to opioid poisonings in children. These 16 studies include original research articles and case reports. Table 3 summarizes 3 studies that investigated health care resource use (HCRU) and costs associated with opioid poisonings. Five studies from Table 2 and one study from Table 3 are described further due to their relevance to the current research.

Table 2: Literature review articles – Prevalence and characteristics

Study	Data source(s)	Sample	Methods	Results
Research studies				
Hayes et al. 2007[46]	RADARS (2002-05)	Children <6 years with buprenorphine exposures	Examined and characterized exposures	Identified 86 children, 52% boys, mean age of 2 years, 96% at-home exposures, and all exposures were unintentional and acute. 74% were treated at a HCF. Drowsiness, lethargy, vomiting and miosis were common clinical effects. 7% suffered from respiratory depression. Severity of symptoms increased with increased mean dose ingested. Decontamination and naloxone administration were commonly performed.
Cohen et al. 2008[33]	NEISS (2004-05)	Children ≤18 years with ED visit for an ADE	Estimated the rate of ED visits for ADE due to unintentional overdose or ingestion, and examined the drugs involved	Total of 71,224 children treated in ED for unintentional overdoses and 18% were hospitalized. About 66.6% of children were 1 to 4 years. Analgesics were involved in 20.5% of the unintentional overdoses.
Schillie et al. 2009[35]	NEISS (2004-05)	Children ≤18 years presented to ED for drug and non-drug exposures	Estimated the rate of ED visits from unintentional drug exposures due to unsupervised ingestions, medication errors and misuse	ED visit rates for drug exposures were twice that of non-drugs, majority due to unsupervised ingestions. Total of 71,224 ED visits for drug exposures annually, mostly among 1-2 year olds and boys. Opioids were second most commonly implicated drug class in unsupervised ingestions.

Bailey et al. 2009[(a)38]	RADARS (2003-06)	Children <6 years with Rx opioid exposures	Examined exposures and its association with Rx opioid availability at 3-digit ZIP Code level	Total of 9,179 children with Rx opioid exposures. The median age was 2 years, 54% were boys, and ≥98% of these exposures involved ingestions or occurred at home. About 265 children had a moderate-to-major effect and naloxone was commonly used for treatment. A positive correlation was found between childhood opioid exposures and the number of opioid Rxs filled in an area.
Coben et al. 2010[47]	NIS (1999-2006)	Inpatient stays with any drug poisoning ICD-9-CM code in first-listed diagnosis	Compared poisoning by Rx opioids, sedatives and tranquilizers to other drug poisonings	Admissions for poisoning by Rx opioids, sedatives and tranquilizers increased by 65% from 1999 to 2006, which was twice that of increase in other drug poisonings. Largest percentage increase was for methadone (400%). Among children ≤18 years, 44.2% admissions were related to intentional and 37.4% were related to unintentional poisoning by Rx opioids, sedatives and tranquilizers.
Tormoehlen et al. 2011[(a)42]	Indiana PC data (1994-2007)	Children aged 12 to 18 years with a Rx opioid exposure	Compared exposures in the pre-period (1994-2000) and post-period (2001-07), following the release of JCAHO 2000 pain initiative	Identified 1,634 opioid exposure cases, 632 in the pre-period and 1,002 in the post-period. The opioid exposure rate and complication (moderate-to-major effects) rate per 1,000 adolescent Indiana PC cases were 1.8 times and 3 times higher in the post-period, compared to the pre-period. The number of deaths increased from 0 to 15 in the two time periods.
Bond et al. 2012[(a)48]	NPDS (2001-08)	Children <6 years exposed to one Rx or OTC drug through self-ingestion or	Examined proportion of admissions and injuries (moderate-to-major effects)	Total of 453,559 ED visits of which 58% were due to Rx drug exposures. Unintentional Rx drug self-ingestions were higher among children 1 to <3 years (71%), and boys (53%). Rx opioid analgesics were associated with about 12% of

		therapeutic error, and presented to ED	following exposure-related ED visits	unintentional Rx drug exposures. There was a 101% increase in the number of ED visits, 86% rise in admission rates, and 92% increase in injury rates, due to unintentional self-ingestions of Rx opioids.
Burghardt et al. 2013[(a)31]	NPDS and NAMCS (2000-09)	Children <20 years with oral, single-ingredient Rx drug exposures	Compared mean monthly number of pediatric exposures and poisonings, and the number of adults' drug prescriptions	Identified 62,416 pediatric prescription opioid exposures and poisonings, which was highest compared to the other drug classes. Nearly 48.4% of the total opioid exposures were associated with an ED visit of these, 26.3% had a moderate-to-major effect and 41.5% had a medical or psychiatric admission. The association between adults' opioids use and pediatric opioid exposures and poisonings was twice as strong compared to other drug classes.
Lavonas et al. 2013[39]	RADARS, pharmacovigilance and IMS Rx data (2009-12)	Children 28d to <6 years with buprenorphine exposures	Examined and characterized exposures	Total of 2,380 pediatric exposures, common in 1 to <3 year olds (74.5%) and males (51.6%), and >90% at-home exposures. About 236 cases with severe outcome including death. Drug stored in sight and parent's medication was identified as the common root cause and source.
Lovegrove et al. 2014[(a)49]	NEISS and IMS Health (2007-11)	Children <6 years presented to ED for unsupervised ingestion of oral Rx drugs	Estimated and characterized ED visits resulting in hospitalization	Nearly 34,503 ED visits of which 27.5% resulted in hospitalization. Admissions were higher among children 1 to 2 years (75.4%) and boys (52%), and 21.9% involved ingestion to >1 drug. About 36.5% of all ED visits for unsupervised ingestion of opioid analgesics resulted in hospitalization. Buprenorphine, hydrocodone and oxycodone were most commonly implicated. One child was hospitalized for every 500 unique patients receiving buprenorphine.

Hasegawa et al. 2014[50]	NHAMCS 1993-2010	Visit with an opioid poisoning ICD-9-CM code	Examined ED visits across different age groups and other demographic characteristics	There were 74,000 ED visits for children <20 years. The visit rate per 100,000 population and per 100,000 ED visits increased disproportionately among <20 year olds.
Borys et al. 2015[51]	NPDS (2008-13)	Children <18 years with single ingestion of tapentadol	Determined the incidence of exposures and associated clinical characteristics	Total of 104 children, 76.9% were ≤6 years, all had acute ingestions and 93 ingestions were unintentional. About 78.8% were treated in a HCF and 40.4% had a clinical effect, mostly drowsiness and lethargy.
Case reports, case series or reviews				
Geib et al. 2006[52]	Case series review of cases presented to the ED at an academic medical center	5 children <2 years with buprenorphine exposures	Investigated adverse effects following unintentional exposures	Drowsiness, lethargy, apnea and respiratory depression were common symptoms. Naloxone was used in 4 cases. LOS varied from 1 to 3 days.
Pedapati and Bateman 2011[53]	Case series review of cases admitted in PICU at an academic medical center (2007-09)	9 children <3 years with buprenorphine exposures	Examined the prevalence and clinical characteristics of exposures	Drowsiness, lethargy were common symptoms followed by miosis, respiratory depression, vomiting, agitation or confusion. Most toddlers were treated with naloxone.
Martin and Rocque 2011[40]	Review of cases admitted at a medical center (1999-2009)	Children ≤18 years admitted for methadone and buprenorphine ingestions	Examined the increase in the number of patients on opioid dependence treatment in the area and corresponding	Rate of admissions per yearly ED visits increased significantly. Total of 22 children were admitted, 16 were in PICU and mean LOS was 2.3 days. Majority were infants and toddlers, and the drug mostly belonged to parents.

			admissions for pediatric ingestions	
Spatial analyses study				
Nguyen et al. 2016[54]	Pittsburg PC at 5-digit ZIP Code level (2006-10)	Children <5 years with unintentional drug exposures wherein, the calls were made from a non-HCF. ZIPs from out-of-state or with no children <5 years were excluded.	Identified ZIP Code clusters of pediatric exposure calls, and examined associated population characteristics.	Identified 26,685 exposures, and 22 exposure clusters with 324 ZIP areas. Area-level population density, education, proportion of Non-white race and household size was significantly associated with the odds of ZIP area being within an exposure cluster.

[(a)]Study is described further (below).
RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance, HCF = Health care facility, ADE = Adverse drug event, NEISS = National Electronic Injury Surveillance System, NIS = Nationwide Inpatient Sample, ED = Emergency department, Rx(s) = Prescription(s), OTC = Over-the-counter, NHAMCS = National Hospital Ambulatory Medical Care Survey, NPDS = National Poison Data System, PICU = Pediatric Intensive Care Unit, LOS = Length of stay, PC = Poison center, HH = Household, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

Bailey et al. 2009[38]

Bailey et al.[38] examined prescription opioid exposures in children under 6 years of age, and its association with prescription opioid availability in a region at 3-digit ZIP Code level. Prescription opioids examined were limited to hydrocodone, oxycodone, buprenorphine, fentanyl, hydromorphone, methadone and morphine. The authors used PCs data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system, from first quarter of 2003 to second quarter for 2006 (3.5 years). The RADARS is a surveillance system that comprises multiple signal detection systems to monitor prescription drug misuse, diversion and abuse throughout the United States. One of the RADARS systems captures detailed data from the PCs on childhood drug exposures.

There were a total of 9,240 opioid exposure mentions in 9,179 children with a median age of 2 years and about 54% were boys. Most of these exposures involved ingestions and were unintentional (≥99%), and commonly occurred at one's own or other's residence (98%). In majority of these exposures, the opioid was intended for an adult. Exposures to hydrocodone (65%) and oxycodone (22%) were most common. About 265 children had a moderate-to-major effect including a total of 8 deaths. Naloxone was commonly used for treating children experiencing a major effect or death. The proportion of opioid mentions associated with any clinical effect was significantly greater for buprenorphine (0.68). Of the total 176 buprenorphine exposures, 136 involved buprenorphine/naloxone combination, and about 30 buprenorphine exposures resulted in a moderate-to-major effect. Naloxone was commonly used for treating children experiencing a major effect or death.

The authors also examined the association between opioid exposures in children and adults' opioid availability in a region by using the unique recipient of dispensed drug (URDD) at 3-digit ZIP

Code level. URDD provides a measure of drug availability, and it represents the number of unique individuals filling a prescription for a particular opioid, excluding refills. A positive correlation coefficient of 0.67 was found between childhood opioid exposure mentions and URDD. This association was highest for hydrocodone (0.81) and oxycodone (0.69).

The RADARS PCs' data used for this study may be more detailed and accurate compared to the NPDS due to additional opioids coding-related training provided to the participating PCs. However, 11 PCs participated in the RADARS in 2003, and about 40 PCs participated in 2006. Compared to the National Poison Data System (NPDS), these data may not be nationally representative. Also, the authors limited these analyses to children aged 6 years or under, and examined a limited number of prescription opioids.

Tormoehlen et al. 2011[42]

Tormoehlen et al.[42] compared prescription opioid exposures involving children aged 12 to 18 years in the period before and after the release of JCAHO 2000 pain initiative. The authors used data from the Indiana PC from 1994 to 2000 (pre-period) and 2001 to 2007 (post-period). Records were examined for exposures involving one of the following opioids: hydrocodone, morphine, methadone, codeine, oxycodone, meperidine, fentanyl, buprenorphine, hydromorphone, propoxyphene, and oxymorphone. Correlation was examined between the Indiana state opioid distribution and the percent of adolescent exposures cases.

There were a total of 1,634 opioid exposure cases, 632 in the pre-period and 1,002 in the post-period, and majority involved females. Total number of adolescent cases increased significantly for hydrocodone exposures (71 to 480 cases) and methadone (8 to 72 cases) however, it decreased for codeine exposures (242 to 124 cases). The opioid exposure rate and complication rate (defined

as moderate or major outcome, or death) per 1,000 adolescent Indiana PC cases were 1.8 times and 3 times higher in the post-period, compared to the pre-period respectively. The number of deaths increased from 0 to 15 in the two time periods. There was a strong positive correlation between the amount of opioids distributed in Indiana and the rate of adolescent cases reported to the Indiana PC.

Tormoehlen et al. concluded that the number of reported adolescent opioid exposures and the associated medical complications have risen following the JCAHO pain initiative, but they did not examine the intent of exposure or the HCRU used following an opioid exposure. They limited the analyses to specific opioids that were listed as the first or second substances involved in an exposure. In addition, this study was based on a single state's PC adolescent cases. Hence these results may not be generalizable to other age groups or states.

Bond et al. 2012[48]

Bond et al.[48] used NPDS data from 2001 to 2008, to examine unintentional pediatric exposures to prescription or OTC pharmaceutical drugs including opioid analgesics. The NPDS is described in the following chapter. The authors examined NPDS records of children less than 6 years that were exposed to one product (single or combination product) through self-ingestion or therapeutic error, and were presented to an ED. Proportion of admissions and injuries following exposure-related ED visits were assessed. Injuries comprised any exposure with a moderate-to-major effect including death. The authors compared ED visits, hospital admissions and injuries associated with drug exposures, with the changes in pediatric population and the number of pediatric drug exposure calls received by the PCs. Although the increase in childhood drug exposure ED visits, admissions, and injuries was significantly greater than the population changes over the 8-year period, these trends were not specifically assessed for opioids. Of the total 453,559 ED visits identified,

prescription drugs were associated with about 58% of unintentional exposures in children, majority due to self-ingestions (95%). Prescription drug exposures due to unintentional self-ingestions were highest for children 1 to 3 years of age (71%), while therapeutic errors were common among ≤1 year olds (37%). These exposures were disproportionately higher for boys (53% to 58%).

Prescription opioid analgesics were associated with approximately 12% of unintentional prescription drug exposures, and were mostly due to self-ingestions. The authors reported a 101% increase in the number of ED visits, 86% rise in admission rates, and 92% increase in injury rates, from 2001 to 2008, due to unintentional self-ingestions of prescription opioids. The authors also examined unintentional exposures due to acetaminophen and cough and cold products, but they not identify opioid-containing formulations within these categories

Although Bond et al. examined unintentional pediatric during exposures over 8-year period, several limitations exist. These analyses excluded children that were exposed to multiple products, exposed through non-ingestion route, were managed at home or at a non-ED setting, and those who did not have complete follow-up information. This may have underestimated the actual burden of unintentional drug and opioid exposures in young children. Additionally, clinical characteristics of exposures were not specifically examined for opioids.

Burghardt et al. 2013[31]

A study by Burghardt et al.[31] used the 2000 through 2009 NPDS and National Ambulatory Medical Care Survey (NAMCS) data to examine the exposures and poisonings in children less than 20 years, and its association with monthly adult prescriptions for hypoglycemics, antihyperlipidemics, β-blockers, and opioid analgesics. Mean monthly number of pediatric

exposures and poisonings was calculated and compared to the mean monthly number of adults' drug prescriptions using time series analyses.

There were 62,416 pediatric prescription opioid exposures and poisonings, which was highest compared to other drug classes. Children under 6 years experienced the greatest number of drug exposure events across all drug classes including opioids. Monthly opioid exposures and poisonings increased by 0.09 per 1,000,000 children under 6 years of age, 0.006 per 1,000,000 children among 6 to 12 year olds, and 0.04 per 1,000,000 children among 13 to 19 year olds. The mean yearly opioid exposures and poisonings in these age groups were 3,293, 590 and 2,330, respectively. Nearly 48.4% of the total opioid exposures were associated with an ED visit of these, 26.3% had a moderate-to-major effect (including death), 35% had a medical admission, and 6.5% had a psychiatric admission.

The association between adults' opioids use and pediatric opioid exposures and poisonings was twice as strong compared to other drug classes, especially for children under 6 years. A 1% increase in adults' opioid use was associated with 1.53 times more exposures and poisonings per 1,000,000 children in this age group.

Although these analyses were done separately for opioids, they were limited to prescription opioids that were single-ingredient or oral formulations. This excluded commonly used opioid combination drugs such as acetaminophen-hydrocodone combinations (e.g., Vicodin®), or non-oral opioids such as fentanyl patch. The authors also excluded exposure and poisoning records that had an indication of the child's own prescription. Further, for HCRU analyses, about 17% of opioid exposure cases were identified as lost to follow-up. These factors would result in an underestimate of the actual burden of pediatric opioid exposures. Lastly, analyses were not separated for one or multiple product ingestions, and by reason (or intent) of exposure.

Lovegrove et al. 2014[49]

Lovegrove et al.[49] used data from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance (NEISS-CADES) and IMS Health, from 2007 to 2011, to estimate ED visits resulting in hospitalizations (emergency hospitalizations) for unsupervised ingestion of oral prescription drugs in children under 6 years. NEISS is an ED-based adverse drug events surveillance system using a nationally representative sample of hospitals in the United States. The authors calculated rates of emergency hospitalization per 100,000 dispensed outpatient prescriptions and per 100,000 unique patients receiving dispensed prescriptions.

Of the total 34,503 ED visits identified, 27.5% resulted in hospitalization. Annual national emergency hospitalizations were highest among children 1 to 2 years of age (75.4%) and boys (52%), and 21.9% involved ingestion to more than 1 medication. Opioid analgesics was the most commonly involved drug class in these emergency hospitalizations (17.6%). About 36.5% of all ED visits for unsupervised ingestion of opioid analgesics resulted in hospitalization.

Buprenorphine, hydrocodone and oxycodone were the most commonly implicated opioid analgesics. Over 62% of ED visits for unsupervised ingestion of buprenorphine, 30.5% of ED visits for hydrocodone ingestions, and 26.1% of visits for oxycodone ingestions resulted in hospitalization. The authors reported that 1 child was hospitalized for unsupervised ingestion for every 500 unique patients receiving buprenorphine.

This study examined drug classes and individual drugs involved in unintentional exposure-related emergency hospitalizations in young children, and compared it to the drug availability at a national level. These estimates indicate severe drug exposures among young children but there exist a few limitations. First, these estimates did not include non-oral medications. Second, analyses were

limited to ED visits that resulted in admission hence, it did not incorporate cases that were managed at-home or were directly admitted. Finally, related clinical effects, scenario and reason of exposure, and deaths were not investigated.

Table 3: Literature review articles – HCRU and costs

Study	Data source(s)	Sample	Methods	Results
Inocencio et al. 2013[(a)55]	NEDS (2009), NIS (2009), DAWN (2009)	Visits in the NEDS and NIS with opioid poisoning ICD-9-CM code. Opioid poisoning cases from DAWN.	Calculated direct and indirect costs related to opioid poisonings including heroin and Rx opioids in 2011 USD	Mean direct cost for Rx opioid poisonings was $4,255. Estimated mean ED treatment cost was $1,967 and inpatient stay cost was $9,696. Total direct cost of prescription opioid poisoning was $1.8 billion and the total indirect cost was $14.1 billion. Absenteeism costs were estimated at $618 per case, and mortality costs at $33,664 per case.
Yokell et al. 2014[56]	NEDS (2010)	Visit with an opioid poisoning ICD-9-CM code	Descriptively examined the characteristics and mean charges in 2010 USD	Total 92,209 ED visits for Rx opioid poisonings. Of these, 4,998 ED visits were for children ≤17 years. Mean charges for opioid poisoning ED visit without admission ranged from $3,640 for Rx opioid poisoning, $3,692 for methadone poisoning and $4,121 for unspecified or multiple opioid poisonings. Mean charges for opioid poisoning inpatient stays ranged from $29,497 for Rx opioid poisoning, $32,647 for methadone poisoning and $29,669 for unspecified or multiple opioid poisonings in 2010 USD. Mean LOS for Rx opioid poisoning hospitalizations was 3.8 days.
Xiang et al. 2012[57]	NEDS (2007)	Visit with any drug poisoning ICD-9-CM code	Estimated population rate of ED visits by age groups, and the total ED charges in 2007 USD	About 19.58% of the total drug poisoning-related ED visits for children ≤17 years. Compared to any other age group, children ≤5 years had the highest rate of unintentional poisonings. Among teens, females had a higher rate of intentional poisonings compared to males. Total charges for drug poisoning ED visits was $1,994 per visit.

[a]Study is described further (below).
NEDS = Nationwide Emergency Department Sample, NIS = Nationwide Inpatient Sample, DAWN = Drug Abuse Warning Network, ED = Emergency Department, Rx = Prescription, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, USD = United States dollar, LOS = Length of stay.

Inocencio et al. 2013[55]

A study by Inocencio et al.[55] evaluated the economic burden of opioid poisonings in the United States. The authors used 2009 Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS) and Nationwide Inpatient Sample (NIS) databases to compute the mean ED and inpatient costs related to opioid poisonings, including heroin and prescription opioids. They computed cost for each component of care, ED, inpatient, ED physician, ambulance and drug costs. The total direct and indirect costs were calculated using prevalence estimates from Drug Abuse Warning Network (DAWN). This database consists of drug-related ED visits and deaths and is used to monitor the impact of drug use, misuse, and abuse across the nation. Cases in DAWN are categorized as suicide attempt, seeking detox, alcohol only, overmedication, adverse reaction, accidental ingestion, malicious poisoning, and other. Inocencio et al. limited their sample to those ED visits that were related to overmedication, suicide attempt, malicious poisoning, or other.

The authors reported a mean direct cost of $4,255 for prescription opioid poisonings. The mean ED treatment costs was estimated as $1,967 and inpatient stay costs at $9,696. The total direct cost of prescription opioid poisoning was $1.8 billion and the total indirect cost was $14.1 billion. The mean costs related to absenteeism were $618 per case, and the mean costs related to mortality were $33,664 per case. All costs were reported in 2011 USD.

Inocencio et al. employed a rigorous study design to estimate the economic costs of opioid poisonings yet, these estimates cannot be used to gauge the costs of opioid poisonings in children for a number of reasons. First, the mean costs of prescription opioid poisonings estimated from HCUP databases were not reported by specific age groups. These estimates include opioid poisonings in adults and older adults. The characteristics of these population groups can vary significantly from children. For example, the burden of adult poisonings can be related to underlying abuse or addiction, while older adults may have multiple comorbidities, resulting in high costs of treatment following a poisoning. Second, accidental ingestions were not included in the authors' poisoning case definition, this may have excluded majority of prescription opioid poisonings in young children.

Summary of the literature – Prevalence and characteristics

The distribution of age for drug exposures and poisonings is mainly found to be bimodal. The number of drug or opioid exposures and poisonings were found to be higher in young children, particularly 1 to 2 year olds, followed by adolescents.[31,35,38–40,48,49,53,58] More than half of the drug exposures and poisonings were in boys among children less than 6 years. Among teenagers, the occurrence of opioid exposures and poisonings was higher among females.[42] Over 90% of opioid exposures occurred at one's home.[38,39] Caller site for drug exposures and poisonings was predominantly one's own residence however, about 20% were reported from a health care facility (HCF).[32,38,39]

Multitude of studies have investigated pediatric exposures and poisonings to various opioid agents including hydrocodone, oxycodone, buprenorphine, methadone, oxymorphone, hydromorphone, tramadol, tapentadol, codeine, meperidine, propoxyphene, fentanyl, and morphine.[38–40,42,46,49,51–53,59,60] One study examined exposures and poisonings from acetaminophen and cough and cold

product combinations.[48] The number of hydrocodone and oxycodone exposures and poisonings in children have been on the rise.[38] Studies also indicated an increase in the number of methadone and buprenorphine exposures and poisonings.[42,47] Severe outcomes were reported following buprenorphine or methadone exposures in children, especially among those under 6 years.[38,40,49,52,53,61,62] The number of exposures involving more than one product varied from 5% to 22%.[39,49]

Ingestion was the most common route of drug exposures in children. Unintentional and intentional exposures to drugs or opioids in children were more common compared to adverse events. Exposures in young children under the age of 6 were unintentional, while exposures among adolescents were mostly intentional. Unintentional exposures due to therapeutic errors were more common in infants, and self-ingestions were more common in children aged 1 to 3 years.[35,38,47,48,61]

Clinical effects were reported in 25% to 40% of children exposed to opioids.[38,39,51] Drowsiness, lethargy, dizziness, nausea and vomiting were the most common symptoms. Respiratory depression, tachycardia, CNS depression, and seizures were reported with severe opioid poisonings.[46,51,53,59,60] Majority of exposures were acute.[51] The proportion of opioid exposures and poisonings resulting in moderate-to-major medical outcome varied from 5% to 13%. These numbers further varied by age group.[31,38,39] For instance, Tormoehlen et al. reported a medical complication (moderate-to-major effect) rate of 4.9 per 1,000 adolescents Indiana PC cases.[42]

Over one-fourth of opioid exposures in young children were associated with storage and access scenarios such as “stored in sight, left out, not secured”, “accessed from bag or purse”, or “drug stored in package other than original packaging”.[39] Naloxone and decontamination procedures were the most common therapies performed following an opioid exposure in children.[46,53,59,61] Naloxone was also commonly used for buprenorphine exposures in young children.[38,62] Nearly

half of the children with opioid exposures and poisonings were presented to the ED, and the proportion of the ED visits resulting in admission ranged from 18% to 42%. These numbers varied by age and the opioid agent involved. For example, Borys et al. reported that 78% of children exposed to tapentadol were presented to the ED. While Lovegrove et al. reported that 62.4% of ED visits for buprenorphine exposures, 30.5% of ED visits for hydrocodone exposures, and 26.1% of the ED visits for oxycodone exposures among children under 6 years resulted in hospitalization.[31,33,49,51,63]

Prescription opioid availability was reported to be significantly associated with the number of opioid exposures and poisonings among children at 3-digit ZIP Code level,[38] at state-level,[42] and at national-level.[31] Nguyen et al. identified 5-digit ZIP Code clusters of pediatric exposure calls, and examined the associated population characteristics in Pennsylvania. The authors found significant association between area-level characteristics including lower education, household size (average household size of 2.36) and Non-white race and lower odds of pediatric drug exposures in the area.[54] Schillie et al. reported a three times higher rate of ED visits for medication overdoses compared to nondrug exposures among White children under the age of 19.[35] Among the studies reviewed, no other study based in the U.S. has examined area-level characteristics associated with pediatric drug exposures. Two studies in Europe have examined the association of socioeconomic factors and childhood drug poisonings. One of these studies reported an increasing rate of hospital admissions for unintentional drug poisonings, including poisonings by analgesics, with lower socioeconomic status among children under 5 years of age. Socioeconomic status was examined using the Townsend scores, which is a widely used measure of deprivation or socioeconomic status in the United Kingdom.[64] While another study found higher rates of unintentional drug or chemical poisonings among children under the age of 15 years to be

associated with lower income and lower educational level. The authors did not find a significant association between the rate of unintentional pediatric poisonings and crowded household.[65] In addition, adults' prescriptions including parents, caregivers and grandparents, are reported to be the common source of opioids in pediatric exposures and poisonings.[39] Hence, it was interesting to explore the association of area-level population characteristics of adults and older adults in households and the number of opioid exposures and poisonings. Based on the knowledge from the literature reviewed above, various sociodemographic and clinical characteristics of opioid exposures and poisonings were examined in the current study.

Summary of the literature – HCRU and costs

Few studies have examined the rate of ED visits and subsequent medical admissions as described above.[31,33,49,51,63] Although not specific to the pediatric population, some previous investigations have reported differences in the sociodemographic, clinical, payer and hospital characteristics associated with ED visits for drug or opioid poisonings.

Drug or opioid poisoning-related ED visits differed by age group, gender, residence location and median area-level income. Proportion of drug poisoning-related ED visits were higher for children less than 6 years and children 12 to 17 years.[57] Drug or opioid poisoning-related ED visits were more common among females, and those from areas with lower median ZIP Code level income and urban areas.[56,57] As for race and ethnicity, rate of opioid poisoning-related ED visits per 100,000 population did not vary much across Whites and Blacks, or Hispanics and non-Hispanics.[50]

Certain clinical characteristics were also found to be related to drug poisoning-related ED visits. Compared to methadone, higher proportion of ED visits were for poisonings related to other

prescription opioids.[56] One study reported a higher rate of ED visits per 100,000 population for unintentional opioid poisonings.[50] Mood disorders, and acute benzodiazepine and alcohol intoxication were the most common concurrent diagnoses among patients presenting to the ED with opioid poisonings.[56] Two studies also found that about 20% to 30% of the total ED visits for opioid or drug-related poisonings involved more than one drug. Benzodiazepines were frequently involved in such multi-drug poisonings.[55,57] Mental disorder was the most commonly recorded chronic condition in opioid poisoning-related ED visits.[56] Kline-Simon at al. examined substance use disorders and co-occurring psychiatric comorbidities, medical comorbidities and chronic conditions in adolescents. The authors reported that about 40% of these children had 2 or more psychiatric comorbidities, commonly depression and anxiety. They also found a significant association between substance use disorders and presence of any medical comorbidities, or chronic conditions such as asthma.[66] Mazer-Amirshahi et al. examined common procedures performed in poisoning-related visits. The authors found that diagnostic procedures such as blood work, electrocardiogram (ECG), urine studies and X-rays were most commonly recorded.[67]

Literature on the common source of payment for drug or opioid poisoning-related ED visits was inconclusive. Two studies reported that private insurance was the more common source of payment,[57,67] whereas another study reported a similar proportion of ED visits had Medicaid or private insurance.[50] Hospitals in southern region had a higher proportion of opioid poisoning-related ED visits.[50,56] Similarly, urban hospitals, non-teaching institutions and non-profit hospitals had a higher number of poisoning-related ED visits.[67]

None of these studies examined hospital trauma status or bedsize. Trauma status of the institution has been associated with severity of injured patients i.e., trauma centers treat more severe cases and have different outcomes compared to non-trauma centers.[68] There is no definitive literature on

the relationship of hospital bed size and health outcome or HCRU. However, it is theorized that bed size affects the average cost per patient. Hospitals with a higher number of beds should have a lower cost per patient due to economies of scale.[69]

The studies reviewed above did not examine the association of various characteristics with inpatient stays or hospital costs of drug or opioid poisonings, especially in children. Yet, these studies illustrate differences in sociodemographic, clinical, payer and hospital characteristics for drug or opioid poisoning-related ED visits. Emergency care is an important component of HCRU for opioid poisonings in children. Similar associations are expected for ED visits, inpatient stays and hospital costs of pediatric opioid poisonings hence, the association of these characteristics with ED visits, inpatient stays and costs was examined in the current study.

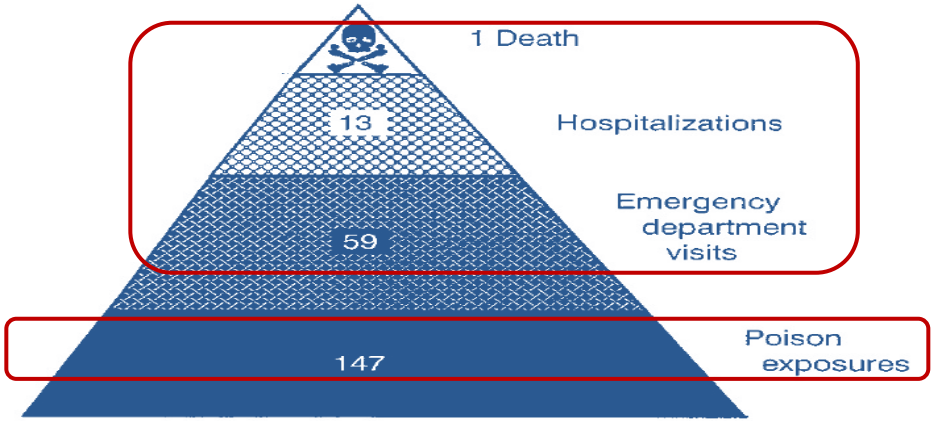
2.2: Gaps in the literature

A number of studies have examined drug exposures and poisonings in children. Few studies have examined the prevalence and characteristics of exposures and poisonings due to opioids. Yet, many of these analyses were either limited to a specific opioid agent, mostly buprenorphine or methadone, to single-substance opioid products or single ingestions, to a specific age group such as children under the age of 6 years or adolescents, or to specific population such as those presenting to the ED. Some of these studies have examined the association between prescription opioid availability among adults and opioid exposures among children. However, none of the studies that were reviewed has assessed the association between area-level socioeconomic status (SES) and opioid exposures and poisonings in children. In addition to individual characteristics, neighborhood factors may also influence health outcomes such as pediatric opioid exposures.

Another gap identified in the literature is that no study has quantified the economic burden related to opioid poisonings in children. A study by Inocencio et al. evaluated the economic burden of opioid poisonings but, it did not specifically estimate economic costs associated with opioid poisonings in the pediatric population.[55] The epidemiology of opioid poisonings and the associated HCRU and costs in children can vary tremendously from that in adults.

2.3: Conceptual framework

Existing research and clinical knowledge was used to guide the conceptual framework for this project. McCaig and Burt (CDC, 1999) depicted the burden of poisonings nationally using the "Poisoning Pyramid" framework. The authors used multiple CDC data sources to delineate various HCRU components associated with a poisoning episode. The bottom of the pyramid corresponds to all exposures and poisonings, followed by poisonings that result in ED visits and subsequent hospitalization, and the tip of the pyramid representing deaths resulting from poisonings.[70] We implemented this framework to guide our approach for examining pediatric opioid exposures and poisonings in two parts. The first part of our study (Specific Aim 1 below) examined the prevalence and characteristics of pediatric opioid exposures and poisonings which corresponds to the bottom of the pyramid. The second part of our study (Specific Aims 2 and 3 below) examined the HCRU and costs associated with pediatric opioid poisonings (Figure 1).



Source: McCaig and Burt (CDC, 1999)[70]
Data from 1995 National Vital Statistics System (NVSS); 1995 National Hospital Discharge Survey (NHDS); 1993-96 National Hospital Ambulatory Medical Care Survey (NHAMCS), and 1995 AAPCC Toxic Exposure Surveillance System (TESS, now known as the NPDS).

Figure 1: The Poisoning Pyramid

2.4: Specific Aims

Aim 1: To examine the prevalence and characteristics of pediatric opioid exposures

A. To determine the prevalence of opioid exposures and poisonings in children

B. To characterize pediatric opioid exposures based on sociodemographic and clinical characteristics

C. To examine the factors associated with severity of opioid exposures in children

D. To examine opioid exposures in children at 5-digit ZIP Code level and study its association with area-level socioeconomic status (SES)

Aim 2: To estimate the economic costs associated with opioid poisonings in children

Aim 3: To examine the characteristics associated with pediatric opioid poisoning-related health care resource use and costs

A. To assess the characteristics associated with pediatric opioid poisoning ED visits

B. To identify factors associated with ED visit costs among children with opioid poisonings

C. To examine the characteristics associated with pediatric opioid poisoning inpatient stays

D. To identify factors associated with inpatient stay costs among children with opioid poisonings

2.5: Significance

The current study provides a more comprehensive assessment of the burden of opioid exposures and poisonings in children. This study examined pediatric exposures and poisonings related to all opioid containing drugs including oral or non-oral opioids, single-substance or combination opioids, or prescription or OTC opioids.

Examination of prevalence of opioid exposures and poisonings in children and the associated sociodemographic, clinical, and area-level characteristics can help to estimate the magnitude of the problem and identify vulnerable areas or subgroups. The study used national PCs data to quantify the prevalence of pediatric opioid exposures and poisonings, instead of health care encounter data, to capture pediatric opioid exposures. Use of PCs data allowed us to measure exposures that are not presented to HCFs as well as exposures that do present to HCFs. Although

cases that are not presented to the ED or admitted do not incur HCRU or costs, there is still an intangible burden associated with them. These cases represent the population that was at risk for opioid poisoning. At the same time, this study distinguished poisonings from exposures thus avoiding an overestimation of the prevalence of opioid poisonings since not all exposures result in poisoning.

On the other hand, this study used national, administrative billing data to quantify HCRU and costs because these sources are probably more precise compared to using self-reported data obtained from PCs. Estimating the economic costs of pediatric opioid poisonings to society can aid in planning and prioritizing interventions. The current study examined the full-spectrum of economic burden associated with pediatric opioid poisonings. This included estimating direct costs for inpatient stays and ED visits as well as indirect productivity costs resulting from morbidity and mortality. Deaths associated with opioid poisonings were examined using the CDC's National Vital Statistics System (NVSS) data. These data record over 99% of registered deaths nationally, hence providing considerable value for mortality research.

Lastly, these analyses allowed for comparison of prevalence and HCRU related to pediatric opioid poisonings across two datasets, the national hospital discharge-level data and the national PCs data. The PCs data is obtained through a passive data collection system, and relies on individual reporting by patients, family, friends, or health care professionals. Although using medical discharge data from a different data source such as the HCUP did not allow for linking or comparing the same cases across the datasets, it provided rough population level comparisons.

Chapter 3: Specific Aim 1

Aim 1: To examine the prevalence and characteristics of pediatric opioid exposures

A. To determine the prevalence of opioid exposures and poisonings in children

B. To characterize pediatric opioid exposures based on sociodemographic and clinical characteristics

C. To examine the factors associated with severity of opioid exposures in children

D. To examine opioid exposures in children at 5-digit ZIP Code level and study its association with area-level socioeconomic status (SES)

3.1: Methods

Design

A retrospective, cross-sectional study design was implemented for this Specific Aim.

Data

Data from the National Poison Data System (NPDS), from January 2010 to December 2014, were used for this study. The American Association of Poison Control Centers' (AAPCC) maintains the NPDS, a national database that logs information from approximately 55 poison centers (PCs) across the nation, serving the entire United States population. The PCs receive roughly 6,000

exposure calls per day which are managed by trained health care professionals and specialists in poison information (SPIs). Case records are based on self-reported calls initiated by the public (family member or friend) or by health care providers (HCP). The SPIs provide exposure management recommendations to the caller and record case related documentation in standard data collection fields that are abstracted into the NPDS every few minutes. The PCs also attempt to follow-up on cases post-exposure, to determine and record medical outcomes associated with the exposure. The NPDS data is captured in near real-time and provides an actual count of exposures.[27,32] NPDS has been validated as a potential pharmaceutical poisoning surveillance system and it has been widely used in drug poisoning studies.[71,72]

Population estimates were obtained at state- and national-level, by single year of age, from the 2010 United States Census. For area-level analyses, SES data were obtained at 5-digit ZIP Code level from ESRI Updated Demographics 2010 United States Census data.

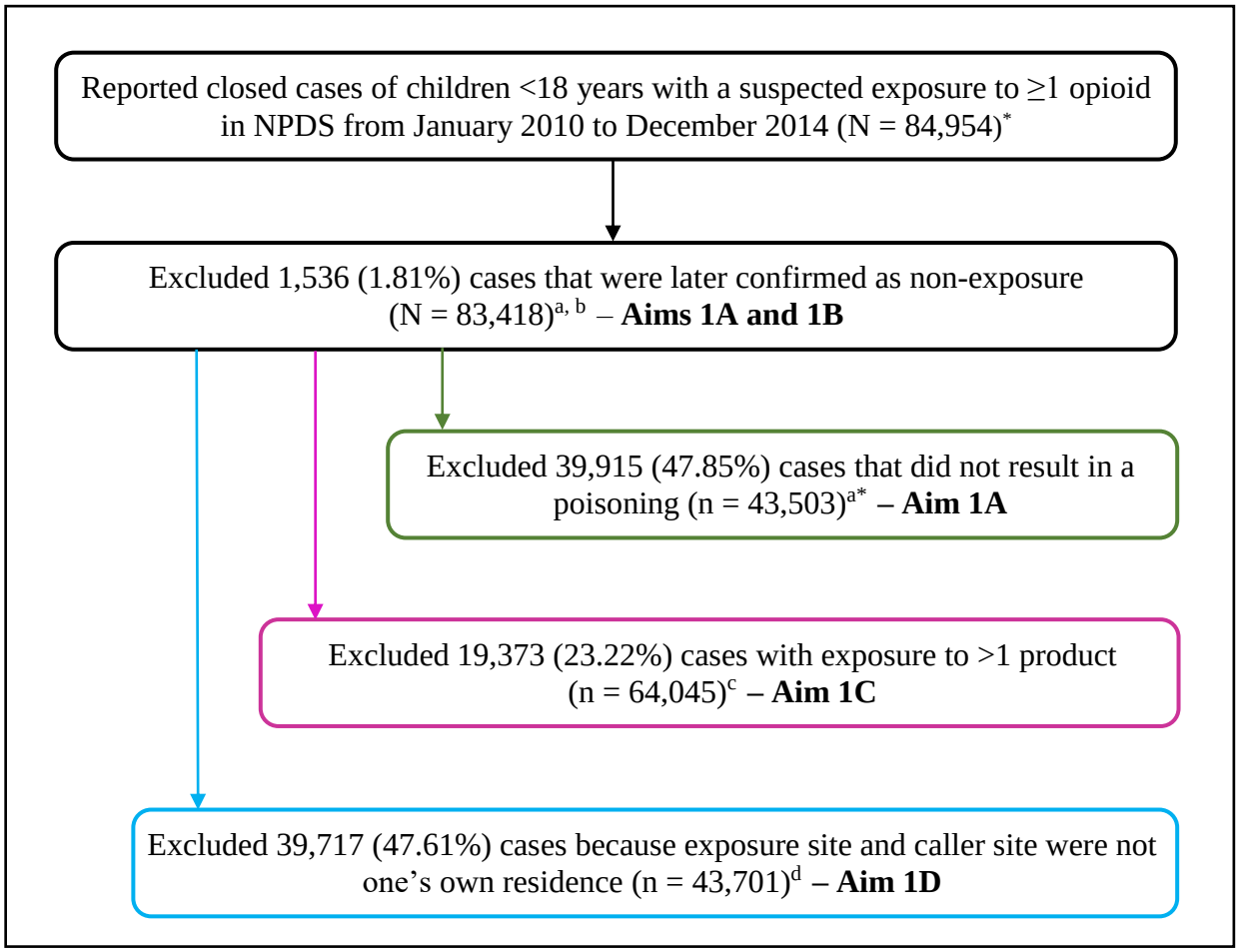
Sample

NPDS data were extracted for opioid exposure-related calls involving children less than 18 years of age. Closed cases with a suspected exposure to 1 or more opioid containing product were included. Cases that were initially recorded as a suspected opioid exposure but confirmed as non-exposure during follow-up were excluded. This was used as the final sample for examining the prevalence and characteristics of opioid exposures. Further exclusions were made for subsequent sub-aims as follows. Figure 2 depicts the final sample size for each of the sub-aims.

A. Cases without a record of 1 or more clinical effect following an opioid exposure were excluded from the opioid poisoning analyses (Specific Aim 1A).

B. Cases with exposure to more than 1 opioid or non-opioid product were excluded for examining the factors associated with severity of opioid exposures. This was done to eliminate any confounding in the association between severity of opioid exposure and various exposure characteristics, due to involvement of additional products. Such an approach has also been implemented in the NPDS annual report analyses (Specific Aim 1C).

C. Cases were excluded if the recorded exposure site and caller site was not one's own residence for area-level analyses (Specific Aim 1D). This was done in an attempt to restrict pediatric opioid exposures that occurred in one's own area, in order to examine area-level factors that may be associated with pediatric opioid exposures. Such exclusion criteria also helped to limit the analyses to cases that were reported by public and not by a health care facility (HCF). However, this led to exclusion of nearly 47.6% of total pediatric opioid exposures. The sample for Specific Aim 1D was compared to the total sample as shown in Appendix H. Compared to the total pediatric opioid exposures, the sample for Specific Aim 1D had a lower proportion of teenagers (14% vs. 27.9%) and more unintentional exposures (89.2% vs. 73.3%), less involvement of HCF care (39.3% vs. 63.2%), and a smaller proportion of exposures resulted in moderate-to-major outcomes (2.3% vs. 10.9%).



[a, b]indicates the final sample used for analyses of pediatric opioid exposures (Aims 1A and B)
[a*]indicates the final sample used for analyses of pediatric opioid poisonings (Aim 1A)
[c]indicates the final sample used for analyses of severity of pediatric opioid exposures (Aim 1C)
[d]indicates the final sample used from the NPDS for area-level analyses of pediatric opioid exposures (Aim 1D)
*Cases represent unique exposures and not unique patients.

Figure 2: Sample flow chart for Specific Aim 1

Variables

Clinical variables

Opioids constituted the entire family of opioid-containing medicinal drugs including OTC and prescription opioid analgesics and opioid containing antidiarrheal and cough preparations. Opioids were identified using generic codes maintained by the AAPCC and comprised single substance opioids (or single-opioids), such as oxycodone, buprenorphine and hydrocodone, and combination opioids including combinations with acetaminophen (APAP), acetylsalicylic acid (ASA), and anti-inflammatory drugs (NSAIDs), gastrointestinal agents (GI) and cough and cold products (CNC). Detailed list of all opioids can be found in Appendix A.

Exposure comprised any suspected opioid exposure, while poisoning was operationalized as any opioid exposure that resulted in 1 or more clinical effect. Hence, every exposure to an opioid did not represent opioid poisoning but opioid poisonings were a subset of opioid exposures. Poisonings were identified using the medical outcome and clinical effects variables in the NPDS. Medical outcome is categorized in the NPDS as follows,

- No effect was defined as no development of symptoms as a result of the exposure
- Minor effect was defined as some minimally bothersome symptoms as a result of the exposure (e.g., drowsiness, nausea)
- Moderate effect was for more pronounced, prolonged or systemic symptoms that required some treatment but was not life threatening (e.g., high fever, single seizure)
- Major effect was any life-threatening symptoms which resulted in significant residual disability (e.g., cardiac arrest, respiratory depression)

- Death if the patient died due to an exposure
- Not followed, judged as nontoxic exposures (clinical effects not expected)
- Not followed, minimal clinical effects possible (no more than minor effect possible)
- Unable to follow, judged as potentially toxic exposure
- Unrelated effect, the exposure was probably not responsible for the effect(s)

When medical outcome is observed and such data is obtained on the call at the PC, it is classified under none, minor, moderate, major effect, or death categories. However, when such information is not obtained during the initial or the follow-up call, outcome is recorded in one of the other four categories listed above, based on the SPI's judgment of anticipated outcome. Further, information on specific clinical effects or symptoms is recorded in the NPDS as related, not related, or unknown if related. Information was combined from these two variables to identify poisonings: (1) Cases were reclassified as no outcome ('no effect', 'not followed but judged as nontoxic' or 'unrelated effect', and had no related clinical effects recorded), minor outcome ('minor effect' or 'not followed but minimal clinical effects possible'), moderate outcome ('moderate effect'), major outcome ('major effect') or death. Based on this grouping, medical outcome was unknown for about 8,843 (10.6%) of the total opioid exposures cases of which, 8,811 cases were 'unable to be followed but judged as potentially toxic exposure'. (2) Poisonings were operationalized as those cases that had minor, moderate, major outcome or death (based on our outcome classification in (1) above), or those that had an unknown outcome but had one or more related clinical symptom.

Additionally, related clinical symptoms were categorized under six system organ classes (SOC) including cardiovascular and lymphatic, ocular, gastrointestinal, neurological, respiratory, and

others (combined all others due to low number of cases), based on Medical Dictionary for Regulatory Activities (MedDRA) and the AAPCC symptoms classification.[73] Symptoms related to an exposure were not recorded for 55,572 (66.62%) cases. The medical outcome variable described above was also used to identify severity (i.e., severe outcome) following an opioid exposure. Cases were operationalized as severe (moderate, major or death outcome) or non-severe (none or minor outcome).

Other exposure related clinical variables were reason, route, chronicity and scenario of exposures, performed therapies and level of health care received following an exposure. AAPCC's standard definitions were used for operationalizing these variables. The AAPCC defines reason for an exposure primarily based on the intent as intentional, unintentional, adverse reaction, or other. An exposure is classified as intentional *"if a purposeful action resulted in an exposure"* and included suspected suicidal, intentional abuse and misuse. An unintentional exposure results from an unforeseen event for instance, *"a child gaining inappropriate access to an opioid without adult supervision and without realizing the danger of the action"*, and it included general accidental exposure, therapeutic error, unintentional misuse or unintentional other. Exposure due to an adverse reaction was recorded *"when unwanted effects develop with normal or recommended use of the product"*. Exposure due to other reasons included tampering, malicious or withdrawal attempts.

Recorded routes of exposures were categorized as ingestion or other route including inhalation, aspiration, dermal, ocular, otic, parenteral, rectal, or any other routes. Chronicity was classified as acute if any single, repeated or continuous exposure occurred over a period of 8 hours or less, and non-acute if it lasted more than 8 hours.

Scenarios related to opioid exposures were grouped as storage or access (for e.g., child resistant closures not secured), therapeutic error (for e.g., confused units of measure), others (for e.g., inhalation abuse) or unknown. Therapies were recorded in the NPDS as performed, recommended and performed, not performed, and recommended but not performed. Only therapies that were recorded as performed or recommended and performed were examined. Performed therapies were grouped under decontamination (e.g., charcoal use), therapeutic intervention (e.g., ventilator use) and naloxone (recommended antidote for opioid poisoning). Categorization of scenarios and performed therapies was similar to that adopted in the annual AAPCC reports and in past research.[32,39] Exposure scenario was unknown or not recorded for 64,458 (70.27%) cases and performed therapies were not recorded for 50,698 (60.78%) cases.

The AAPCC provides information on level of HCF used and management site. Data was combined from these two elements to identify the level of HCF involved. Level of HCF was recorded in the NPDS as treated, evaluated and released (T/E & R), admitted for critical care, non-critical care or psychiatric care. For cases that were recorded as no HCF treatment received with management on site or other were reclassified as no HCF involved, while those with a record of no HCF treatment with unknown management site were reclassified as unknown. Cases wherein the patient refused referral or left against medical advice (AMA) were reclassified as other HCF involved, since they were either in (or en route to) a HCF, or were referred to a HCF. Additionally, there were 8 records of children aged less than 5 years that had a psychiatric care admission. After manual inspection, level of HCF was recoded as unknown for these 8 cases.

Sociodemographic variables

As for sociodemographics, age was categorized into ≤5 (young children), 6 to 12 (middle-aged children), and 13 to 17 (teenagers) years groups. This age grouping is consistent with previous child developmental research.[74,75] The AAPCC also provided information on child's gender, exposure site and caller site, and the caller's residential 5-digit ZIP Code and state. It was assumed that caller's residential information represented patient's residential location. This may be a reasonable assumption since over 90% of exposures occur at one's own home, and are mostly reported by the patient's (child's) family member.[32] Exposure and caller sites were identified as residence (own/other), HCF, school, or other which included public area, restaurant, workplace, or others. The operational definitions of the variables listed above were reviewed by the clinical expert on the team (Table 4).

Table 4: NPDS variables considered for Specific Aim 1

<table>
<tr><th colspan="5">Clinical variables</th></tr>
<tr><td colspan="5">Exposures and Poisonings</td></tr>
<tr><td colspan="5">Opioid drug involved[a]</td></tr>
<tr><td colspan="5">Severity</td></tr>
<tr><td>Medical outcome
None
Minor
Moderate
Major
Death</td><td>Related effects
CVS/lymphatic
Ocular
GI
Neurological
Respiratory
Others</td><td>Reason
Intentional
Unintentional
ADR
Others</td><td>Route
Ingestion
Others</td><td>Chronicity
Acute
Non-acute</td></tr>
<tr><td>Scenario
Therapeutic error
Storage/Access
Others</td><td>Performed therapy
Decontamination
Naloxone
Others</td><td colspan="3">Level of HCF care
None
T/E & R
Non-critical care
Critical care
Psychiatric care</td></tr>
</table>

		Others		
Sociodemographic variables				
Age group (years) 0-5 (0<1, 1-2, 3-5) 6-12 13-17	*Gender* Male Female	*Exposure site* Residence (own/other) School Other	*Caller site* Own residence HCF Other	*5-digit ZIP Code and State*

[a]Opioids constituted all opioid-containing medicinal (prescription and OTC) drugs.
CVS = Cardiovascular; GI = Gastrointestinal; ADR = Adverse drug reaction; HCF = Health care facility; T/E & R = Treated/evaluated and released.

Area-level socioeconomic status (SES) variables

For SES analyses at 5-digit ZIP Code level, the final sample obtained in the NPDS (n = 43,701) after applying the selection criteria, was aggregated at 5-digit ZIP Code level. This resulted in 13,751 unique 5-digit ZIP Code areas that had one or more pediatric opioid exposures in the 5-year study period. These data were merged to the 2010 Census 5-digit ZIP Code file. Areas that did not have corresponding Census information, or areas with total or persons under 18 years population of zero were excluded from further analyses. A total of 12,821 unique 5-digit ZIP Code areas was used in the final analyses (Specific Aim 1D).

Census data on total population of adults, minority, males and females, different racial and ethnic groups were examined. Proportion of pediatric opioid exposures in a 5-digit ZIP Code area was calculated using the number of pediatric exposures reported in the NPDS and the total Census population of children (<18 years of age) in that area. Population of children in a 5-digit ZIP Code area was calculated from the total population and the total adult population in that area. Proportions of adults, minority, males and females in a 5-digit ZIP Code area were calculated using the total

area-level population, while the proportions of different race and ethnic groups were calculated using the total race base population denominator reported in the Census.

Additionally, area-level household variables for median household income, average household and family size, and older adults population (>65 years of age) in households and family households, were also included. Proportions of older adults in households and family households in an area were calculated using the total population in households and family households in that area, respectively. For median household income, the variable was used as defined in the Census data. Area-level median household income data was missing for 12 observations or areas, and 11 of these observations had information on area-level per capita income. Median household income for these 11 areas was imputed using the corresponding per capita income.

Statistical Analyses

Prevalence rate of opioid exposures and poisonings was calculated using the number of cases reported in the NPDS and the United States Census *Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2014* file. Total 5-year and annual prevalence rates were calculated for pediatric opioid exposures and poisonings. Annual prevalence rates were compared to study the trend of pediatric opioid exposures and poisonings. We further adjusted annual prevalence estimates of opioid exposures for the number of child exposure calls reported in the AAPCC Annual Report in the respective year. This approach was undertaken to account for differences in the annual number of exposures calls made to the PCs. Total (5-year) and annual case fatality rates were calculated using the number of cases of opioid exposures and number of deaths among these cases, reported in the NPDS.

Age specific prevalence rates of opioid exposures were computed to account for population level changes that may have affected the number of exposure cases reported to the PCs. We further examined prevalence by regrouping the young children (≤5 years age group) into 0 to <1 year (infants), 1 to 2 years (toddlers) and 3 to 5 years (preschoolers). This was done to examine if the prevalence of opioid exposures was different among infants and toddlers.

Prevalence rates of opioid exposures were also calculated at state-level using the number of cases reported in NPDS for each state and the United States Census *Annual Estimates of the Resident Population: April 1, 2010 to July 1, 2014* state-level file. A generalized linear mixed model (GLMM) using PROC GLIMMIX with Poisson distribution and log-link function was used to examine the statistical significance of the trend of pediatric opioid exposures, from 2010 to 2014, and the state-level differences. The log of population of children (<18 years of age) in the state for the respective year, was used as an offset in this model. In linear models, the error term is assumed to be independently and identically distributed with constant variance (i.i.d.). However, this assumption is violated in mixed models. Mixed effects model with fixed and random effects can be used when the dependent variable is correlated. For example, number of opioid exposures (dependent variable) may be correlated within a state (random-effect variable). Mixed effects allow the effect of the year of exposure (fixed-effect independent variable) to vary randomly by states. GLMMs are considered as an extension of generalized linear models (GLMs) by incorporating random effects or correlations in the data.[76,77] SAS provides few procedure options for estimating such mixed models including PROC MIXED, PROC NLMIXED and PROC GLIMMIX. PROC MIXED is commonly used to model linear data whereas PROC NLMIXED models non-linear data, but it is reported to be programmatically complex. PROC GLIMMIX is a newer procedure and is used to model non-linear data.

Descriptive statistics (frequency, %, mean, SD) were calculated to describe the sociodemographic and clinical characteristics of children with opioid exposures. Separate analyses were done for children with any opioid exposure, those with one opioid product exposure and those with more than one product (at least one opioid) exposure. Chi-square tests were used to examine the association of various characteristics by age group and reason (or intent) of exposure.

Bivariate analyses using Chi-square tests and multivariable analyses using logistic regression (PROC LOGISTIC) were performed to estimate the association between severity of opioid exposures and various sociodemographic, drug and clinical characteristics. These analyses were limited to cases with one opioid, either single or combination, exposure (64,045 cases). Bivariate analyses were exploratory and examined all sociodemographic, drug and clinical factors described above. The logistic regression model was intended to be parsimonious, hence predictor variables were chosen based on practical significance and knowledge from literature. These included age, gender, chronicity, reason, type of opioid (single or combination) and specific opioid drug (buprenorphine or methadone). Interaction terms were also tested in the model. Roughly 2.7% cases had no information (unknown) recorded for age, gender, reason and chronicity. These observations were set as missing (i.e., excluded) in the logistic model analyses.

Based on our initial operationalization of medical outcome and severity, about 11% cases had no data on severity (i.e., unknown outcome). These cases were excluded in the initial logistic model. Sensitivity analysis was performed to avoid biases due to missing data. Severity was recoded by reclassifying unknown outcome cases that were unable to be followed, but judged as potentially toxic exposure by the SPI, as severe cases (these cases were grouped as unknown and excluded in the initial model).

For SES analyses, 5-digit ZIP Code level pediatric opioid exposures data from the NPDS was merged with 2010 Census 5-digit ZIP Code data. Further, centroid information (latitude and longitude) for each of these 5-digit ZIP Code areas was obtained from SAS Maps. The final sample of 5-digit ZIP Code areas consisted of areas that had 1 or more pediatric opioid exposures from 2010 to 2014 with exposure and caller site as one's own residence, and had corresponding Census information. Univariate analyses were performed, and the top and bottom 1% of the values of each of the Census variables were examined to identify outliers. There were 12 observations or areas with the rate of opioid exposures in children greater than 1 (or proportion >100%). After manually inspecting, these observations were excluded from further analyses.

Next, Spearman correlation tests were used to examine the unadjusted correlation between the proportion of pediatric opioid exposures in a 5-digit ZIP Code area and the corresponding SES variables. Covariates that were found to be significant and not highly multicollinear with other factors were chosen for adjusted analyses. Multicollinearity was assessed using a correlation matrix. Adjusted Poisson regression with log link function was performed initially to obtain the residuals for testing spatial autocorrelation as explained below. The log of population of children (<18 years of age) in an area was used as an offset in the Poisson model, since it represented the pediatric population at risk in a 5-digit ZIP Code area.

Moran's I test using PROC VARIOGRAM was then performed to examine the spatial autocorrelation in these data. Spatial autocorrelation is based on the premise that observations in closer locations are correlated, and this correlation decreases with increasing distance. Existence of spatial autocorrelation, if not accounted for, can distort the standard errors and mean estimates from the regression model. Moran's I is a frequently used global test for detecting such spatial autocorrelation in continuous data. The Moran's I index varies from -1 to +1, with zero indicating

no spatial autocorrelation. A positive test value denotes positive spatial autocorrelation and indicates clustering (i.e., similar observations are clustered), while a negative value denotes dispersion (i.e., dissimilar observations are clustered).

Moran's I tests the hypothesis (H_o) that there is zero spatial autocorrelation in the data. Hence, rejection of the null hypothesis (Z-score >|1.96| and p-value <.05) denotes that positive or negative (depending on the index value) spatial autocorrelation exist. Moran's I was performed by varying the width of distance bins (from 1 to .01) on both the number of opioid exposures in a 5-digit ZIP Code area (dependent variable) and on the raw residuals obtained from an adjusted Poisson regression model described above (residual spatial autocorrelation).[78,79] Multilevel model using GLMM (PROC GLIMMIX) was attempted to examine the association of number of pediatric opioid exposure and SES variables, adjusting for random effects at 5-digit ZIP Code level and accounting for any spatial autocorrelation in the data. The log of population of children (<18 years of age) in an area was used as an offset in this model.

PROC GLIMMIX is an iterative procedure and due to large size of the ZIP Code level data, certain strategies had to be adopted to ensure the convergence of the statistical model. After attempting various strategies, the likelihood-based estimation method (METHOD = LAPLACE), instead of the default pseudo-likelihood, was used in combination with PARMS statement. PARMS assigns a starting value to the covariance parameter based on the value(s) specified by the programmer (instead of the default value). It is one of the recommended techniques for addressing convergence failures in mixed models. Values from 0.1 to 1 with increments of 0.1 were specified with the PARMS statement. When a set of initial values is supplied in the PARMS statement, PROC GLIMMIX performs a grid search and uses the best point on the grid for further analyses.[80,81]

All statistical tests were performed with a two-sided significance level of 0.05. All analyses were done in SAS version 9.4, Microsoft Excel 2013 and ArcGIS version 10.3.1. The study was approved under exempt status by the Virginia Commonwealth University Institutional Review Board (IRB) (ID: HM20004393).

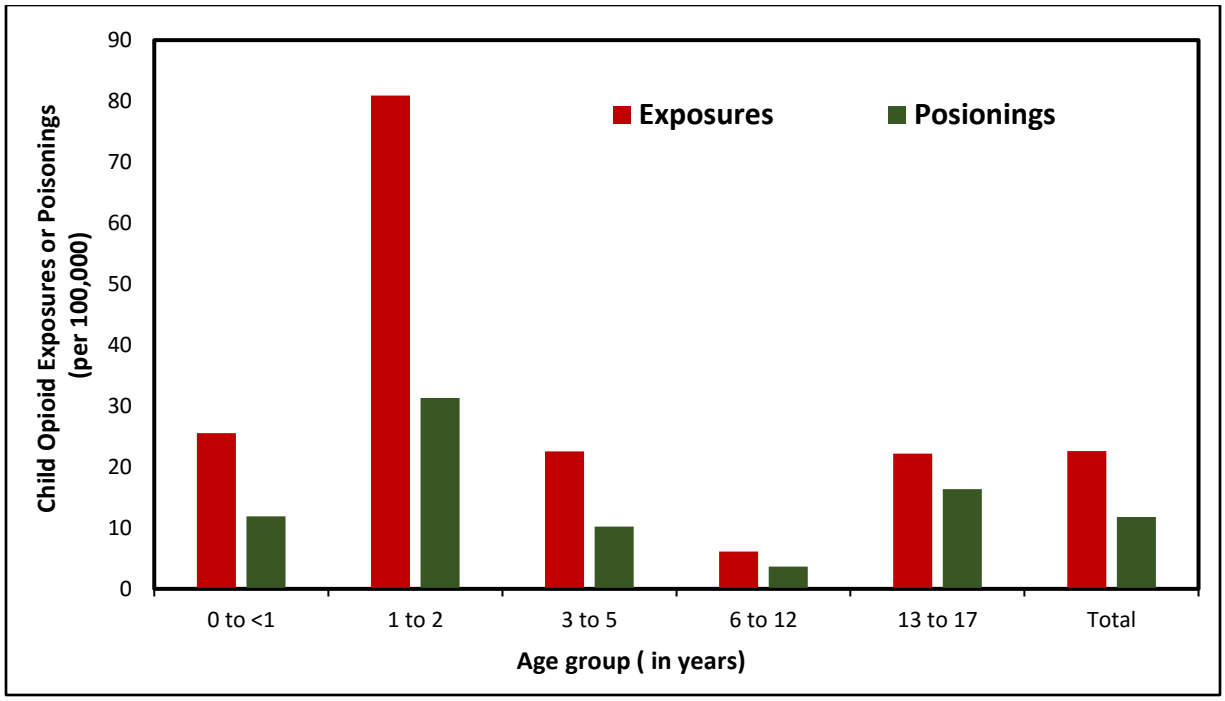
3.2: Results

Aim 1A: To determine the prevalence of opioid exposures and poisonings in children

There were a total of 83,418 pediatric opioid exposures over the 5-year period and nearly half of them (52.15%) resulted in poisoning. Total (5-year) prevalence rates of opioid exposures and opioid poisonings were 22.6 and 11.8 per 100,000 children, respectively. Total prevalence rates of opioid exposures and poisonings were higher among children under 6 years, especially those 1 to 2 years of age. Total prevalence rate of opioid exposures was 42.4 per 100,000 children in ≤5 year olds, 6.1 per 100,000 children in 6 to 12 years and 22.2 per 100,000 children in 13 to 17 years. Total prevalence rate of opioid exposures among infants was found to be 25.6 per 100,000 children, among toddlers was 80.9 per 100,000 children, and among preschoolers was 22.6 per 100,000 children (Figure 3).

Total prevalence of pediatric opioid exposures varied by state. There was some clustering observed in the western states. Alabama, Arizona, Maine, New Mexico, Oklahoma, Oregon, South Dakota, Utah, West Virginia and Wyoming had a higher number of pediatric opioid exposures per 100,000, compared to other states (Figure 4). Total case fatality rate was 0.13%. It was higher among 13 to 17 year olds (0.27%) compared to ≤5 year olds (0.08%) and 6 to 12 year olds (0.09%). Annual case fatality rate did not vary much across years.

The annual prevalence rate of pediatric opioid exposures decreased from 25.5 to 20 per 100,000 children from 2010 to 2014. Decline in the annual prevalence rate was greater among 1 to 2 year olds compared to other age groups (94.4 to 70.8 per 100,000 children from 2010 to 2014). The annual prevalence rate of pediatric opioid poisonings decreased from 13.1 to 10.7 per 100,000 children from 2010 to 2014 (Figures 5 and 6). Decline in pediatric opioid exposures was found to be statistically significant. The overall mean number of pediatric opioid exposures decreased significantly from 2010 to 2014, after adjusting for random effects of states (28 to 22 per 100,000 children respectively, $p<.0001$). There was a significant amount of variability in the rate of pediatric opioid exposures across states (Covariance parameter estimate = 0.077, $p<.0001$). There were statistically significant differences in the random effects by state in this adjusted model. The state-level relative rates (obtained from exponentiated state-level random effects) exhibited in Figure 8 help to examine which particular states had significant random effects (i.e., variability in pediatric opioid exposure rates) from 2010 to 2014. In addition to the states listed above, Arkansas, Delaware, Idaho, Indiana, Kentucky, Louisiana, Maryland, Missouri and Vermont had a significantly higher relative rate (Table 5, Figures 7 and 8). This indicates that after controlling for trend, there are certain state-level factors that may be associated with the number of pediatric opioid exposures. Residual analysis showed that the GLMM for trend fits the data well. Test for covariance parameters in the model was significant, indicating that random effects of states cannot be eliminated from the model (Chi-square = 5930.81, $p<.0001$).



Note: 364 cases with unknown age were included in total prevalence analyses.

Figure 3: Prevalence of pediatric opioid exposures by age, 2010-2014

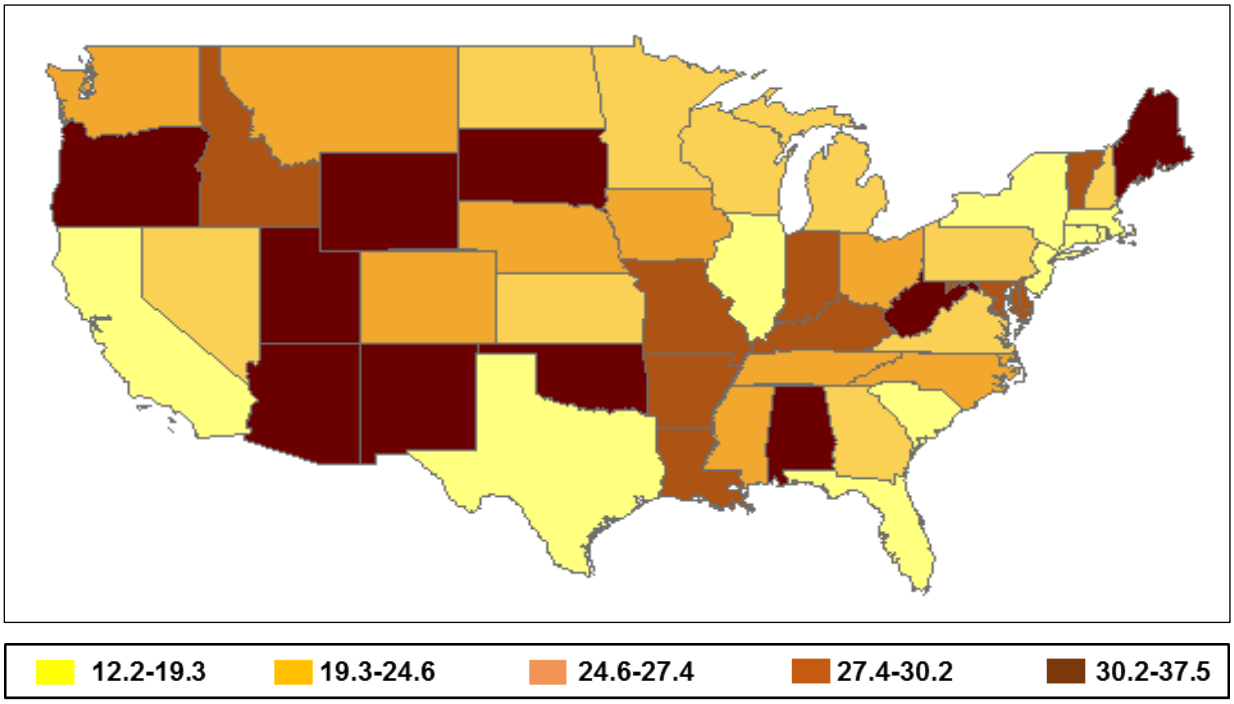


Figure 4: Prevalence of pediatric opioid exposures by state, 2010-2014 (per 100,000 children)

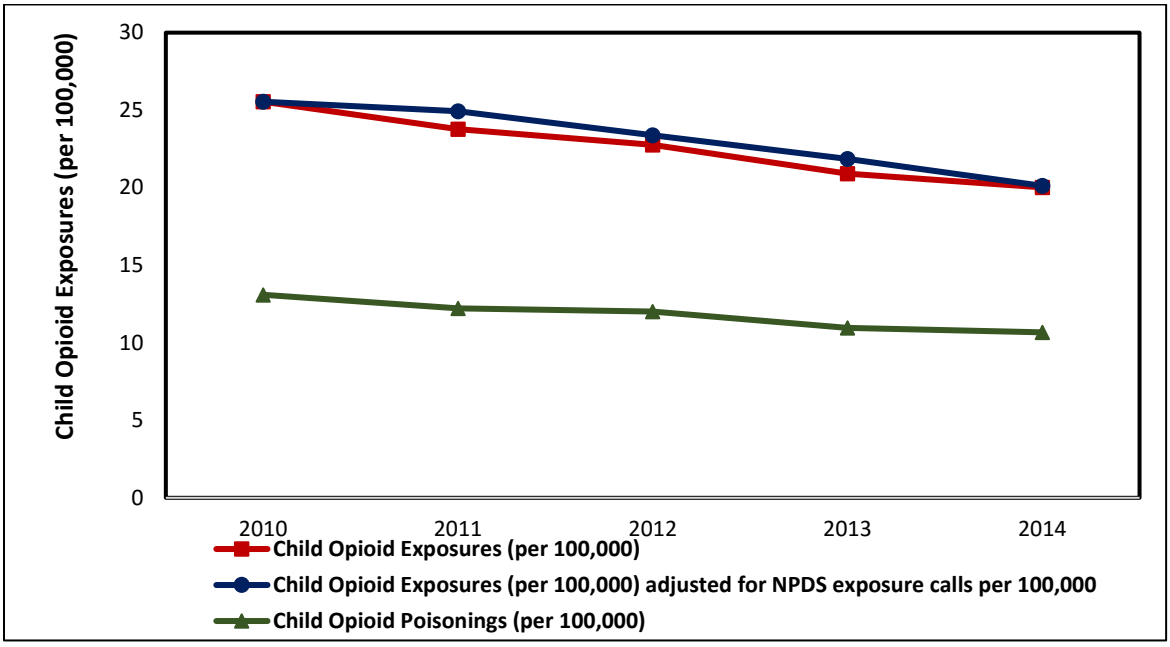
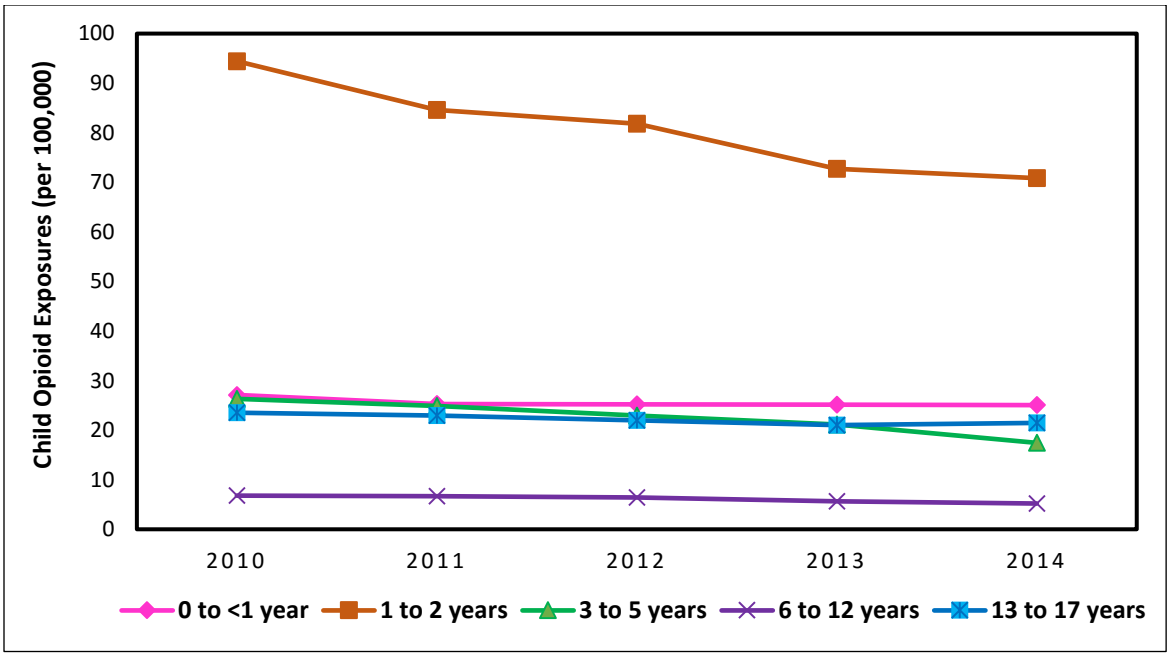


Figure 5: Annual prevalence of pediatric opioid exposures, 2010-2014



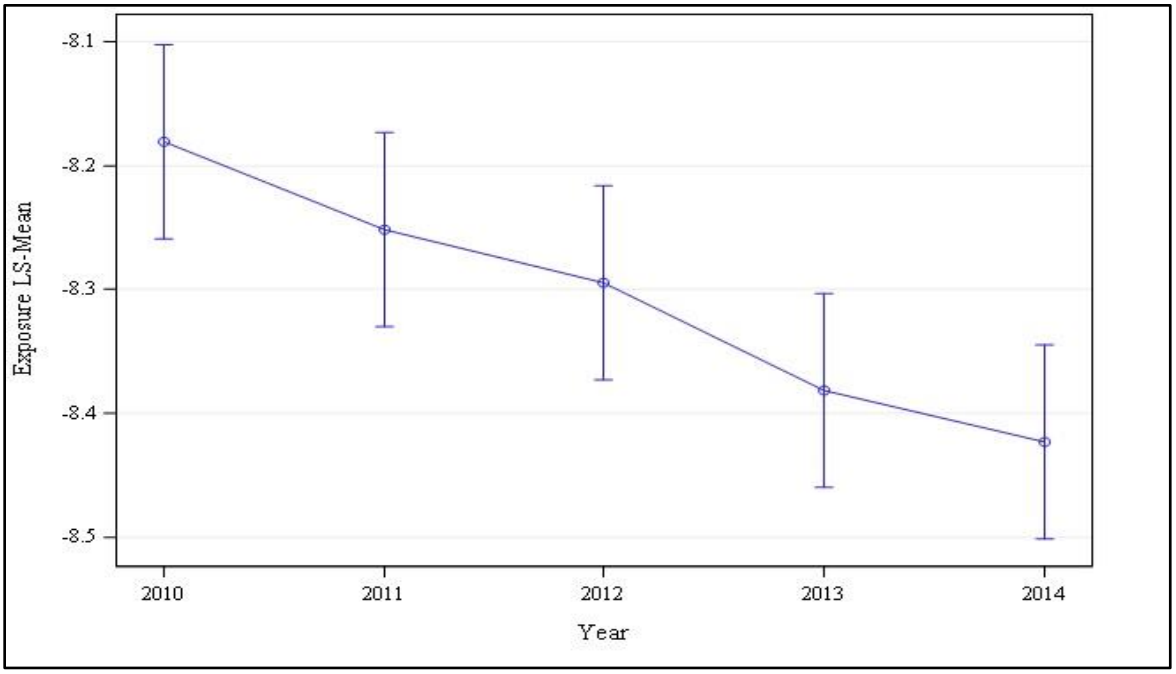
Note: 364 cases with unknown age were included in total prevalence analyses (above).

Figure 6: Age-specific annual prevalence of pediatric opioid exposures, 2010-2014

Table 5: Trend analysis of pediatric opioid exposures, 2010-2014

Variable	Estimate	SE	Mean per 100,000 (95% CI)	t-value	p-value
Covariance parameter estimate					
Intercept (Subject = State)*	0.077	0.016	--	--	
Solutions for fixed effects					
Intercept	-8.181	0.040	--	-206.49	<.0001
2010 (reference)[a]	--	--	28.0 (25.9 - 30.3)	--	
2011[a]	-0.071	0.011	26.1 (24.1 - 28.2)	-6.72	<.0001
2012[a]	-0.114	0.011	25.0 (23.1 - 27.0)	-10.72	<.0001
2013[a]	-0.201	0.011	22.9 (21.2 - 24.8)	-18.39	<.0001
2014[a]	-0.242	0.011	22.0 (20.3 - 23.8)	-21.94	<.0001

*Z-value = 4.92; p<.0001. Generalized Chi-square/degrees of freedom = 1.36 indicates no overdispersion. [a]Type III tests of fixed effects (year): F-value = 157.27, p<.0001.



p<.0001. Least Square (LS) means with 95% CI.

Figure 7: Trend analysis of pediatric opioid exposures, 2010-2014

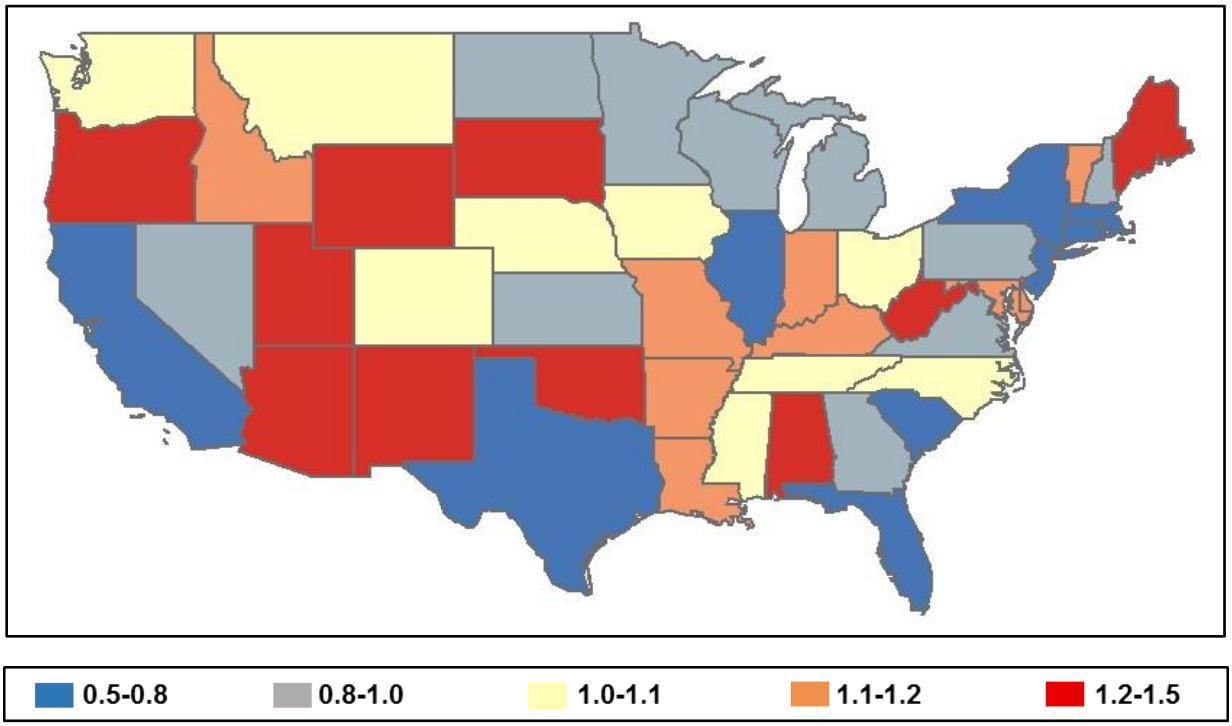


Figure 8: Relative rate of pediatric opioid exposures by state, 2010-2014

Aim 1B: To characterize pediatric opioid exposures based on sociodemographic and clinical characteristics

Sociodemographic and clinical characteristics were examined for total number of reported cases of pediatric opioid exposures (83,418), one product (opioid) exposures (64,045), and more than one product (at least one opioid) exposures (19,373). Separate analyses were performed for cases with single-opioid exposures (31,775) and combination opioid exposures (32,270), within the category of one product exposures. The results are summarized in tables 6 and 7 as follows.

Of the total 83,418 exposure cases identified, 61.1% were under 6 years of age and 27.9% were teenagers. The median age was 3 years. Over 90% of exposures occurred at home, involved ingestion, and were acute in nature. Nearly half of the total cases involved single-opioid exposures

(48.7%). The number of products involved in an exposure ranged from 1 to 36, while the number of opioids involved ranged from 1 to 5. About 73.4% of total opioid exposure cases were unintentional and 18.8% resulted from a therapeutic error. At least one related clinical effect was recorded in 33.4% of exposures, mainly neurological (25.8%), gastrointestinal (9.3%), cardiac (6.2%), ocular (3.8%), and respiratory (3.4%) effects. One-third (31.2%) of these exposure cases were treated in an ED and 20.2% were admitted for medical care, including psychiatric and critical care. Almost half of the total cases had a negative outcome following an opioid exposure of which 22.1% had a moderate-to-major outcome (including death).

Among one opioid product exposure cases, median age was lower among those exposed to single-opioids compared to those exposed to combination opioids (2 vs. 3 years, respectively). Exposures in younger children had a higher involvement of single-opioids whereas exposures in teenagers had a higher involvement of combination opioids. Tramadol, oxycodone, buprenorphine and codeine were the most common single-opioid exposures while acetaminophen with hydrocodone, acetaminophen with oxycodone and acetaminophen with codeine were the most common combination-opioid exposures (Figure 9).

Combination opioids were involved in a slightly higher number of intentional exposures compared to single-opioid exposures (16.6% vs. 13.0%, respectively). Related clinical effects were recorded for a higher proportion of single-opioid exposures compared to combination opioid exposures (33.1% vs. 21.3%), especially neurological (27.1% vs. 15.2%), ocular (5.1% vs. 1.1%) and respiratory (4.9% vs. 0.8%) effects, respectively. Poisonings (50.9% vs. 45.6%) and naloxone treatment (9.1% vs. 1.7%) were more common among cases with single-opioid exposures compared to combination-opioid exposures, respectively. Similarly, proportion of hospital admissions was higher among cases with single-opioid exposures (20% vs. 7.8%). Moderate-to-

major outcomes were recorded for 11.1% and 3% of cases following a single-opioid and a combination opioid exposure, respectively.

One-fourth of total exposure cases involved co-ingestants or multiple opioid and non-opioid products. More than one product (at least one of these products was an opioid) exposures were mostly among teenagers (median age = 14 years) and females (56.4%). Most of these cases were reported from a HCF (62.9%). Exposures to opioid combinations with APAP were most common (55.8%), followed by single-opioids (45.8%). Over half of these exposure cases were intentional (54.5%), and had at least one related clinical effect (54%). Nearly 75.3% were treated in the ED or admitted for medical care, 24.2% had moderate-to-major outcomes (including death), and 65.1% of these exposures resulted in poisoning (Tables 6 and 7).

Exposures were further examined by age group and reason (or intent) of exposure. Tables 8 and 9 summarize sociodemographic and clinical characteristics of opioid exposures by age group. Opioid exposures commonly occurred in boys among the younger children (52.7% to 55.2%). However, they were more common among teenage girls (60.5%). Although majority of the exposures occurred at one's own residence across all age groups, teenagers had a higher proportion of exposures at school compared to the younger children (3.5% vs. 0.1% to 1%). Exposures among younger children were mostly reported from one's own residence (63% to 74.7%), while exposures among teenagers were mostly reported by a HCF (61.3%). About 48.8% of exposures among teens had more than one product involvement, 6.2% had more than one opioid involvement, 4.4% were through non-ingestion routes and 11% were non-acute. Single-opioid exposures were more common among children under 6 years of age, while exposure to opioid combinations with APAP were more common among teenagers.

Majority of exposures among young children were unintentional (98.7%). Over one-fifth of exposures in children under 6 years of age had one or more related effect recorded (21.5%), 35% were treated in an ED and 13.1% were admitted for medical care. About 41.2% of these exposures resulted in poisoning and 5.8% were treated with naloxone. On the contrary, nearly 81% of exposures in teenagers were intentional. At least one related clinical effect was recorded for 62.6% of opioid exposures in teenagers and about 69% were treated in the ED or admitted for medical care, particularly critical or psychiatric care. Nearly three-fourths of these exposures resulted in poisoning and 23.5% had a moderate-to-major outcome (including death). A total of 9.3% of opioid exposures in teenagers were treated with naloxone (Tables 8 and 9).

Tables 10 and 11 summarize the sociodemographic and clinical characteristics of pediatric opioid exposures by reason (or intent). Intentional opioid exposures were more common among teenagers, whereas unintentional exposures were more common among children under 6 years of age. The sociodemographic and clinical characteristics associated with intentional and unintentional exposures were similar to those described above for exposures in teenagers and young children (≤5 years), respectively. Unintentional exposures mostly involved single-opioids (50.5%) and over two-fifths of these exposures were treated in the ED or admitted for medical care (43.2%). On the contrary, intentional exposures mostly involved opioid APAP combinations (57.3%), and nearly 77.4% of those involved in an intentional exposure were treated in the ED or admitted (Tables 10 and 11).

Table 6: Sociodemographic characteristics of pediatric opioid exposures

Characteristic, n (%)	Total opioid exposures (N = 83,418)	One opioid product exposures (n = 64,045)		>1 opioid product exposures[b] (n = 19,373)
		Single-opioid[a] (n = 31,775)	Combination opioid[a] (n = 32,270)	
Age, years (range)				
Mean	6.42 (0-17)	4.72 (0-17)	5.67 (0-17)	10.44 (0-17)
Median	3 (0-17)	2 (0-17)	3 (0-17)	14 (0-17)
Age group				
0 < 1	5,042 (6.04)[c]	2,388 (7.52)	2,163 (6.7)	491 (2.53)
1 - 2	32,204 (38.61)	14,771 (46.49)	12,987 (40.24)	4,446 (22.95)
3 - 5	13,744 (16.48)	5,994 (18.86)	6,052 (18.75)	1,698 (8.76)
6 - 12	8,819 (10.57)	3,463 (10.9)	4,031 (12.49)	1,325 (6.84)
13 - 17	23,245 (27.87)	4,982 (15.68)	6,912 (21.42)	11,351 (58.59)
Unknown (child)	364 (0.44)	177 (0.56)	125 (0.39)	62 (0.32)
Gender				
Female	42,022 (50.38)	15,117 (47.58)	15,973 (49.5)	10,932 (56.43)
Male	41,081 (49.25)	16,505 (51.94)	16,183 (50.15)	8,393 (43.32)
Unknown	315 (0.38)	153 (0.48)	114 (0.35)	48 (0.25)
Exposure site				
Own residence	76,577 (91.80)	29,057 (91.45)	30,110 (93.31)	17,410 (89.87)
Other residence	3,518 (4.22)	1,467 (4.62)	1,236 (3.83)	815 (4.21)
School	949 (1.14)	325 (1.02)	319 (0.99)	305 (1.57)
Other	1,131 (1.36)	477 (1.5)	329 (1.02)	325 (1.68)
Unknown	1,243 (1.49)	449 (1.41)	276 (0.86)	518 (2.67)

Caller site				
Own residence	45,693 (54.78)	18,327 (57.68)	21,791 (67.53)	5,575 (28.78)
HCF	29,749 (35.66)	10,148 (31.94)	7,415 (22.98)	12,186 (62.9)
Other	7,699 (9.23)	3,170 (9.98)	2,961 (9.18)	1,568 (8.09)
Unknown	277 (0.33)	130 (0.41)	103 (0.32)	44 (0.23)

[a]Analyses within single opioid and combination opioid were limited to cases with one product (opioid) exposures.
[b]At least one of the products was an opioid.
[c]None of these children had scenario recorded as "exposure through breastmilk".

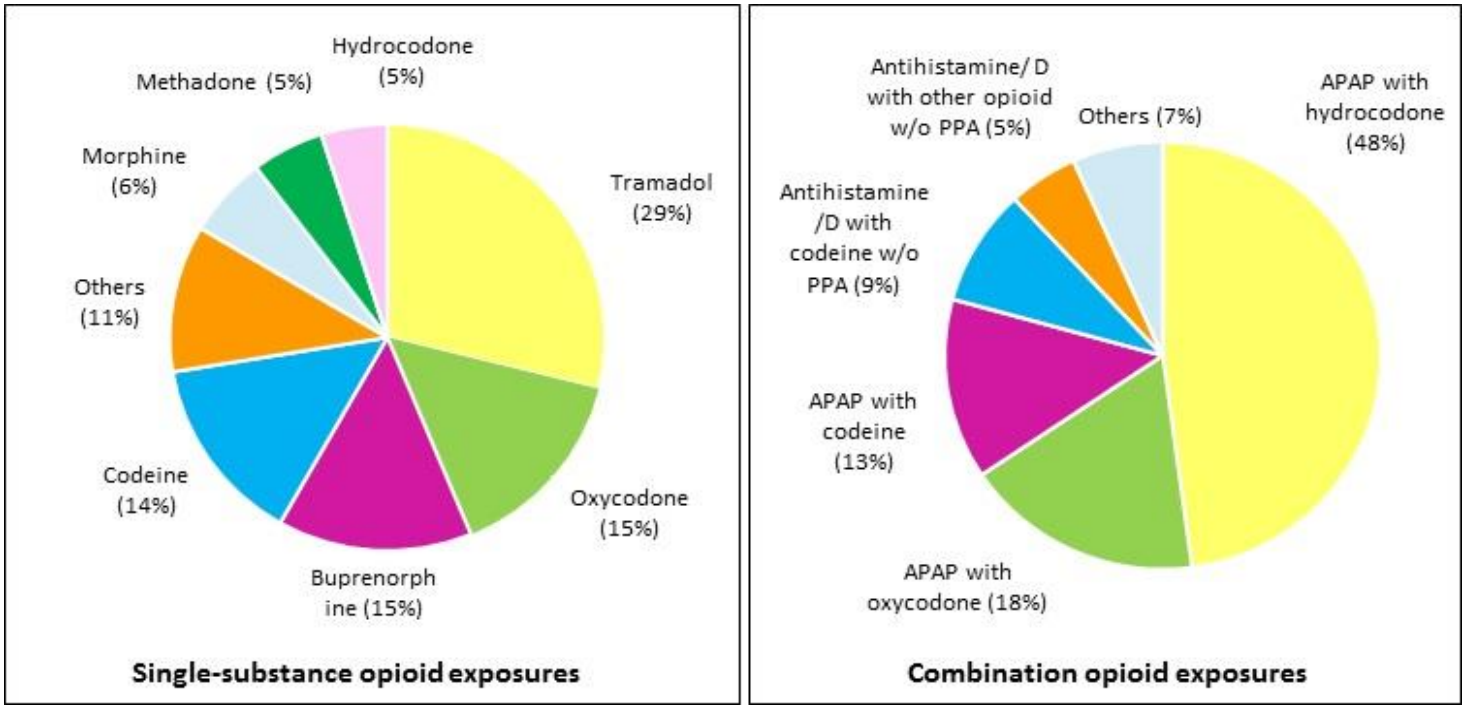
Table 7: Clinical characteristics of pediatric opioid exposures

Characteristic, n (%)	**Total opioid exposures (N = 83,418)**	**One opioid product exposures (n = 64,045)**		**>1 Product exposures[b] (n = 19,373)**
		Single-opioid[a] (n = 31,775)	Combination opioid[a] (n = 32,270)	
Opioid type involved				
Single substance	40,651 (48.73)	31,775 (100)	--	8,876 (45.82)
APAP combinations	37,472 (44.92)	--	26,657 (82.61)	10,815 (55.83)
CNC combinations	5,406 (6.48)	--	4,825 (14.95)	581 (3)
Other combinations	1,028 (1.23)	--	788 (2.44)	240 (1.24)
No. of products [b] (range)				
Mean	1.48 (1-36)	--	--	3.07 (2-36)
Median	1 (1-36)	--	--	2 (2-36)
No. of opioid products (range)				
Mean	1.03 (1-5)	--	--	1.03 (1-5)
Median	1 (1-5)	--	--	1 (1-5)

Route				
Ingestion	82,322 (98.69)	31,151 (98.04)	32,089 (99.44)	19,082 (98.5)
Other	1,602 (1.92)	541 (1.7)	189 (0.59)	872 (4.5)
Unknown	375 (0.45)	153 (0.48)	37 (0.11)	185 (0.95)
Chronicity				
Acute	77,602 (93.03)	30,389 (95.64)	30,255 (93.76)	16,958 (87.53)
Non-acute	4,609 (5.53)	1,049 (3.3)	1,770 (5.48)	1,790 (9.24)
Unknown	1,207 (1.45)	337 (1.06)	245 (0.76)	625 (3.23)
Reason				
Unintentional	61,206 (73.37)	26,925 (84.74)	26,137 (80.99)	8,144 (42.04)
Intentional	20,064 (24.05)	4,143 (13.04)	5,361 (16.61)	10,560 (54.51)
Adverse reaction	1,088 (1.3)	223 (0.7)	495 (1.53)	370 (1.91)
Other	227 (0.27)	132 (0.42)	36 (0.11)	59 (0.3)
Unknown	833 (1)	352 (1.11)	241 (0.75)	240 (1.24)
Scenario				
Therapeutic error	15,666 (18.78)	6,258 (19.69)	7,676 (23.79)	1,732 (8.94)
Storage/Access	2,917 (3.5)	1,282 (4.03)	1,248 (3.87)	387 (2)
Other	778 (0.93)	342 (1.08)	267 (0.83)	169 (0.87)
Unknown	64,458 (77.27)	24,086 (75.8)	23,237 (72.01)	17,135 (88.45)
Related effect				
Any	27,846 (33.38)	10,527 (33.13)	6,868 (21.28)	10,451 (53.95)
Neurological	21,544 (25.83)	8,601 (27.07)	4,911 (15.22)	8,032 (41.46)
Gastrointestinal	7,751 (9.29)	2,793 (8.79)	2,137 (6.62)	2,821 (14.56)
Cardiovascular	5,136 (6.16)	1,169 (3.68)	443 (1.37)	3,524 (18.19)
Ocular	3,126 (3.75)	1,625 (5.11)	357 (1.11)	1,144 (5.91)
Respiratory	2,863 (3.43)	1,563 (4.92)	243 (0.75)	1,057 (5.46)
Other	4,275 (5.12)	1,461 (4.6)	904 (2.8)	1,910 (9.86)

Performed therapy				
Decontamination	19,571 (23.46)	7,247 (22.81)	8,162 (25.29)	4,162 (21.48)
Naloxone	5,300 (6.35)	2,884 (9.08)	549 (1.7)	1,867 (9.64)
Other therapy	14,591 (17.49)	4,831 (15.2)	2,807 (8.7)	6,953 (35.89)
HCF				
None	30,093 (36.07)	10,830 (34.08)	16,114 (49.93)	3,149 (16.25)
T/E and R	25,983 (31.15)	10,089 (31.75)	9,316 (28.87)	6,578 (33.95)
Critical care	7,097 (8.51)	3,012 (9.48)	662 (2.05)	3,423 (17.67)
Non-critical care	6,122 (7.34)	2,869 (9.03)	895 (2.77)	2,358 (12.17)
Psychiatric care	3,658 (4.39)	459 (1.44)	975 (3.02)	2,224 (11.48)
Other	9,836 (11.79)	4,259 (13.4)	4,021 (12.46)	1,556 (8.03)
Unknown	629 (0.75)	257 (0.81)	287 (0.89)	85 (0.44)
Outcome				
No effect	32,944 (39.49)	12,478 (39.27)	14,599 (45.24)	5,867 (30.28)
Minor	32,443 (38.89)	11,820 (37.2)	13,120 (40.66)	7,503 (38.73)
Moderate	7,709 (9.24)	2,900 (9.13)	888 (2.75)	3,921 (20.24)
Major	1,368 (1.64)	581 (1.83)	81 (0.25)	706 (3.64)
Death	111 (0.13)	46 (0.14)	7 (0.02)	58 (0.3)
Unknown	8,843 (10.6)	3,950 (12.43)	3,575 (11.08)	1,318 (6.8)
Poisoning	43,503 (52.15)	16,180 (50.92)	14,714 (45.60)	12,609 (65.09)

APAP = Acetaminophen, CNC = Cough and cold products, T/E and R = Treated/evaluated and released, HCF = Healthcare facility.
[a]Analyses within single opioid and combination opioid were limited to cases with one product (opioid) exposures.
[b]At least one of the products was an opioid.
Other opioid combinations include combinations with acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), and gastrointestinal agents (GI).
There can be more than 1 opioid type involved, route, scenario, clinical effect and therapies recorded hence, the sub-categories under each of these variables are not mutually exclusive. Also, scenarios, related effect and performed therapy are missing for 60-70% of cases.



APAP = acetaminophen; PPA = phenylpropanolamine; D = Decongestant; w/o = without.

Figure 9: Opioids commonly involved in pediatric exposures

Table 8: Sociodemographic characteristics of pediatric opioid exposures by age

Characteristic, n (%)	Age Group		
	≤5 years [a] (n = 51,072)	6 to 12 years (n = 8,819)	13 to 17 years (n = 23,245)
Gender*			
Female	23,919 (46.83)	3,933 (44.60)	14,056 (60.47)
Male	26,935 (52.74)	4,866 (55.18)	9,159 (39.40)
Unknown	218 (0.43)	20 (0.23)	30 (0.13)
Exposure site*			
Own residence	47,578 (93.16)	8,253 (93.58)	20,510 (88.23)
Other residence	2,660 (5.21)	290 (3.29)	552 (2.37)
School	50 (0.10)	89 (1.01)	805 (3.46)
Other	543 (1.06)	130 (1.47)	452 (1.94)
Unknown	241 (0.47)	57 (0.65)	926 (3.98)
Caller site*			
Own residence	32,192 (63.03)	6,584 (74.66)	6,725 (28.93)
HCF	14,025 (27.46)	1,449 (16.43)	14,246 (61.29)
Other	4,728 (9.26)	755 (8.56)	2,167 (9.32)
Unknown	127 (0.25)	31 (0.35)	107 (0.46)

*Chi-square p<.05. Unknown age group not shown here.
Unknown category for characteristics was included in Chi-square tests.
[a]Number of opioid exposures in ≤5 in Tables 6 and 10 do not add up to the number in this table. Exposures recorded as unknown age but ≤5 years in the NPDS were added to the ≤5 years subgroup here, but these exposures were set as unknown for analyses in other tables.

Table 9: Clinical characteristics of pediatric opioid exposures by age

Characteristic, n (%)	Age Group		
	≤5 years[a] (n = 51,072)	6 to 12 years (n = 8,819)	13 to 17 years (n = 23,245)
Opioid type involved*			
Single substance	26,752 (52.38)	3,970 (45.02)	9,765 (42.01)
APAP combinations	20,544 (40.23)	3,564 (40.41)	13,249 (57.00)
CNC combinations	3,442 (6.74)	1,235 (14.00)	724 (3.11)
Other combinations	695 (1.36)	99 (1.12)	230 (0.99)
No. of products*			
1	44,431 (87.00)	7,494 (84.98)	11,894 (51.17)
≥2	6,641 (13.00)	1,325 (15.02)	11,351 (48.83)

No. of opioid products[*]			
1	50,322 (98.53)	8,708 (98.74)	21,796 (93.77)
≥2	750 (1.47)	111 (1.26)	1,449 (6.23)
Route[*]			
Ingestion	50,599 (99.07)	8,708 (98.74)	22,742 (97.84)
Other	447 (0.88)	126 (1.43)	1,017 (4.38)
Unknown	161 (0.32)	23 (0.26)	188 (0.81)
Chronicity[*]			
Acute	49,646 (97.21)	8,018 (90.92)	19,702 (84.76)
Non-acute	1,285 (2.52)	738 (8.37)	2,561 (11.02)
Unknown	141 (0.28)	63 (0.71)	982 (4.22)
Reason[*]			
Unintentional	50,390 (98.66)	7,283 (82.58)	3,361 (14.46)
Intentional[b]	118 (0.23)	1,035 (11.74)	18,829 (81.00)
Adverse reaction	253 (0.50)	258 (2.93)	560 (2.41)
Other	127 (0.25)	23 (0.26)	74 (0.32)
Unknown	184 (0.36)	220 (2.49)	421 (1.81)
Scenario[*]			
Therapeutic error	7,904 (15.48)	5,295 (60.04)	2,436 (10.48)
Storage/Access	2,766 (5.42)	108 (1.22)	29 (0.12)
Other	604 (1.18)	71 (0.81)	91 (0.39)
Unknown	40,112 (78.54)	3,393 (38.47)	20,718 (89.13)
Related effect[*]			
Any	10,975 (21.49)	2,271 (25.75)	14,546 (62.58)
Neurological	9,069 (17.76)	1,719 (19.49)	10,722 (46.13)
Gastrointestinal	2,450 (4.80)	708 (8.03)	4,577 (19.69)
Cardiovascular	827 (1.62)	232 (2.63)	4,075 (17.53)
Ocular	1,751 (3.43)	153 (1.73)	1,220 (5.25)
Respiratory	1,534 (3.00)	111 (1.26)	1,216 (5.23)
Other	1,370 (2.68)	354 (4.01)	2,539 (10.92)
Performed therapy[*]			
Decontamination	13,633 (26.69)	2,042 (23.15)	3,883 (16.70)
Naloxone	2,939 (5.75)	188 (2.13)	2,171 (9.34)
Other therapy	5,225 (10.23)	892 (10.11)	8,462 (36.40)
HCF[*]			
None	20,541 (40.22)	5,595 (63.44)	3,871 (16.65)
T/E and R	17,888 (35.03)	1,539 (17.45)	6,538 (28.13)
Critical care	3,257 (6.38)	283 (3.21)	3,551 (15.28)
Non-critical care	3,415 (6.69)	315 (3.57)	2,392 (10.29)
Psychiatric care	--	105 (1.19)	3,550 (15.27)
Other	5,635 (11.03)	899 (10.19)	3,154 (13.57)

Unknown	336 (0.66)	83 (0.94)	189 (0.81)
Outcome*			
None	25,441 (49.81)	2,926 (33.18)	4,532 (19.50)
Minor	17,188 (33.65)	4,651 (52.74)	10,536 (45.33)
Moderate	2,727 (5.34)	376 (4.26)	4,601 (19.79)
Major	499 (0.98)	63 (0.71)	805 (3.46)
Death	40 (0.08)	8 (0.09)	63 (0.27)
Unknown	5,177 (10.14)	795 (9.01)	2,708 (11.65)
Poisoning*	21,037 (41.19)	5,237 (59.38)	17,128 (73.68)

*Chi-square p<.05. Unknown age group not shown here.
[a]Number of opioid exposures in ≤5 in Tables 6 and 10 do not add up to the number in this table. Exposures recorded as unknown age but ≤5 years in the NPDS were added to the ≤5 years subgroup here, but these exposures were set as unknown for analyses in other tables.
[b]Children ≤5 years can be coded as intentional if someone intentionally gave the child a wrong drug or dose.
Unknown category for characteristics was included in Chi-square tests.
APAP = Acetaminophen, CNC = Cough and cold products, T/E and R = Treated/evaluated and released, HCF = Healthcare facility.
Other opioid combinations include combinations with acetylsalicylic (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), and gastrointestinal agents (GI).
There can be more than 1 opioid type involved, route, scenario, clinical effect and therapies recorded hence, the sub-categories under each of these variables are not mutually exclusive.

Table 10: Sociodemographic characteristics of pediatric opioid exposures by intent

Characteristic, n (%)	**Intent of exposure**	
	Unintentional (n = 61,206)	**Intentional (n = 20,064)**
Age group*		
0 < 1	4,800 (7.84)	17 (0.08)
1 - 2	31,978 (52.25)	59 (0.29)
3 - 5	13,534 (22.11)	41 (0.20)
6 - 12	7,283 (11.90)	1,035 (5.16)
13 - 17	3,361 (5.49)	18,829 (93.84)
Unknown (child)	250 (0.41)	83 (0.41)
Gender*		
Female	28,653 (46.81)	12,290 (61.25)
Male	32,296 (52.77)	7,745 (38.60)
Unknown	257 (0.42)	29 (0.14)

Exposure site*		
Own residence	57,285 (93.59)	17,546 (87.45)
Other residence	2,910 (4.75)	540 (2.69)
School	138 (0.23)	768 (3.83)
Other	641 (1.05)	356 (1.77)
Unknown	232 (0.38)	854 (4.26)
Caller site*		
Own residence	40,331 (65.89)	4,265 (21.26)
HCF	15,117 (24.70)	13,822 (68.89)
Other	5,604 (9.16)	1,888 (9.41)
Unknown	154 (0.25)	89 (0.44)

*Chi-square p<.05. Exposures due to adverse reaction, others reasons or unknown shown here. Unknown category for characteristics was included in Chi-square tests.

Table 11: Clinical characteristics of pediatric opioid exposures by intent

Characteristic, n (%)	Intent of exposure	
	Unintentional (n = 61,206)	Intentional (n = 20,064)
Opioid type involved*		
Single substance	30,936 (50.54)	8,635 (43.04)
APAP combinations	25,003 (40.85)	11,493 (57.28)
CNC combinations	4,866 (7.95)	441 (2.20)
Other combinations	812 (1.33)	194 (0.97)
No. of products*		
1	53,062 (86.69)	9,504 (47.37)
≥2	8,144 (13.31)	10,560 (52.63)
No. of opioid products*		
1	60,334 (98.58)	18,699 (93.20)
≥2	872 (1.42)	1,365 (6.80)
Route*		
Ingestion	60,746 (99.25)	19,636 (97.87)
Other	486 (0.79)	939 (4.68)
Unknown	126 (0.21)	155 (0.77)
Chronicity*		
Acute	58,817 (96.10)	17,203 (85.74)
Non-acute	2,274 (3.72)	1,954 (9.74)
Unknown	115 (0.19)	907 (4.52)

Scenario*		
Therapeutic error	15,649 (25.57)	4 (0.02)
Storage/Access	2,902 (4.74)	10 (0.05)
Other	695 (1.14)	71 (0.35)
Unknown	42,359 (69.21)	19,979 (99.58)
Related effect*		
Any	13,302 (21.73)	13,310 (66.34)
Neurological	10,823 (17.68)	9,924 (49.46)
Gastrointestinal	3,320 (5.42)	4,085 (20.36)
Cardiovascular	894 (1.46)	4,053 (20.20)
Ocular	1,813 (2.96)	1,208 (6.02)
Respiratory	1,511 (2.47)	1,192 (5.94)
Other	1,642 (2.68)	2,232 (11.12)
Performed therapy*		
Decontamination	16,121 (26.34)	3,263 (16.26)
Naloxone	2,972 (4.86)	2,160 (10.77)
Other therapy	5,852 (9.56)	8,140 (40.57)
HCF*		
None	27,802 (45.42)	1,529 (7.62)
T/E and R	19,473 (31.82)	6,116 (30.48)
Critical care	3,315 (5.42)	3,537 (17.63)
Non-critical care	3,564 (5.82)	2,329 (11.61)
Psychiatric care	83 (0.14)	3,543 (17.66)
Other	6,539 (10.68)	2,880 (14.35)
Unknown	430 (0.70)	130 (0.65)
Outcome*		
None	28,819 (47.09)	3,813 (19.00)
Minor	22,945 (37.49)	8,485 (42.29)
Moderate	2,960 (4.84)	4,409 (21.97)
Major	485 (0.79)	786 (3.92)
Death	22 (0.04)	61 (0.30)
Unknown	5,975 (9.76)	2,510 (12.51)
Poisoning*	27,137 (44.34)	14,749 (73.51)

*Chi-square $p<.05$. Exposures due to adverse reaction, others reasons or unknown shown here. Unknown category for characteristics was included in Chi-square tests.
APAP = Acetaminophen, CNC = Cough and cold products, T/E and R = Treated/evaluated and released, HCF = Healthcare facility.
Other opioid combinations include combinations with acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), and gastrointestinal agents (GI).
There can be more than 1 opioid type involved, route, scenario, clinical effect and therapies recorded. Hence, the sub-categories under each of these variables are not mutually exclusive.

Aim 1C: To examine the factors associated with severity of opioid exposures in children

Bivariate and multivariable analyses were performed to examine the sociodemographic, drug and clinical characteristics associated with severity (i.e., severe medical outcome) following an opioid exposure. These analyses were limited to cases with one opioid exposure, either single or combination. Of the total 64,045 cases, 7% had a severe outcome. All factors, except gender, were found to be statistically significant in the bivariate analyses. Table 12 summarizes the results from bivariate analyses. Compared to those with non-severe outcomes, cases with severe outcomes were more likely to be older (37.9% vs. 15.8%) and have a single-opioid (78.3% vs. 46.7%), especially buprenorphine (21.7% vs. 5.7%) or methadone (10.9% vs. 1.8%) involved in an exposure. Nearly 34.6% of severe cases were intentional, 96.8% had at least one related clinical effect, largely neurological (83.7%) or respiratory effects (37%), and were commonly treated with naloxone (45.8%). Majority of cases with severe outcomes following an opioid exposure were either treated in the ED or admitted for medical care, especially for critical care (94.1%) (Table 12).

Table 12: Characteristics associated with severe pediatric opioid exposures (bivariate analyses)

Characteristics, n (%)	**Total[a] (N = 64,045)**	**Non-severe outcome (n = 52,017)**	**Severe outcome (n = 4,503)**
Sociodemographic			
Age group[*]			
$0 \leq 5$	44,431 (69.37)	37,161 (71.44)	2,555 (56.74)
$6 \leq 12$	7,494 (11.7)	6,531 (12.56)	236 (5.24)
$13 \leq 17$	11,894 (18.57)	8,240 (15.84)	1,708 (37.93)
Unknown	226 (0.35)	85 (0.16)	4 (0.09)

Gender			
Female	31,090 (48.54)	25,414 (48.86)	2,184 (48.50)
Male	32,688 (51.04)	26,509 (50.96)	2,308 (51.25)
Unknown	267 (0.42)	94 (0.18)	11 (0.24)
Exposure site*			
Own residence	59,167 (92.38)	48,512 (93.26)	4,042 (89.76)
Other residence	2,703 (4.22)	2,105 (4.05)	157 (3.49)
School	644 (1.01)	474 (0.91)	77 (1.71)
Other	806 (1.26)	599 (1.15)	96 (2.13)
Unknown	725 (1.13)	327 (0.63)	131 (2.91)
Caller site*			
Own residence	40,118 (62.64)	33,686 (64.76)	841 (18.68)
HCF	17,563 (27.42)	13,615 (26.17)	3,258 (72.35)
Other	6,131 (9.57)	4,640 (8.92)	395 (8.77)
Unknown	233 (0.36)	76 (0.15)	9 (0.20)
Drug			
Combination opioid*[b]	32,270 (50.39)	27,719 (53.29)	976 (21.67)
Opioid type involved*			
Single-substance	31,775 (49.61)	24,298 (46.71)	3,527 (78.33)
APAP combination	26,657 (41.62)	22,603 (43.45)	809 (17.97)
CNC combination	4,825 (7.53)	4,485 (8.62)	119 (2.64)
Other combination	788 (1.23)	631 (1.21)	48 (1.07)
Buprenorphine*	4,602 (7.19)	2,982 (5.73)	977 (21.70)
Methadone*	1,715 (2.68)	937 (1.80)	492 (10.93)
Hydrocodone*	1,559 (2.43)	1,319 (2.54)	47 (1.04)
Oxycodone*	4,722 (7.37)	3,379 (6.50)	445 (9.88)
Tramadol*	9,175 (14.33)	7,649 (14.70)	683 (15.17)
Clinical			
Route*			
Ingestion	63,240 (98.74)	51,486 (98.98)	4,353 (96.67)
Other	730 (1.14)	531 (1.02)	105 (2.33)
Unknown	190 (0.3)	80 (0.15)	69 (1.53)
Chronicity*			
Acute	60,644 (94.69)	49,420 (95.01)	4,109 (91.25)
Non-acute	2,819 (4.4)	2,311 (4.44)	269 (5.97)
Unknown	582 (0.91)	246 (0.47)	125 (2.78)

Reason*			
Unintentional	53,062 (82.85)	44,936 (86.39)	2,691 (59.76)
Intentional	9,504 (14.84)	6,167 (11.86)	1,560 (34.64)
Adverse reaction	718 (1.12)	564 (1.08)	80 (1.78)
Other	168 (0.26)	98 (0.19)	47 (1.04)
Unknown	593 (0.93)	252 (0.48)	125 (2.78)
Scenario*			
Therapeutic error	13,934 (21.76)	13,132 (25.25)	276 (6.13)
Storage/Access	2,530 (3.95)	2,114 (4.06)	149 (3.31)
Other	609 (0.95)	509 (0.98)	38 (0.84)
Unknown	47,323 (73.89)	36,549 (70.26)	4,071 (90.41)
Related effect*			
Any	17,395 (27.16)	11,585 (22.27)	4,359 (96.80)
Neurological	13,512 (21.1)	8,708 (16.74)	3,770 (83.72)
Gastrointestinal	4,930 (7.7)	3,504 (6.74)	1,020 (22.65)
Cardiovascular	1,612 (2.52)	373 (0.72)	1,184 (26.29)
Ocular	1,982 (3.09)	919 (1.77)	1,000 (22.21)
Respiratory	1,806 (2.82)	90 (0.17)	1,664 (36.95)
Other	2,365 (3.69)	1,269 (2.44)	878 (19.50)
Performed therapy*			
Decontamination	15,409 (24.06)	14,346 (27.58)	628 (13.95)
Naloxone	3,433 (5.36)	1,336 (2.57)	2,060 (45.75)
Other therapy	7,638 (11.93)	4,699 (9.03)	2,706 (60.09)
HCF*			
None	26,944 (42.07)	26,219 (50.40)	135 (3.00)
T/E and R	19,405 (30.3)	18,035 (34.67)	1,127 (25.03)
Critical care	3,674 (5.74)	1,749 (3.36)	1,869 (41.51)
Non-critical care	3,764 (5.88)	2,675 (5.14)	1,036 (23.01)
Psychiatric care	1,434 (2.24)	1,225 (2.35)	203 (4.51)
Other	8,280 (12.93)	1,928 (3.71)	127 (2.82)
Unknown	544 (0.85)	186 (0.36)	6 (0.13)

*Chi-square p<.05. HCF = Health care facility; T/E and R = Treated, evaluated and released.
[a]Numbers in severe and non-severe outcome columns do not add up to the total since severity was unknown (i.e., unknown medical outcome) for 7,525 (11.8%) of the cases.
[b]Combination opioid indicated if the child was exposed to one of the combination opioid products or a single-opioid product.

As stated earlier, covariates for the adjusted regression model of severity following an opioid exposure were chosen based on practical significance and prior knowledge. These included age,

gender, chronicity, reason, type of opioid (single or combination) and specific opioid drug. Previous literature has shown differences in drug exposures in children by age and gender, chronicity, reason of exposure and characteristics of the drug involved. Drug characteristics in the current adjusted model were limited to the type of opioid drug involved (single or combination), and involvement of buprenorphine or methadone since these two agents have been associated with severe or fatal outcomes following an exposure in children (refer to Literature Review chapter).

Table 13 summarizes the results from adjusted analyses of severity of pediatric opioid exposures and poisonings. All covariates were found to be significantly associated with severity in the initial adjusted model. However, this model exhibited poor fit (Hosmer and Lemeshow test: Chi-square = 66.01, p-value <.0001). Different models, with inclusion and exclusion of the interaction terms of age and reason with various predictors, were then compared based on the log-likelihood (-2 Log L) and Akaike Information Criterion (AIC) model fit statistics. The model with the best fit was selected for the final results. The final model included all the covariates listed above and the interaction terms of age x type of opioid, age x buprenorphine, age x methadone, age x reason and age x chronicity.

Holding other variables constant, older age, non-accidental intent (i.e., intentional exposure or exposure resulting from an adverse reaction), involvement of a single-substance opioid and presence of buprenorphine or methadone were significantly associated with severity following pediatric opioid exposures. Among unintentional and non-acute exposures involving combination opioids, non-buprenorphine or non-methadone opioids, exposures involving children aged 6 to 12 years and 13 to 17 years were 1.72 (95% CI = 1.02 - 2.91) times and 2.34 (95% CI = 1.57 - 3.48) times more likely to be severe compared to those involving children under 6 years of age. Other things constant, males had 15% (95% CI = 8% - 23%) higher odds of a severe opioid exposure

compared to females. Among exposures involving children under 6 years of age, intentional exposures or adverse reactions were 2.66 (95% CI = 1.29 - 5.47) to 4.25 (95% CI = 2.63 - 6.86) times more likely to be severe than unintentional exposures. Exposures to single-opioids were 4.34 (95% CI = 3.79 - 4.96) times more likely to be severe than exposures to combination opioids among children under 6 years of age. Similarly, exposures to buprenorphine or methadone involving young children were 5.15 (95% CI = 4.66 - 5.69) to 6.44 (95% CI = 5.54 -7.48) times more likely to be severe.

Association of these factors with severity varied by age. The odds of a severe outcome following single-opioid exposures were not significantly different in children 6 to 12 years of age compared to the young children. However, single-opioid exposures among teenagers had 1.5 (95% CI = 1.02 - 2.21) times higher odds of severity compared to exposures among children less than 6 years of age. Buprenorphine exposures were 62% (95% CI = 33% - 78%) less likely to be severe in teenagers compared to children under 6 years. Severity for methadone exposures was not significantly different among teenagers compared to the young children. However, exposures involving methadone were 2.51 (95% CI = 1.18 - 5.34) times more likely to be severe in children 6 to 12 years of age compared to their younger counterparts. Exposures involving teenagers had 4.02 (95% CI = 1.81 - 8.93) times higher odds of a severe outcome following an intentional exposure while exposures among children 6 to 12 years of age had 4.48 (95% CI = 2.17 - 9.27) times higher odds of severity following an adverse reaction, compared to exposures in children under 6 years. The odds of a severe outcome following an adverse reaction exposure were not significantly different among teenagers compared to the young children. Lastly, exposures among teenagers had 2.24 (95% CI = 1.78 - 2.83) times higher odds of a severe outcome after an acute

opioid exposure than exposures in children under 6 years. These odds were not significantly different for exposures involving 6 to 12 year olds compared those in young children (Table 13).

Goodness-of-fit test, model fit statistics and residual analysis showed that the model fits the data well. Three observations were found to be highly influential. The logistic regression model was rerun after removing these influential points and the results did not change much. These observations were included in the final analyses. As part of the sensitivity analysis, adjusted analyses were performed after imputing the response variable (severity) as described in methods. In this logistic regression model, older age was no longer associated with severity however, acute exposures were found to be associated with higher odds of severity.

Table 13: Characteristics associated with severe pediatric opioid exposures (multivariable analyses)

Characteristic (N = 64, 045)[a]	**Estimate (β)**	**SE**	**AOR (95% CI)**	**Chi-square**	**p-value**
Intercept*	-4.207	0.159	--	703.02	<.0001
Age group (years)*					
≤ 5	--	--	--	--	--
6-12	0.544	0.267	1.72 (1.02 - 2.91)	4.16	0.0413
13-17	0.849	0.204	2.34 (1.57 - 3.48)	17.41	<.0001
Gender*					
Female	--	--	--	--	--
Male	0.140	0.034	1.15 (1.08 - 1.23)	16.54	<.0001
Chronicity					
Non-acute	--	--	--	--	--
Acute	-0.083	0.150	0.92 (0.69 - 1.24)	0.30	0.5833
Reason*					
Unintentional	--	--	--	--	--
Intentional	0.976	0.369	2.66 (1.29 - 5.47)	7.00	0.0081
ADR	1.446	0.245	4.25 (2.63 - 6.86)	34.83	<.0001
Other	1.348	0.280	3.85 (2.23 - 6.66)	23.27	<.0001

Type of opioid*					
Combination opioid	--	--	--	--	--
Single	1.467	0.068	4.34 (3.79 - 4.96)	459.92	<.0001
Buprenorphine*					
No	--	--	--	--	--
Yes	1.639	0.051	5.15 (4.66 - 5.69)	1032.37	<.0001
Methadone*					
No	--	--	--	--	--
Yes	1.862	0.077	6.44 (5.54 -7.48)	586.18	<.0001
Interaction terms[b]					
Age group (years) x single opioid*					
6-12 x single opioid	-0.588	0.178	--	10.95	0.0009
13-17 x single opioid	-0.444	0.091	--	23.75	<.0001
Age group (years) x buprenorphine*					
6-12 x buprenorphine	0.041	0.287	--	0.02	0.8863
13-17 x buprenorphine	-1.807	0.191	--	89.51	<.0001
Age group (years) x methadone*					
6-12 x methadone	0.374	0.273	--	1.87	0.1712
13-17 x methadone	-0.814	0.160	--	25.98	<.0001
Age group (years) x reason*					
6-12 x Intentional	0.317	0.416	--	0.58	0.4468
6-12 x ADR	0.956	0.344	--	7.74	0.0054
6-12 x Other	-0.474	1.183	--	0.16	0.6888
13-17 x Intentional	0.542	0.382	--	2.01	0.1558
13-17 x ADR	-0.787	0.333	--	5.58	0.0182
13-17 x Other	0.121	0.459	--	0.07	0.7923
Age group x chronicity*					
6-12 x acute	-0.808	0.259	--	9.74	0.0018
13-17 x acute	-0.042	0.178	--	0.05	0.8153

*p<.05. ADR = Adverse drug reaction; AOR = Adjusted odds ratio. Goodness-of-fit tests showed that the model fits the data well (p=0.8248). AIC = 24965.93 and -2 Log L = 24915.93. Buprenorphine and methadone add up to ≤10% of all opioid exposures so there were included as covariates.

[a]8382 observations were deleted due to missing values for the response or explanatory variables.

[b]AOR for each interaction term in comparison to those under 6 years of age were calculated by using a combination of parameter estimates from the table. For example, AOR of severity

associated with buprenorphine exposures among teenagers compared to the young children was calculated as follows,

$AOR = Exp (\beta_{1\ (13\text{-}17)} + \beta_{9\ (13\text{-}17\ x\ buprenorphine)}) = Exp (0.849 + (-1.807)) = 0.384$

where, β_1 is the parameter estimate of age group (13-17 years group) and β_9 is the parameter estimate of age group (13-17 years group) x buprenorphine.

Aim 1D: To examine opioid exposures in children at 5-digit ZIP Code level and study its association with area-level socioeconomic status (SES)

Table 14 summarizes bivariate analyses of the proportion of pediatric opioid exposures in a 5-digit ZIP Code area and the corresponding area-level characteristics. ZIP Code areas with pediatric opioid exposures were descriptively compared to all the ZIP Code areas in the Census data. This was done to explore how areas in our study sample compared to all the ZIP Codes areas. A total of 12,809 5-digit ZIP Code areas were identified that had one or more pediatric opioid exposure (mean number of exposures at area-level = 3.1). The mean proportion of adults in these areas was 76.2%, which was similar to the average proportion of adults across all United States ZIP Codes. The mean proportion of minorities was 28.1%, which was higher compared to the mean proportion of minorities across all ZIP Codes. There was a higher proportion of Non-Hispanic Whites in areas with one or more pediatric opioid exposures. However, compared to the average racial composition across all ZIP Code areas, areas with one or more pediatric opioid exposure had a lower proportion of Non-Hispanic Whites (71.9%), and a slightly higher proportion of Hispanic Whites (6.2%), Blacks (10.4%), and other races (8.9%). The median household income in these areas was $50,330, which was higher compared to the average across all ZIP Codes. The average household size of 2.6 did not differ much from the average household size across all ZIP Codes. However, ZIP Code

areas with one or more pediatric opioid exposure had a lower proportion of older adults in households compared to the average across all ZIP Codes (13.8%).

Bivariate analyses of pediatric opioid exposures at 5-digit ZIP Code level showed statistically significant associations between SES characteristics and the area-level proportion of pediatric opioid exposures among 5-digit ZIP Code areas with one or more pediatric opioid exposure. Positive correlations were observed for proportion of adults, males, Non-Hispanic Whites and older adults in households and family households (Table 14).

Table 14: Pediatric opioid exposure and SES characteristics (bivariate analyses)

Characteristic	**Total ZIP Code areas, mean (SD) (N = 32,086)[a]**	**Sample ZIP Code areas, mean (SD) (N = 12,809)[b, c]**	**Spearman correlation (r)[c]**
Pediatric opioid exposures			
Number	--	3.07 (3.46)	--
%	--	0.29 (2.47)	--
% Adults	76.97 (5.04)	76.24 (4.85)	0.217*
% Minority	21.28 (23.87)	28.06 (24.92)	-0.392*
Gender			
% Males	50.18 (3.50)	49.48 (2.72)	0.270*
% Females	49.84 (3.51)	50.52 (2.72)	-0.270*
Race and Ethnicity			
% Non-Hispanic Whites	78.77 (23.90)	71.95 (24.93)	0.393*
% Hispanic Whites	4.56 (9.11)	6.25 (10.32)	-0.367*
% Blacks	7.62 (15.39)	10.41 (16.78)	-0.323*
% Other races	6.91 (11.73)	8.85 (11.33)	-0.380*
Median HH income (in $000s)[d]	46.65 (19.75)	50.33 (20.60)	-0.267*
Average HH size	2.56 (3.14)	2.58 (0.98)	-0.273*
Average FHH size	3.04 (4.46)	3.08 (0.56)	-0.381*
% Population >65 in HHs	15.30 (5.47)	13.79 (5.03)	0.312*
% Population >65 in FHHs	12.68 (4.89)	11.32 (4.34)	0.315*

[a]Represents all 5-digit ZIP code areas from the U.S. Census 2010 file (Total).
[b]Represents all 5-digit ZIP Code areas with ≥1 pediatric opioid exposure (Sample).
[c]Spearman correlations computed for 5-digit ZIP Code areas with ≥1 pediatric opioid exposures.
[d]Median household income was imputed using the corresponding per capita income to the extent possible.
[*]p<.0001. HH = Household. FHH = Family household.
Other races = American Indians, Pacific Islanders, Asians and others.

Adjusted analyses of pediatric opioid exposures and SES characteristics included proportion of adults, males, Non-Hispanic Whites, Hispanic Whites and Blacks, median household income, average household size and proportion of older adults in households. Moran's I test on the residuals obtained from the adjusted Poisson model was found to be significant (Moran's I value = 0.175, Z-statistic = 28.83, p <.0001) (Semivariogram is shown in Appendix B). This indicated presence of positive spatial autocorrelation in the data. Hence, GLMM was used for the final analyses, adjusting for spatial autocorrelation.

Table 15 summarizes the results of adjusted analyses performed at 5-digit ZIP Code level. All covariates, except proportion of Blacks, were found to be significantly associated with the rate of pediatric opioid exposures in a 5-digit ZIP Code area. Higher rates of pediatric opioid exposures in an area were associated with the area-level proportion of males, Non-Hispanic Whites and older adults in a household. Holding other variables constant, the rate of pediatric opioid exposures was found to increase by 10% for every 1% increase in the proportion of males in an area, by 1% for every 1% increase in the proportion of Non-Hispanic Whites, and by 1% for every 1% increase in the proportion of older adults in households. Interestingly, an increase in the proportion of adults and Hispanic Whites, median household income and average household size was found to be associated with a decline in the rate of pediatric opioid exposures in an area. Test for covariance parameters in the model was significant, indicating that random effects of 5-digit ZIP Code cannot

be eliminated from the model (Chi-square = 6120.46, p<.0001). Also, Moran's I test on the residuals obtained from the adjusted GLMM model was no longer significant (Moran's I value = 9.49E-06, Z-statistic = 0.0214, p = 0.9829), indicating that the spatial autocorrelation in the data has been addressed (Table 15).

Table 15: Pediatric opioid exposure and SES characteristics (multivariable analyses)

Characteristic	Estimate (β)	SE	Exp (β) (95% CI)	t-value	p-value
Covariance Parameter Estimates					
Intercept (Subject = ZC)[a]	0.299	0.008	--	--	--
Solution for fixed effects					
Intercept	-8.719	0.320	--	-27.22	<.0001
% Adults[*]	-0.020	0.003	0.98 (0.97 - 0.99)	-6.33	<.0001
Gender					
% Males[*]	0.092	0.003	1.10 (1.09 - 1.10)	26.63	<.0001
Race and ethnicity					
% Non-Hispanic Whites[*]	0.007	0.001	1.01 (1.01 - 1.01)	8.62	<.0001
% Hispanic Whites[*]	-0.008	0.001	0.99 (0.99 - 0.99)	-6.0	<.0001
% Blacks	-0.001	0.001	1.00 (1.00 - 1.00)	-1.4	0.1628
Median HH income (in $000s)[*]	-0.011	0.001	0.99 (0.99 - 0.99)	-24.49	<.0001
Average HH size[*]	-0.616	0.043	0.54 (0.50 - 0.59)	-14.48	<.0001
% Population >65 in HHs[*]	0.011	0.002	1.01 (1.01 - 1.02)	5.12	<.0001

[*]Type III analysis, F-test p<.05. HH = Household. ZC = ZIP Code.
[a]Z-vlaue = 38.83, p<.0001

3.3: Discussion

Annually there were about 16,684 opioid exposures in children and roughly half of these resulted in poisonings. Nearly 10,214 of these opioid exposures occurred in children under 6 years of age. These constituted exposures to any opioid containing drugs including prescription or OTC, single-substance or combination, and oral or non-oral formulations. No study provides direct comparison for these results mainly due to methodological differences. One previous investigation by Burghardt et al. reported 6,213 yearly prescription opioid exposures among children less than 20 years, majority of which occurred in young children.[31] Two other studies examined opioid exposures in children under the age of 6 years, and reported 2,640 to 3,823 opioid exposures per year. However, these analyses were either limited to a few single-substance opioids or to one drug involvement exposures that were presented to the ED.[38,48]

There was an overall decline in the prevalence of opioid exposures over the 5-year period, even after adjusting for the number of calls received by PCs annually. This contrasts with previous studies that have found an increasing trend in drug, specifically opioid, exposures in children.[31,48] Past studies were based on data prior to 2010, while the current analyses used data from recent years thus providing an update to research conducted in the last decade. The decline in prevalence of opioid exposures and poisonings was largely in the 1 to 2 years age group. This decrease may be attributed to various interventions such as CDC's Preventing Overdoses and Treatment Errors in Children Taskforce (PROTECT) collaborative initiative in 2008,[82,83] advances in the use of child-resistant packaging such as unit packaging of opioids like buprenorphine,[35,39] or the release of abuse-deterrent opioid formulations that resist crushing or chewing of pills. One study found a 51% decrease in unintentional exposures of extended-release oxycodone among children 1 to 2.5 years of age, after the release of the abuse-deterrent formulation.[84] It can be postulated that because

these formulations deter adults from crushing pills, it prevents accidents in children that would otherwise result from licking the remnants of crushed pills found at home.

Comparatively, the decline in opioid poisonings was smaller than the drop in opioid exposures in children from 2010 to 2014. This indicates that more opioid exposures among children are resulting in poisonings. This may be attributed to the corresponding rise in the use of stronger opioids among adults. A CDC survey found that the percentage of adults using weaker than morphine opioids had decreased from 26.5% to 20%, while the percentage of stronger opioids use had grown from 22.4% to 37% from 2007-2010 to 2011-2012.[13] To our knowledge, none of the previous studies has examined such a parallel trend in pediatric opioid exposures and poisonings.

State-level variations were observed in the rate of pediatric opioid exposures and poisonings. No previous studies have examined state-level differences. States vary in adoption of laws for prescription drug misuse and abuse such as controlling opioid prescribing practices, prescription drug monitoring or regulation of pain clinics.[85] These laws may impact adults' opioid availability at state-level, indirectly influencing the number of opioid exposures in children. States also differ with regards to the number of opioid prescriptions per 100 people and the nonmedical use rate, especially in the western region of the country. Most of the states that had a high prevalence of pediatric opioid exposures also had a corresponding high number of opioid prescriptions per 100 persons in 2012. In fact, states such as Oklahoma and Oregon also had a higher percentage of prescription opioid nonmedical use.[86,87]

The prevalence rate of opioid exposures was high among children under the age of 6 years, the rate then declined with age and then increased among adolescents. The total prevalence of opioid exposures and poisonings was particularly high among children 1 to 2 years of age. Past studies

have unanimously found a similar pattern for drug exposures and poisonings.[31,35,38,48,49] This has been attributed to a combination of childhood factors such as increased mobility and dexterity since an average child starts to walk around the age of 12 months, observing and imitating adult drug-taking behavior, or attraction to "candy-like" appearance of the pills or eye-catching containers.[35,88,89] Younger children are constantly exploring their environment and tend to put things in their mouth. These children are also cognitively less developed to realize the danger of their actions compared to their older counterparts.[89]

Roughly half of total opioid exposures in children were from single-substance opioids and about one-fourth involved more than one product. No study has compared single-substance and combination opioid exposures in children. One prior study reported that 21.9% of young children with emergency hospitalization for prescription drug exposures had two or more products implicated.[49] The morbidity in regards to poisoning, occurrence of clinical effects particularly moderate-to-severe effects, presentation to HCF or death were much higher among single-substance opioid and multiple product exposures. This can be attributed to high potency of single-substance opioid agents and increased medical complications following multi-product exposures.

Buprenorphine and methadone were the two single-substance opioids that were significantly associated with negative medical outcomes in children following an exposure. Numerous prior studies including multiple case studies have reported similar results.[38–40,42,43,52,53,62,90] A focused expert review of adverse events in young children with moderate-to-major clinical effects following buprenorphine exposures reported that 43.2% had a medically significant (defined as disabling or limiting) or life-threatening effect such as respiratory or CNS depression.[39] Compared to other opioids, Bailey et al. found that buprenorphine and methadone exposures in young children resulted in a higher percentage of moderate-to-major effects.[38] Among teenagers,

methadone exposures have been associated with high medical complication rates.[42] In fact, methadone was associated with the most deaths among teenagers due to intentional exposures.[43] Buprenorphine and methadone are used for the treatment of opioid dependence and addiction and are prescribed heavily in the United States. There is also increasing evidence of misuse and abuse of these agents.[16,39,91] It is possible that adults undergoing treatment with these agents for their opioid dependence or addiction may not be able to ensure proper storage of these drugs at home. Thus, it is imperative to increase awareness among adults of the dangers of unintentional exposures in young children and intentional exposures among teens at home.[92]

The epidemiology of opioid exposures varied by age. Exposures in children under the age of 6 years were mainly unintentional and had a higher involvement of single-substance opioids. Young children are generally not the intended recipients of single-substance opioids hence, exposure to these drugs may indicate that these children accidentally expose themselves to adults' opioids. More young boys had opioid exposures compared to girls, which is analogous to previous studies that have examined drug or opioid exposures among young children.[38,39] One possible explanation for this could be gender dissimilarities in risk-taking behavior.[93]

On the contrary, exposures in teenagers were largely intentional. This is similar to past studies that have examined the intent of drug exposures among children.[32,35] Multiple product involvement was more common among teenagers which conforms to previous findings that have reported frequent use of multiple substances such as alcohol or other drugs by teens.[94] We also found that a higher proportion of exposures among teenagers involved combination opioids. This may suggest a high availability or easy accessibility of these drugs for recreational purposes or self-harm. Based on a national survey of adolescent drug use in 2011, one out of every 12 high schoolers reported nonmedical use of acetaminophen/hydrocodone combination (Vicodin®) in the past year, making

it one of the top abused drugs among adolescents.[95,96] Opioid exposures among teenagers, specifically intentional opioid exposures, were more common in girls. Similar results were reported by a previous study that examined prescription opioid exposures among adolescents.[43] High prescription drug use among teenage girls has been attributed to numerous factors such as depression, peer pressure or suicidal ideation.[42,43,97] In fact, 59.6% of the total opioid intentional exposures in the current study were recorded as suspected suicide and nearly three-fourth of these exposures were in girls. Although opioid exposures in children were predominantly acute and through oral routes, teenagers also had involvement of non-oral routes and non-acute exposures. This could indicate that teenagers are frequently involved in risky drug-taking behavior and may be using opioids for longer periods. A survey study that explored oxycodone abuse patterns among adolescents reported that intranasal administration (for example, snorting) was one of the preferred routes in addition to ingestion among these children.[98]

Similar to findings from other studies, the current research indicated that the majority of pediatric opioid exposures occurred at home irrespective of the child's age.[38,39] This implies that children get into other's opioids at home. A recent survey showed that over 60% of adults store leftover opioid medications at home for future use. Many of these adults reported that they did not receive information on safe storage or proper disposal practices for these drugs and only a few adults stored these medications in locked cabinets.[99] Young children may gain access to opioids that are not securely stored such as medication left out on a nightstand or countertop thus, resulting in exposures and poisonings. Although the scenarios for opioid exposures were incompletely recorded in the current data, a previous study by Lavonas et al. identified improper storage as the root cause of buprenorphine exposures among young children.[39] Exposure at home was also

common among children 13 to 17 years of age. This may suggest that teenagers may be misusing opioids or recreationally using opioids at home that belong to a family member.

Pediatric opioid exposures in general were associated with considerable morbidity in regards to occurrence of negative medical outcomes, presentation to ED and hospital admissions. Among exposures that had information on clinical effects recorded, neurological effects such as dizziness or drowsiness were documented for 77.4% of exposures, followed by gastrointestinal effects and cardiovascular effects recorded for 27.8% and 18.4% of exposures, respectively. Previous studies have observed similar clinical effects following opioid exposures in children.[39,44,46,53,100] Clinical effects were frequently recorded for teenagers which may be related to multiple product involvement or intentional exposures in this age group. Additionally, about 20,414 (40%) opioid exposures in children under the age of 6 years had negative medical outcomes, 15.8% of these were moderate-to-major medical outcomes. Nearly 15,942 (68.6%) exposures in teenagers had a negative medical outcome documented and 33.9% of these were moderate-to-major medical outcomes. These findings are comparable to those from previous investigations. Bailey et al. reported that 25% of exposures in children under 6 years of age had negative medical outcomes. However these analyses were limited to specific opioid agents.[38] Another study found that about 62.9% of opioid exposures among teenagers had moderate-to-major effects.[43]

Nearly 1 in every 2 opioid exposures in children was presented to a HCF. On average, approximately 3,578 (35%) opioid exposures in children under the age of 6 years were admitted to the ED and another 1,334 (13.1%) were admitted to the hospital annually. While among opioid exposures involving adolescents, yearly 1,308 (28.1%) were admitted to the ED and about 1,899 (40.8%) were admitted for medical or psychiatric care. These results are congruent with past research but with some discrepancies owing to different study periods, data sources and sampling

criteria. One study that examined HCF use following oral prescription opioid exposures reported approximately 4,565 ED visits and 1,666 admissions annually among young children.[49] Another study reported yearly 3,823 ED visits and 447 admissions among young children with one opioid product ingestions.[48] Burghardt et al. found nearly 48.4% ED visits and 20.1% admissions among children under the age of 20 years that were exposed to an oral, single-substance opioid. They found ED visit and admission rates of 46.4% and 12.9% among children less than 6 years, and 58.2% and 33.4% among teenagers, respectively.[31] Zosel et al. reported that 29.8% teenagers with intentional drug exposures, including opioids and stimulants, were treated in a HCF, and roughly half of them were admitted for care.[43]

Naloxone was commonly used for the treatment of opioid exposures with severe outcomes. Prior research has also reported naloxone to be successfully used for the management of severe pediatric opioid exposures, even in young children.[32,38] It is a recommended antidote for respiratory depression following opioid, particularly buprenorphine and methadone, exposures in children.[45]

In addition to patient-level characteristics, area-level socioeconomic status factors were examined at 5-digit ZIP Code level for areas with one or more pediatric opioid exposures during the study period. It should be noted that there is no previous study that has examined such area-level factors associated with pediatric opioid exposures. These analyses were exploratory and certain unexpected findings, such as the inverse association of proportion of adults and the direct association of proportion of males with the rate of pediatric opioid exposures at area-level, merit further investigation. We found that a higher proportion of Non-Hispanic Whites in an area was significantly associated with a higher rate of pediatric exposures. Although not a direct comparison for these results, Schillie et al. found a higher rate of ED visits for medication overdoses compared to nondrug exposures among White children under the age of 19 years. [35] In fact, prescription

opioid use from 2007 to 2012 was reported to be highest among Non-Hispanic White adults compared to other racial groups.[13] Area-level median household income was inversely associated with the rate of pediatric opioid exposures. Household income is reported to be an important indicator of socioeconomic status,[101] and lower socioeconomic status has been linked to higher unintentional drug poisonings among young children.[64,65] It can be postulated that areas with higher median household income may have access to better child care facilities thus resulting in lower rates of pediatric opioid exposures. Furthermore, higher average household size was associated with a lower rate of pediatric opioid exposures. Such an association is hard to explain since it was expected that over-crowding in households may lead to less parental supervision, thereby higher chances of opioid exposures among children. However, similar results have been found by some prior studies that have examined SES characteristics associated with unintentional pediatric drug exposures.[54,65] Lastly, higher proportions of older adults in households was associated a higher rate of opioid exposures in children at area-level. This may be related to the substantial growth in opioid prescriptions among older adults,[85] since grandparents are a common source of drugs among young children with unintentional drug exposures.[88]

These analyses are limited by the biases inherent to a retrospective study design and the database used. First, NPDS data is collected passively and is based on voluntary reporting by a child's family or healthcare professional. Hence these data may be under-reported or subjected to self-reporting bias or coding errors. NPDS does not capture every occurrence of exposure and poisoning, it is limited to those occurrences that are reported to PCs. It is possible that parents may rush the child to the ED and neither the parents nor the treating provider may have reported the case to a PC thus underestimating the true frequency of exposures and poisonings. Also, these data are based on self-reported calls subjecting it to reporting bias. For example, intentional exposures

among teenagers may be under-reported by self or the family member. Previous researchers have also suggested variations in cases reported to the PCs due to lack of awareness, or cultural, language or literacy barriers among the general public.[102,103] At least one prior study has found that fatal cases are underreported to the PCs.[104] Hence these data may not accurately represent mortality associated with opioid exposures in children. To account for this limitation, we used the NVSS mortality data to examine deaths related to pediatric opioid poisonings (described in Specific Aim 2). Additionally, PC specialists are trained to collect data over the phone but the amount of data that can be collected may be limited or variable from case to case and may be subjected to data coding errors or misjudgment of the specialist. However, the use of standard coding fields and additional review processes used by the AAPCC may reduce such data coding and human errors.

Second, prevalence of opioid exposures and poisonings was calculated assuming that each exposure case was unique. It is possible that a child may have been exposed to opioids more than once during the study period which may lead to double-counting in our analyses. The NPDS captures relevant information related to a single opioid exposure event, which can involve more than one product. However, it does not have a mechanism to link multiple (repeated) exposure events of the same patient. To identify the extent of repeated cases of pediatric opioid exposures, Virginia PC data for children under the age of 18 years with opioid exposures, from 2010 to 2014, were manually inspected under the supervision of a PC employee. This search showed about 6% of potentially repeated opioid exposure cases. Such estimates cannot be derived for the national data. However, if this state-level estimate is similar to national-level data then existence of such repeated cases is expected to have a small impact on the prevalence estimates.

Third, the data on exposures obtained from the NPDS are limited to those that are reported to PCs. Annual calls to the PCs have been declining in recent years due to various factors such as increased

use of text communications and internet resources.[32] To account for this limitation, the prevalence of pediatric opioid exposures was examined after accounting for the total number of calls received by PCs each year during the study period.

Fourth, the study sample included suspected opioid exposures since the lack of clinical lab data in the NPDS does not allow for confirmation of exposures. Yet, the NPDS has been validated as an effective pharmaceutical poisoning surveillance system and the data have been shown to correlate well with poisoning hospital data.[71,105]

Next, Census data from 2011 to 2014 were estimates based on the base year (2010) and are likely to be reported with margins of errors (MOEs). However, it is a standard practice to use these data since these MOEs are expected to be small. Although some previous studies have established an association between opioid availability in an area and the corresponding pediatric opioid exposures, the current state-level analyses could not control for factors such as number of opioid prescribers or opioid availability in the state. However, these results still provide value for future state-level research.

Additionally, area-level analyses were limited to 5-digit ZIP Codes. Census block groups or tracts are considered to be better area-level socioeconomic measures than ZIP Codes.[106] The NPDS does not provide geographic data beyond patient's 5-digit ZIP Code to identify Census block group or tract. Also, area based analyses did not control for area-level employment and education due to unavailability of such data. Further, ZIP Code area-level analyses were limited to cases whereby exposure and caller site were one's own residence. But we found that cases reported by HCFs tend to be more severe, involving teenagers and those with intentional exposures. It is possible that our area-level analyses missed many such severe or intentional exposure cases, particularly among

teenagers. Despite these limitations, the current area based analyses at 5-digit ZIP Code level provide a starting point for future investigations.

Chapter 4: Specific Aim 2

Aim 2: To estimate the economic costs associated with opioid poisonings in children

4.1: Methods

Conceptual framework

After quantifying the prevalence of an illness, the subsequent step was to examine the economic burden of the illness to the society. In a typical opioid poisoning event, the child would be transported to the ED where he/she would be evaluated and treated using various diagnostic and therapeutic procedures and professional care. Depending on prognosis, the child would be released from the ED or admitted to the hospital. During the inpatient stay, there may be a multitude of other therapeutic, diagnostic and professional care resources used. Since opioid poisoning is an acute, reversible condition, we expected most of the children to be treated and released from the hospital. However, some children would be transferred to other short-term care facilities, or have a premature death, following a severe opioid poisoning. In addition, parents or caregivers would spend time taking care of the child in the hospital or during recovery. These various components following an opioid poisoning in children can add significantly to the economic burden. The economic burden of pediatric opioid poisonings was calculated using the cost-of-illness framework. Cost-of-illness has been widely used for decades to quantify the economic burden

related to an illness. It includes measurement of direct, indirect and intangible costs related to an illness.

Direct medical costs constitute costs that are incurred from providing medical care for prevention and treatment such as hospitalization cost. Direct nonmedical costs are costs which are not directly related to prevention and treatment but aid in provision of care such as transportation cost. Indirect costs provide a measure of the value of resources lost due to productivity losses because of an illness or injury. It includes short-term productivity losses due to morbidity and lifetime productivity losses due to premature mortality. Intangible costs are costs such as pain and suffering inflicted by the health condition and are hard to quantify in monetary value.[107,108] The current analyses did not consider intangible costs because first, these analyses aim to examine the economic burden associated with an acute event of opioid poisoning in children and intangible costs are an important part of economic analyses for more chronic conditions. Second, there is lack of data on long-term effects of pediatric opioid poisonings on quality of life of these children.

The three-step health care costing approach was used for this Specific Aim as follows: [109]

- Step 1: Identification of relevant HCRU (cost-items)
- Step 2: Measurement of identified HCRU (cost-items)
- Step 3: Valuing these HCRU (cost-items)

The HCRU to be incorporated in these analyses was based on existing literature on pediatric opioid poisonings and the "Poisoning Pyramid" (refer to the Literature Review chapter). ED visits and hospital stays are major resources used following opioid poisonings in children. The ambulatory/outpatient department or office visits related to pediatric opioid poisonings were not examined because a majority of costs were expected to be incurred from ED and inpatient visits.

ED visits, inpatient stays, physician-related hospital services, transportation to health care facility, and mortality associated with pediatric opioid poisonings were identified and quantified. For valuing or assigning costs to the identified HCRU items, the bottom-up approach was used for estimating direct costs and the human capital method was used for estimating indirect costs.

Methods for estimating direct costs

The bottom-up costing approach allows for identification of costs at granular level. This method involves calculation of costs by multiplying the average cost of treatment of an illness with its prevalence. The average cost of a resource item is calculated by multiplying the average quantity used with the unit cost of that particular resource. This is repeated for every resource input, and summed to obtain average total cost per patient, which is then combined with illness prevalence to estimate the total costs. The total costs (TC) are expressed as (adapted from Haddix et al. (2003))[107,108]

$$(TC)_i = (Q1 * P1)_i + (Q2 * P2)_i + \ldots.. + (Qn * Pn)_i$$

$$(TC) = (TC)_i + (TC)_j + \ldots. + (TC)_n$$

Where: (TC) = TC for i^{th} patient,

Q1 = quantity of resource 1 and so on, and

P1 = value of resource 1 and so on.

Methods for estimating indirect costs

Indirect productivity costs are the value of lost or reduced production of an individual due to morbidity and mortality. Productivity losses from morbidity result from absenteeism or presentism. Absenteeism refers to a patient or caregiver being unable to attend work or perform normal housekeeping services due to one's illness, while presentism refers to reduced production

output of a patient or caregiver while at work. Lost productivity due to premature mortality is based on the premise that an individual would have contributed to the societal production if he/she had not died prematurely due to an illness. The human capital method and the friction cost method are the two commonly used methods for estimating lost productivity. The two methods produce very different estimates especially for productivity costs calculated over lifetime and have been heavily debated in the literature with no real consensus.[107,108,110]

The human capital method measures lost productivity as the sum of lost earnings and household production from a societal or patients' perspective. For example, if an individual dies prematurely at the age of 15 then the expected earnings and household production of that individual over the lost lifetime are calculated and discounted to the present value. The human capital method measures the potential or expected loss in future productivity. It has been criticized for overestimating the productivity losses thereby exaggerating the economic impact of an illness.[111]

The friction cost method was developed in an attempt to measure the actual rather than the expected production loss. This method measures lost productivity only for the period required to replace the sick worker. This period needed for replacement is called the friction period. An average friction period of 6 months has been suggested by some researchers, but it can vary based on various factors such as the employment rate or industry. This method has been criticized for vastly underestimating productivity losses, and it is suggested to be more relevant for studies conducted from employers' perspective or in a society with surplus of skilled labor.[112,113]

The use of friction cost method may be complicated for analyses based on the pediatric population that is not currently in the work force. Despite the recognized limitations of the human capital method, it is still the dominant method used for cost-of-illness research. Thus, the human capital method was used for calculating productivity losses due to morbidity and mortality related to

pediatric opioid poisonings. The total costs of productivity loss due to morbidity were calculated as follows:

(Number of ED or inpatient days + Number of recovery days) * Daily production value (DPV)

- DPV = Daily market production + Daily household production
- Daily market production = Average daily hours working at a job * usual hourly market compensation
- Daily household production = Average daily hours of household service * usual hourly household compensation

The sum of hospital days and recovery time provides a proxy for time off work. The DPV data was obtained from an analysis conducted by Grosse et al.[110] In this analysis, DPV was calculated for the United States noninstitutionalized population over 15 years of age, weighted by age and gender.

The value of productivity loss due to mortality was obtained by estimating the present value of expected future productivity (PVFP) which included earnings and household services. Grosse et al. calculated the average PVFP for the noninstitutionalized population in the United States by single-year of age and gender, after adjusting for 1% increase in annual labor productivity and survival probabilities obtained from the 2004 United States Life Tables. These total production estimates for 0 to 17 years of age and gender were used for calculating the lost future productivity costs due to premature deaths following opioid poisoning.

Empirical Framework

A comprehensive societal perspective was employed for these analyses. All cost calculations were made for the 2012 base-year since that was the most recent data available at the time of data

acquisition. An annual time horizon was used for calculating direct costs and indirect costs were calculated for lifetime. A prevalence-based approach was used for estimating the economic costs of pediatric opioid poisonings. Using this approach, all relevant annual direct costs and indirect costs due to morbidity were calculated for the base year and lifetime indirect costs due to mortality were calculated using present discounted value of future productivity losses. This approach is employed for illnesses that commonly do not extend beyond one year.[108,114]

As for the costing method(s), Sum_All Medical method was used for estimating the total cost of pediatric opioid poisonings in the base-case. Total costs were calculated for all pediatric patients with any-listed diagnosis of opioid poisoning on their discharge record. This method assumes that all hospital costs incurred following an acute injury such as opioid poisoning were related to the poisoning.[115]

As discussed above, the human capital method was employed for estimating indirect costs related to opioid poisonings in children. Since the target study population was less than 18 years of age, we considered indirect costs of short-term productivity loss due to morbidity for parents' or caregivers' alone, whereas future productivity losses due to premature mortality were considered for children with opioid poisoning. We assumed one caregiver per child. Discounting is used in economic evaluations to calculate the present value of future costs. A discount rate of 3% was used for these analyses as recommended by the Panel on Cost-Effectiveness in Health and Medicine.[107]

Direct medical costs

Data

The Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP) 2012 Nationwide Emergency Department Sample (NEDS) and 2012 Kids'

Inpatient Database (KID) were used. HCUP databases contain the largest publicly-available, multistate, all-payer, encounter-level information for community hospitals. The NEDS includes ED discharge data from over 950 hospitals located in 30 states which comprises data from approximately 130 million ED visits per year. It captures information on all ED visits that may or may not have resulted in hospital admissions. The KID yields national estimates of hospital inpatient stays for patients younger than 21 years. It is based on administrative hospital discharge data and contains roughly 7 million pediatric discharges each year from about 44 states. The most recently available data (at the time of data acquisition) were used for these analyses.

Sample

Discharge records from HCUP's NEDS and KID databases were extracted for children under 18 years of age with 1 or more opioid poisoning-related International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes in any-listed diagnosis. Opioid poisoning-related ICD-9-CM codes are listed in Table 16. The sample for ED visits was limited to discharges that did not result in hospital admission to avoid double counting. ED visits that resulted in hospitalization were captured in the inpatient data. Also, it was assumed that if opioid poisoning was recorded in the patient's discharge record then it was related to the reason for admission. This may be a reasonable assumption for a number of reasons. Firstly, opioid poisoning is an acute illness or injury and it is less likely to be a pre-existing condition. Secondly, the first-listed diagnosis is the principal diagnosis in the HCUP inpatient databases such as the KID. However, the first-listed diagnosis may not be the principal diagnosis in the HCUP outpatient databases such as the NEDS. Lastly, of the total opioid poisoning-related discharges, opioid poisoning was listed as the first or second-listed diagnosis in 91.6% of the ED data and 66.9% of the inpatient data. A

final total of 1,048 ED visits was identified from the NEDS and a total of 1,334 inpatient visits were identified from the KID.

Table 16: Opioid poisoning-related ICD-9-CM diagnosis and E-codes

ICD-9-CM Codes	**Description** (to identify diagnosis)
965.00 965.02 965.09	Poisoning by opium (alkaloids), unspecified Poisoning by methadone Poisoning by other opiates
E-codes	**Description** (to identify intent)
E850.1[a] E850.2[a]	Accidental poisoning by methadone Accidental poisoning by other opiates and related narcotics
E950.0[b]	Suicide and self-inflicted poisoning by analgesics, antipyretics, & antirheumatics
E980.0[c]	Poisoning by analgesics, antipyretics & antirheumatics, undetermined whether accidentally or purposely inflicted

[a]Unintentional; [b]Intentional; [c]Undetermined.
ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification,
E-codes = External Cause of Injury codes.

Converting charges to costs and calculation of SE

The HCUP databases provide total charges for ED visits and inpatient visits which include any facility charges or charges for any diagnostic labs or procedures. These charges represent the amount billed by the hospitals and not the payment amount reimbursed to hospitals or the actual cost of services. Charges are often higher than the underlying costs but actual costs are not obtainable.[107] HCUP provides hospital-specific cost-to-charge ratios (CCR) for inpatient stay charges based on all-payer inpatient costs. HCUP obtains this cost information from hospital accounting reports collected by the CMS. Identified records from KID were merged to the 2012 KID CCR linkable file using the 'HOSP_KID' (HCUP hospital identification number) variable.

Inpatient stay costs for every discharge record were obtained by multiplying inpatient charges with the appropriate CCR.

HCUP NEDS does not provide CCR for ED charges. Detailed ED charges and accounting data are required for calculating a hospital specific CCR since the ratios can vary by state and between cost centers within a hospital. HCUP conducted a preliminary analysis for estimating the cost of T/E & R ED visits by grouping hospitals based on characteristics such as hospital ownership and location. Although these ratios cannot be used for calculating an institution specific ED costs, they still provide an estimate of average ED CCR based on certain hospital characteristics. The group average ED CCR from the HCUP report were used to convert ED visit charges to costs in the current study.[116] The details of the HCUP report and the procedure used for estimating ED visit-related CCR is described in Appendix C.

Additionally, calculation of standard errors (SEs) of ED and inpatient costs accounted for the sampling design of NEDS and KID respectively, which is specified by HCUP**.**

Dealing with outlier charges

Outliers in the ED charge (or cost) data were examined (top/bottom 5%). Upon manual inspection, these charges looked reasonable and were included in further analyses. Suspiciously high charges in inpatient data were examined using the approach described by HCUP.[117] To identify suspiciously high inpatient charges, average charge per day was calculated for each stay. HCUP calculates length of stay (LOS) by subtracting the admission date from the discharge date therefore, same-day inpatient stays are coded as 0. For these calculations, LOS that was recorded as 0 in the data was set to 1 prior to calculating charge per day. The top 1% of charges per day were identified. The difference between the 75th percentile and median average charge per day was multiplied by

4, and added to the median. This value was used as the cutoff value for suspiciously high charges in the inpatient data ($45,600 per day). Two observations were above this cut-off value and were excluded from cost analyses.

Dealing with missing charges and CPT codes

ED charges were missing for 182 (17.4%) of the total ED visits for opioid poisonings in children. Using only non-missing charges could result in an underestimate of total ED-related costs. Also, all the visits with missing ED charges were examined and they had corresponding diagnosis and all observations, except one, had procedures recorded. This indicates that non-zero charges may have been incurred during the visit. Similarly, inpatient charges were missing for 20 (1.5%) of total inpatient stays. HCUP suggests that the missing data are likely missing at random (MAR) and not missing completely at random (MCAR), hence deleting the missing observations may not be justified.[118] Missing ED and inpatient charges were imputed. Several single and multiple imputations were undertaken as outlined below, in order to compare and contrast the results from these various methods.

- Imputation 1 set missing charges as zero: This approach was used for both ED and inpatient data. Although straightforward, this is a very conservative approach that assumes that the observations with missing charges truly had zero charges incurred during their ED visit or hospitalization.

- Imputation 2 used single imputation methods: Two single imputation techniques were used for the missing ED charges, overall mean imputation and subset mean imputation. First, the mean estimate of charges from the non-missing observations was used to impute the missing charges. Second, the mean estimates of charges from subgroups of the sample were used to impute the

missing charges. These subgroups were created based on age group and the intent of opioid poisoning. Medical outcomes following an opioid poisoning are shown to differ among children of different age groups and by intent (refer to Specific Aim 1). For instance, if the observation with missing charges was for a teenager with an intentional exposure then the mean estimate of non-missing ED charges of all teenagers with intentional exposure was used for imputation. Single imputation method using mean charges/day was used for the inpatient data. The mean charge per day was calculated for all observations with non-missing charges. This was then combined with the length of inpatient stay with missing charges to impute the missing charge for that stay. These single imputation methods have an advantage of computational ease, but are often criticized for deflating the sample variability.[119]

- Imputation 3: Multiple imputation using Markov chain Monte Carlo (MCMC) was used to impute the missing charges. Multiple imputation is the recommended method of choice by HCUP for dealing with missing data.[118] MCMC imputation is found to be a suitable technique for continuous data such as charges. This method involved three phases, imputation phase, analysis phase and pooling phase. In the imputation phase, the missing patterns of total charges were evaluated across all the variables of interest. The imputation model was then defined for ED charges and inpatient charges, respectively. The imputation models are recommended to be extensive rather than parsimonious. The imputation model for ED charges included child's age group; gender; median household income at ZIP Code level and residence location; type of opioid; intent; indicators for multi-drug poisonings, multi-injuries and chronic conditions; number of diagnosis and procedures on record; disposition status; payer; hospital characteristics including hospital region, location, ownership, teaching status and trauma status; and (non-missing) ED physician cost. The imputation model for inpatient charges

included child's age group; gender; race; median household income at ZIP Code level and residence location; type of opioid; intent; indicators for multi-drug poisonings and chronic condition; number of diagnosis and procedures on record; All Patients Refined Diagnosis Related Groups (APR-DRG) severity and mortality risk indices; Elixhauser comorbidities; disposition status; transfer-in and prior ED event indicators; LOS; payer; hospital characteristics including hospital region, ownership, bedsize, location and teaching status.

The number of imputations was chosen as 5 which is a reasonable number unless the rate of missing data is unusually high. The relative efficiency of using 5 imputations was calculated as follows:[120]

$$RE = (1 + \lambda / m)^{-1}$$

where, RE = relative efficiency

λ = rate of missing information

m = number of imputations

Using m = 5, the relative efficiency for the estimation of ED charges and inpatient charges was 96.6% and 99.7%, respectively. Subsequently in the analysis phase, the parameters of interest were estimated i.e., unweighted and weighted mean ED charges and inpatient charges were estimated for each imputation dataset. Finally, the respective mean estimates were combined from the 5 imputation datasets to produce a single estimate and its variance in the pooling phase. This variance incorporates within-imputation and between-imputation variances, resulting in more unbiased estimates. The results from imputation were examined by comparing the distribution of non-missing observed and imputed charges from 5 imputations as shown in Appendix D. The distribution of imputed ED charges (mean = $2,968) was similar

to the distribution of non-missing observed ED charges (mean = $3,290). Distribution of imputed inpatient charges (mean = $21,239) was different from the distribution of non-missing observed inpatient charges (mean = $45,756). This may partly be attributed to low sample size for missing inpatient charges. Model convergence was assessed by inspecting the trace plot and the autocorrelation plot. PROC MI and PROC MIANALYZE were used in SAS for the MCMC multiple imputation.[118,119]

Current Procedural Terminology (CPT) procedure codes were missing for 340 (32.44%) ED visits and could not be mapped to the CMS Medicare Physician Fee Schedule (explained below). Missing physician services-related costs were imputed using imputation techniques similar to those described above. Imputations were performed by: (i) Setting missing physician costs as zero, (ii) Overall mean imputation and (iii) Subset mean imputation. The subset mean imputation was performed using subsets of age group, gender and quintile of non-missing total ED charges. It was assumed that if a child had high ED charges following an opioid poisoning then there is a high likelihood of corresponding high physician-services related costs. For example, if an ED visit for a young child with an unintentional poisoning had total recorded charges in the fifth quintile (80^{th} percentile) but had missing physician costs, then the group mean physician cost of children under 6 years of age with unintentional opioid poisoning and 80^{th} percentile ED charges was used for imputation.

Multiple imputation using MCMC was attempted for missing ED physician-related costs, but the imputation model exhibited poor fit with significant autocorrelation. The number of iterations were increased in the MCMC procedure but it did not help to overcome the autocorrelation in the sequence of the physician costs estimates. Thus, imputed mean using the subset mean imputation method was used for missing ED physician-related costs.

ED-related costs

Total ED-related hospital costs were calculated using the total number of ED visits for pediatric opioid poisonings and its estimated mean cost of treatment. HCUP databases do not include physician service costs for hospital encounters. However, up to 15 CPT-4 procedure codes are recorded in the NEDS. The physician fee per ED visit was calculated by linking the CPT codes from NEDS to the publicly-available CMS 2012 Physician Fee Schedule. This schedule provides the national reimbursement rate for each CPT code. The sum of all CPT codes, after linking to their respective payment amount, was calculated for each ED visit. This was aggregated across visits to obtain the total ED-related physician service costs.

Inpatient-related costs

Total inpatient stay costs were calculated using the number of inpatient stays and the estimated mean cost of hospitalization for pediatric opioid poisonings. KID does not include physician service fees or CPT codes for calculating inpatient physician costs. Procedures are recorded in the inpatient data using ICD-9-CM procedure codes which cannot be used for estimating inpatient physician costs. Three standard CPT codes were assumed for all the inpatient stays as listed in Table 17. These CPT codes were then linked to their respective payment amount from the CMS 2012 Physician Fee Schedule. This approach has been used by previous studies examining inpatient physician costs.[121,122] The CPT codes were retrieved from the 2011 CMS Physician Fee Schedule manual.

Table 17: CPT codes used for calculating inpatient physician costs

CPT code	Description	CMS national reimbursement rate (in 2012 USD)
99222	Initial hospital care (50 minutes)	133.09
99231	Subsequent hospital care (15 minutes)	38.12
99238	Hospital discharge day (30 minutes)	69.78

Using these CPT codes, inpatient stays with LOS ≤ 1 day were assigned CPT codes for initial care (99222) and discharge day care (99238), and the total physician costs was the combined sum of their corresponding rates. Inpatient stays with LOS >1 were assigned CPT codes for initial admission care and discharge day care, and the CPT code for subsequent care (99231) for every additional day in between the admission and the discharge day. HCUP calculates LOS by subtracting the admission date from the discharge date so the same-day stays are coded as 0. This was accounted for in the physician costs calculations. For example, if the LOS was 3 days then the total physician costs for that stay was calculated as,

(CPT 99222 rate + CPT 99238 rate) + (CPT 99231 rate x 2 days)

Total direct medical cost

Total ED costs were calculated by aggregating ED hospital-related costs and physician-related costs. Similarly, total inpatient costs were computed by aggregating inpatient hospital-related costs and physician-related costs. Total direct medical costs of opioid poisonings in children were calculated by combining total ED costs and inpatient costs.

Direct non-medical costs

Ambulance service use was not available in the HCUP databases. Larkin et al. used National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1997-2003 and estimated ambulance use in about 39% of injury-related ED visits.[123] A similar estimate has been used by another opioid poisoning study.[55] However, these analyses were not specific to the pediatric population. Adults with opioid poisoning may avoid ED transport for various reasons such as fear of legal involvement or discrimination. These factors may not be a concern when using ambulance services for children. Hence, it was assumed that half of the total ED visits (50%) used ambulance services. This estimate is higher than the previous analyses but still provides a conservative assumption. The estimate was multiplied with the cost per ambulance transport to compute total ambulance costs. A report by Government Accountability Office (GAO) estimated the cost per ground ambulance transport at $429 in 2010.[124] This cost was inflated to 2012 USD using Bureau of Labor Statistics' (BLS) Medical Care Component of the Consumer Price Index (CPI).[125]

Indirect productivity costs

Morbidity-related costs

Morbidity costs were calculated for caregivers' lost productivity due to absenteeism during the child's ED visit or average hospital stay plus a reasonable post-admission care time. There is no data on the average number of recovery days following pediatric opioid poisonings. For ED visit related morbidity costs, one recovery day was assumed following a day of the ED visit. A total of 2 absent work days was combined with the total weighted number of ED visits identified from the NEDS. This was then combined with the DPV obtained from Grosse et al.[110] These DPV values

were reported in 2007 USD and were inflated to 2012 USD using the BLS Employment Cost Index (ECI) for all civilian workers.[126]

For inpatient stays, different recovery days were assumed based on the severity of opioid poisoning, identified using the APR-DRG severity index in the KID. Average LOS was calculated by severity group (none-to-minor, moderate, or major-to-extreme severity). One, 3 and 7 recovery days were assumed for none-to-minor, moderate and major-to-extreme severity groups, respectively. A maximum of one week of recuperation time was assumed based on previous poisoning-related hospital analyses by Inocencio et al. and Walsh et al.[55,127] Total caregiver absent days were calculated for each severity group and combined with the weighted number of inpatient stays for the respective group. This was then combined with the inflated DPV value from Grosse et al.[110] Total morbidity costs were obtained by aggregating the ED-related and inpatient-related morbidity costs.

Mortality-related costs

The National Vital Statistics System's (NVSS) 2012 Mortality Multiple Cause-of-Death (MCOD) file was used to estimate indirect costs due to premature mortality. Although deaths were recorded in the HCUP databases, they may be limited to cases that died during hospitalization and there was no data element to verify cause of death in these datasets. NVSS data are provided by the National Center for Health Statistics (NCHS) and vital registration systems and are widely used in research for studying mortality trends. Detailed information is recorded on decedent's demographics, including age and gender, and medical characteristics including underlying cause of death identified using ICD-10 codes. Data is also documented on the record axis conditions which describes the cause of death and any other comorbidities that may exist.

Records of decedent's less than 18 years of age that had a poisoning-related ICD-10 code recorded in the underlying cause of death field were extracted (ICD-10 code X42, X44, X62, X64, Y12, or Y14). From these records, decedent's that had an indication of opioid as a contributing cause of death were identified using the opioid specific ICD-10 code in the record axis fields (ICD-10 code T40.0, T40.2, or T40.3). Intent and type of opioid involved in a poisoning-related death were identified using the ICD-10 codes (Table 18). Number of opioid poisoning deaths were identified by single-year of age and gender of the deceased children. The PVFP values obtained from Grosse et al. were weighted by age and gender in 2007 USD.[110] These PVFP values at 3% discount rate were inflated to 2012 USD using the using the BLS ECI for all civilian workers. Total costs of mortality-related productivity loss were calculated by combining the number of deaths and PVFP for each age and gender group

Table 18: Opioid poisoning-related ICD-10 diagnosis codes

ICD-10 Codes	Description
X42[a]	Accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), NEC
X44[a]	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
X62[b]	Intentional self-poisoning by and exposure to narcotics and psychodysleptics, NEC
X64[b]	Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
Y12[c]	Poisoning by and exposure to narcotics and psychodysleptics, NEC, undetermined intent
Y14[c]	Poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances, undetermined intent
T40.2[d]	Other opioids (codeine, morphine)
T40.3[e]	Methadone
T40.4[d]	Other synthetic narcotics (pethidine)

[a]Unintentional (or accidental poisonings); [b]Intentional poisonings; [c]Undetermined poisonings; [d]Other opioids-related poisonings; [e]Methadone-related poisonings.
NEC = not elsewhere classified.

Methods used to estimate the economic costs associated with opioid poisonings in children are summarized in Table 19. Deterministic one-way sensitivity analyses were performed using a range of plausible parameter values to examine the robustness of cost estimates. All analyses were done in SAS version 9.4 and Microsoft Excel 2013.

Table 19: Summary of methods for economic cost analyses

Costs		Data source(s)	Data elements(s)	Cost calculations
Direct Medical	ED visits (without hospitalization)	HCUP NEDS (2012)	ED visits, total ED charges*	# of ED visits x mean ED costs
	ED physician costs	HCUP NEDS (2012), CMS MPFS (2012)	CPT codes, CPT codes national rate	∑ (Sum of CPT codes (rate) per record)
	Inpatient stays	HCUP KID (2012)	Inpatient stays, total inpatient charges*	# of inpatient stays x mean inpatient costs
	Inpatient physician costs	HCUP KID (2012), CMS MPFS (2012)	CPT codes, CPT codes national rate	∑ (Sum of CPT codes (rate) per record)
Direct Non-medical	Transportation	HCUP NEDS (2012), Larkin et al. (2005), assumption GAO Report (2010), BLS CPI	ED visits, Ambulance runs, Ambulance costs	# of ED visits x 0.5 x cost per ambulance run
Indirect (productivity loss)	Absenteeism	HCUP NEDS & KID (2012) Assumption, Grosse et al. (2009), BLS ECI	ED visit or LOS, Recovery time,** DPV	# of absent days x DPV
	Mortality	NVSS MCOD (2012), Grosse et al. (2009), BLS ECI	Premature mortality, PVFP	# of deaths x PVFP

*Charges were converted to costs using CCR.
**Recovery days for ED visits = 1; Recovery days for inpatient stays = 1 to 7 days (depending on severity-of-illness).
HCUP = Healthcare Cost and Utilization Project; NEDS = Nationwide Emergency Department Sample; KID = Kids' Inpatient Database; CMS = Centers for Medicare & Medicaid Services; MPFS = Medicare Physician Fee Schedule; GAO = Government Accountability Office; BLS = Bureau of Labor Statistics; CPI = Consumer Price Index; ECI = Employment Cost Index; NVSS MCOD = National Vital Statistics System Multiple Cause-of-Death; LOS = Length of stay; DPV = Daily production value; PVFP = Present value of expected future productivity.

4.2: Results

Direct costs

There were a total of 4,584 ED visits and 1,874 inpatient stays for opioid poisonings among children in 2012. The mean ED hospital and physician costs and inpatient hospital and physician costs calculated by various imputation methods are summarized in the Tables 20 and 21. The mean cost for an ED visit for treatment of pediatric opioid poisonings was calculated at $1,496, and the mean cost for an inpatient stay was estimated at $7,045. The total direct medical costs of pediatric opioid poisonings were estimated to be about $20.1 million annually. Approximately $13.2 million (65.8%) of these total direct costs were due to inpatient admissions, while ED visits constituted about $6.9 million (34.2%). For a total of 4,584 ED visits identified in the NEDS, 2,292 were assumed to have arrived to the ED using ambulance transport. Using this estimate, the total direct non-medical costs of opioid poisonings in children were calculated to be $1,050,318 per year (cost per ambulance run in 2012 USD = $458.25). The total direct medical and non-medical costs of pediatric opioid poisonings in the United States were estimated to be over $21.1 million per year.

Table 20: ED costs associated with pediatric opioid poisonings (in 2012 USD)

ED costs	Costs, mean (SE)		Costs, total
	Unweighted (N = 1,048)	Weighted (N = 4,584)	
Hospital costs			
Original costs (not imputed)[a]	1,318.57 (45.13)	1,288.92 (54.10)	--
Imputation 1 (missing values as 0)	1,089.58 (40.36)	1,071.66 (51.28)	--
Imputation 2a (overall mean)[b]	1,334.78 (37.39)	1,310.10 (45.17)	--
Imputation 2b (subset mean)[b, c]	1,332.92 (38.02)	1,307.24 (45.35)	--
Imputation 3 (MCMC)	1,362.65 (41.58)	**1,338.55 (46.62)**	--
Total hospital costs[f]			**6,135,913**
Physician costs			
Physician costs (not imputed)[d]	162.88 (4.35)	164.88 (5.09)	--
Imputation 1 (missing values as 0)	110.04 (3.77)	107.57 (5.37)	--
Imputation 2 (overall mean)	162.88 (2.94)	164.19 (3.32)	--
Imputation 3 (subset mean)[e]	156.61 (3.22)	**157.42 (3.77)**	--
Total physician costs[f]			**721,613**
Total ED costs[f]	1,519.26	**1,495.97**	**6,857,526**

MCMC = Markov chain Monte Carlo.
Total costs = Weighted mean cost x Weighted prevalence (N).
[a]ED costs were missing for 182 (17.4%) visits (N = 866). These were not included in the not imputed mean.
[b]Imputations 2a and 2b are single imputation methods.
[c]Subset based on age group and intent.
[d]CPT codes were missing for 340 visits. These were not included in the not imputed mean.
[e]Subset based on age group, intent and quintiles of (non-missing) total ED charges.
[f]Hospital costs obtained from the multiple imputation using MCMC and physician costs obtained from the subset mean imputation were used.

Table 21: Inpatient costs associated with pediatric opioid poisonings (in 2012 USD)

Inpatient costs	Costs, mean (SE)		Costs, total
	Unweighted (N = 1,332)	**Weighted (N = 1,874)**	
Hospital costs			
Original costs (not imputed)[a]	6,624.60 (613.53)	6,633.41 (630.21)	--
Imputation 1 (missing values as 0)	6,525.13 (604.71)	6,537.48 (622.68)	--
Imputation 2 (mean cost/day)	6,623.42 (604.82)	6,632.48 (621.48)	--
Imputation 3 (MCMC)	6,759.91 (607.26)	**6,766.03 (624.07)**	--
Total hospital costs[b]			**12,679,540**
Physician costs			
Total physician costs[b]	279.63 (6.28)	**279.18 (6.24)**	**523,183**
Total inpatient costs[b]	7,039.54	**7,045.21**	**13,202,723**

MCMC = Markov chain Monte Carlo.
Total costs = Weighted mean cost x Weighted prevalence (N).
[a]Inpatient costs were missing for 20 (1.5%) stays (N = 1,312) and were not included in the not imputed mean.
[b]Hospital costs obtained from the multiple imputation using MCMC and calculated physician costs were used.

Indirect costs

Table 22 summarizes the morbidity-related costs associated with pediatric opioid poisonings. Assuming 1 recovery day resulted in 2 caregiver absent days per child for opioid poisoning ED visit. Using the KID, the average LOS among children following an opioid poisoning with minor or moderate severity was 2 days, and average LOS following an opioid poisoning with major severity was 6 days. Total of 1 day, 3 days and 7 days of recuperation time was assumed following an opioid poisoning with minor, moderate or major severity, respectively. This resulted in a total of 3 to 13 caregiver absent days from work. The DPV for a caregiver in 2012 USD was estimated

at $142.99. The total morbidity-related costs due to caregiver absenteeism were estimated to be over $2.9 million annually. Inpatient stays for opioid poisonings in children constituted about 55.5% of these total morbidity-related costs, and ED visits added up to the remainder of the costs (Table 22).

Using MCOD 2012 file, 123 pediatric opioid poisoning-related deaths were identified. About 69.9% of these children were teenagers and 26% were under the age of 6 years. Over three-fourths of the opioid poisoning related deaths in children were unintentional (77.2%). Table 23 shows the characteristics of children with opioid poisoning-related deaths. Using the PVFP estimates from Grosse et al.,[110] the total mortality costs were estimated to be $206,761,044 in 2012 USD. The total productivity costs for opioid poisonings in children in the United States were estimated at approximately $209.7 million. Mortality-related costs constituted about 98.6% of the total indirect costs for opioid poisonings in children. The total economic costs of opioid poisonings in children were calculated at $230.8 million in 2012 USD.

Table 22: Morbidity-related absenteeism costs associated with pediatric opioid poisonings (in 2012 USD)

	Absent days			**Weighted N**	**DPV loss**[b] (Avg. DPV = 142.99)
	LOS	Recovery	Total		
ED visit	1	1	2	4,584	**1,310,955**
Inpatient stay					
None to minor severity[a]	2	1	3	700	280,911
Moderate severity[a]	2	3	5	747	573,229
Major to extreme severity[a]	6	7	13	427	778,586
Total	--	--	--	1,874	**1,632,726**
Total					**2,943,681**

DPV = Daily Production Value; LOS = Length of stay; Avg = Average.
[a]Based on APR-DRG severity-of-illness assigned in the KID.
[b]Assumed one caregiver per child.

Table 23: Characteristics of children with opioid poisoning-related deaths in 2012

Characteristic	N	%
Total	**123**	**100**
Sociodemographic		
Age groups (years)		
≤ 5	32	26.02
6 - 12	5	4.07
13 - 17	86	69.92
Female	35	28.46
Clinical		
Intent[a]		
Unintentional	95	77.24
Intentional	6	4.88
Undetermined	22	17.89
Opioid[b]		
Methadone	31	25.2
Other opioids	96	78.05

[a]Intent of opioid poisonings was identified using ICD-10 codes which vary from the AAPCC intent definitions. For example, assume a teenager misused opioids not with an intent to suicide but to get a high and had subsequent poisoning. This scenario would be recorded as unintentional using ICD codes. However, the same situation would be recorded as intentional in the NPDS by the PC specialist.
[b]Total does not add up to 100% as there were cases with more than one opioid involvement.

Sensitivity analyses

Scenario analyses and multiple other one-way sensitivity analyses were performed primarily to examine the assumptions made for calculating the economic costs of opioid poisonings in children. In direct medical costs estimation, discharges with diagnosis of opioid poisoning in any-listed diagnosis field were included. The weighted mean cost of ED hospital visits was found to be $1,338.55 (SE = 46.62), and the mean inpatient hospital stay cost was $6,766.03 (SE = 624.07). To examine if the mean costs of ED or inpatient treatment were different for discharges with and

without principal diagnosis of opioid poisoning, mean ED cost was calculated for visits with opioid poisoning as the first-listed diagnosis (weighted N = 3,555). Also, mean inpatient stay cost was calculated by limiting the sample to discharges with opioid poisoning as the principle diagnosis (weighted N = 1,127). The weighted mean cost of ED visits with opioid poisoning as first-listed diagnosis was $1,227.63 (SE = 52.44). The weighted mean cost of inpatient stays with principal diagnosis of opioid poisonings was estimated at $5,587.66 (SE = 441.99). Total economic costs were examined using the mean costs of ED visits and inpatient stays with opioid poisoning as first-listed or principal diagnosis. Total economic costs were also examined using the mean ED and inpatient costs for discharges with non-missing (non-imputed) costs.

A series of other one-way sensitivity analyses were performed to examine the robustness of base-case cost estimates by varying the proportion of ED visits involving ambulance runs, ambulance cost per run, caregiver absent days following an ED visit and inpatient stay, DPV and discount rate of PVFP. Proportion of ED visits involving ambulance runs and DPV were varied to +/- 25% of the base-case estimate. Cost per ambulance run was varied between the 95% CI from GAO report. Caregiver absent days following an ED visit was assumed to be 1 day i.e., 1 day of ED visit with no recovery days. Caregiver absent days following an inpatient stay was assumed to be 6 days which included average LOS of 3 days (obtained from the KID) and assumed 3 days of recovery, without accounting for severity-of-illness as done in the base-case analyses. Discount rate of PVFP was varied to 5% and 10%. Table 24 below summarizes the input parameters and their respective ranges or values tested in sensitivity analyses.

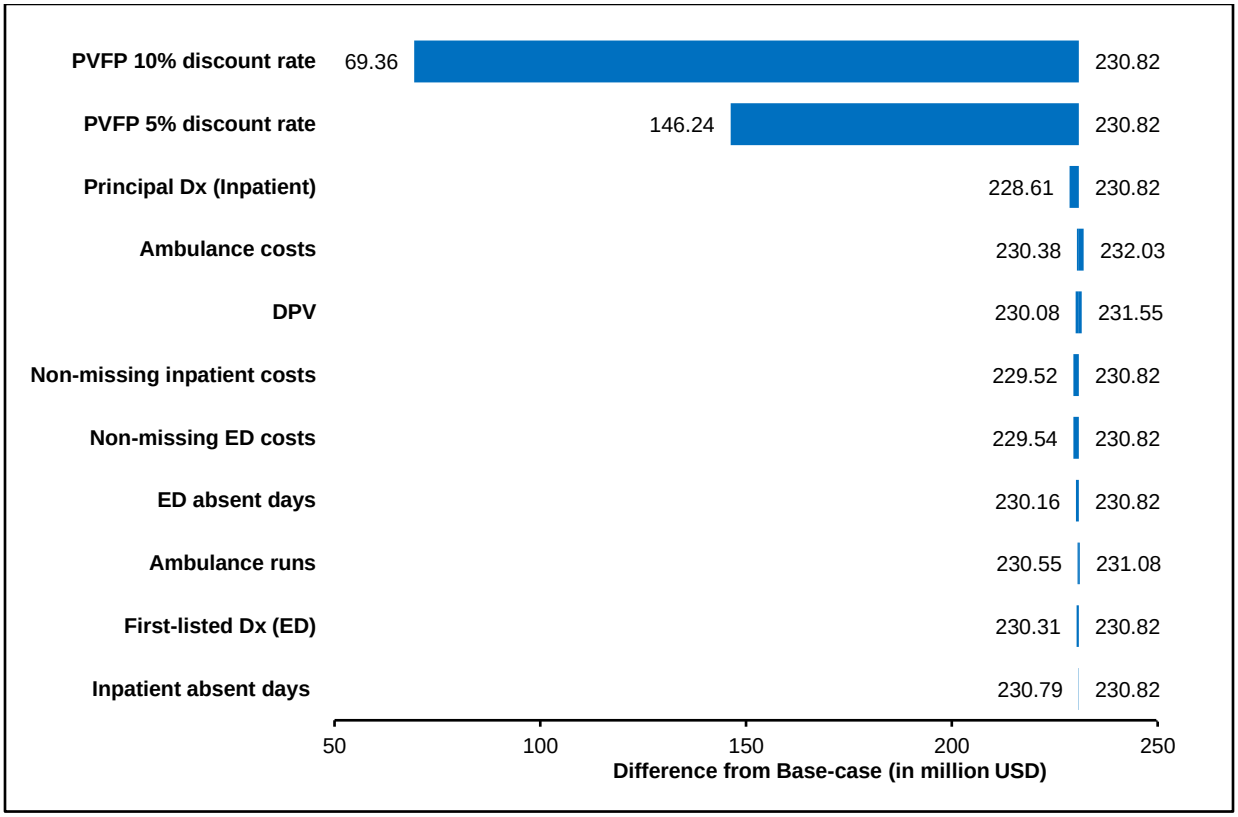
Tornado diagram displays the results from sensitivity analyses (Figure 10). The total economic cost estimates were most sensitive to the discount rate of PVFP. Varying the discount rate to 5% and 10% (from base-case value of 3%) yielded total economic costs of $146.24 million and $69.36

million, respectively. Restricting the prevalence estimates for inpatient discharges to those with principal diagnosis of opioid poisoning yielded a total economic cost estimate of $228.61 million. Using the 95% CI limit for ambulance costs, the total economic costs varied from $230.38 million to $232.03 million. Varying the DPV value by +/- 25% resulted in total economic costs between $230.08 million and $231.55 million. Using the mean inpatient and ED costs for discharges with non-missing (non-imputed) costs lowered the total economic costs by about $1.30 million and $1.28 million, respectively. The shift in the base-case cost estimates was minimal for other parameters tested.

Table 24: Parameters tested in sensitivity analyses

Parameter	Value or range tested
Scenario analyses	
First-listed diagnosis (ED)	Mean cost ($1,227.63)
Principal diagnosis (Inpatient)	Mean cost ($5,587.66)
Non-missing ED costs	Mean cost ($1,288.92)
Non-missing inpatient costs	Mean cost ($6,633.41)
One-way sensitivity analyses	
Ambulance runs	Base-case (50%)
	+/- 25%
Ambulance costs	Base-case ($458.25)
	95% CI limit ($270.25 - $987.01)
Absent days after ED visit	Base-case (2 days)
	1 day (0 recovery day)
Absent days after inpatient stay	Base-case (3 to 13 days)
	6 days (3 LOS and 3 recovery days)
DPV	Base-case ($142.99)
	+/-25%
PVFP discount rate	Base-case (3%)
	5% and 10% discount rate

ED = Emergency department; DPV = Daily production value; PVFP = Present value of expected future productivity.



Base-case estimate = $230.82 million.
PVFP = Present value of expected future productivity; DPV = Daily production value;
Dx = Diagnosis; ED = Emergency department.

Figure 10: One-way sensitivity analyses on selected parameters (Tornado diagram)

4.3: Discussion

Economic costs associated with opioid poisonings in children

To our knowledge, this is the first study that estimated the economic burden of pediatric opioid poisonings in the United States. The mean cost for an ED visit related to opioid poisonings in children was calculated at $1,496 and the mean cost for an inpatient stay was estimated at $7,045 in 2012. As a rough comparison, pediatric opioid poisoning-related inpatient costs are higher than

the national mean costs of $6,415 for all-hospital stays among children under the age of 18 years.[128] Three previous studies have examined opioid poisoning-related costs. Inocencio et al. estimated mean ED costs at $2,008 and inpatient costs at $9,897 for opioid poisonings, converted to 2012 USD.[55] Another study calculated the mean charges (did not report costs) for prescription opioid poisoning ED visits at $3,833 to $4,339, and mean hospitalization charges at $31,058 to $34,374, converted to 2012 USD.[56] Xiang et al. estimated mean charges (did not report costs) for drug poisoning-related ED visits at $2,208, converted to 2012 USD.[57] The costs from current analyses are lower than the costs reported by prior studies. One reason may be that previous cost estimates represent opioid poisonings in all age groups. Prognosis and management of opioid poisonings in adults and older adults can vary considerably from that in children due to factors such as higher prevalence of multiple health conditions, chronic opioid use and misuse, substance use disorders, or polypharmacy among adults. These factors may result in higher cost of treatment following an opioid poisoning in adults compared to children.

The total direct costs for opioid poisonings in children were estimated to be over $21 million (or $0.02 billion) in the United States in 2012. Inocencio et al. examined economic costs associated with opioid poisonings and reported total direct costs of over $1.8 billion for opioid poisonings, converted to 2012 USD.[55] As stated earlier, this study did not limit its analyses to children yet it provides an upper bound for cost results from the current study.

As for indirect costs, the total morbidity costs due to absenteeism were estimated to be over $2.9 (or $0.003 billion) million. Mortality costs for opioid poisonings in children were estimated at about $207 million (or $0.207 billion). The total indirect costs associated with opioid poisonings in children were calculated to be nearly $210 million (or $0.21 billion) in 2012. Similar to current analyses, Inocencio et al. reported mortality costs to be the largest contributor to the total costs for

opioid poisonings. The authors estimated absenteeism costs at about $261 million, mortality costs over $14 billion, and total indirect productivity costs at approximately $14.4 billion in the United States, converted to 2012 USD.[55] These indirect cost estimates for opioid poisonings are much greater than the costs we calculated which is related to a higher number of opioid poisoning-related ED visits, inpatient stays and mortality rates found in the prior study compared to current analyses. Inocencio et al. examined opioid poisoning-related costs mainly in adults, and the number of opioid poisonings and related ED visits, hospitalization and deaths are higher among adults due to various factors described above. Opioid poisonings in adults may be more likely to be intentional and severe resulting in more deaths compared to young children.[47,50,86] Additionally, the present value of expected future productivity estimated using the human capital method tends to be higher for younger, working adults due to their higher earnings and higher labor force participation compared to children.[111]

The total economic costs of opioid poisonings in children were calculated at $230.8 million (or $0.23 billion) in 2012 USD. Comparison of these cost estimates to other childhood health conditions may provide some contextual reference for the societal burden of pediatric opioid poisonings. Wang et al. estimated the total economic burden for asthma in children aged 5 to 17 years at $2.5 billion which comprised direct medical costs at approximately $1.3 billion, absenteeism costs at about $0.9 billion, and mortality costs at $0.3 billion (all costs converted to 2012 USD).[129] Patel et al. calculated annual total direct costs at $0.25 billion and indirect costs at $0.13 billion for allergic reactions due to food allergy and anaphylaxis. The annual direct medical costs were further calculated for children under the age of 19 years, which were estimated at approximately $0.13 billion (all costs converted to 2012 USD).[121] The emergency associated with an asthma attack or food-allergy reaction can be acute and fatal which is analogous to an opioid

poisoning event. The economic costs associated with pediatric opioid poisonings is comparable to food allergy and anaphylaxis but is lower than asthma. The total economic burden of opioid poisonings in children is also considerably lower compared to the top five most costly health conditions in terms of medical expenditures among children in 2012: (1) Mental health disorders at $13.9 billion, (2) Chronic obstructive pulmonary disease (COPD) and asthma at $8.3 billion, (3) Trauma-related disorders at $7.8 billion, 4) Acute bronchitis and upper respiratory infections at $3.2 billion, and 5) infectious diseases at $2.5 billion.[130] It should be noted that many of these pediatric health conditions are more chronic or long-term conditions and entail longer preventive and treatment efforts, and are much broader than opioid poisonings.

These analyses have several limitations. Database(s) and methodological limitations are described under Specific Aim 3. Additionally, downstream costs could not be captured due to inability to identify downstream hospitalizations and other costs related to the opioid poisonings from the current data. Nearly 31% of children with an opioid poisoning inpatient stay were transferred to a short-term or intermediate care facility. Outcomes and costs related to long-term disability or post-discharge care following an opioid poisoning hospitalization could not be examined. This indicates that our study probably underestimated the true economic burden associated with pediatric opioid poisonings.

Second, HCUP ED and inpatient data did not include professional fees. ED physician costs were calculated using CPT codes made available in ED data. CPT codes were not available in the inpatient database so physician costs associated with hospitalizations were estimated based on some fundamental hospital stay-related CPT codes, as described earlier in the Methods. Some hospitalizations may have required fewer or additional physician services which could affect the estimated total inpatient physician costs in either direction. However, this is expected to have a

small impact on the economic cost estimates since hospital physician costs were less than 4% of total inpatient costs and less than 0.1% of total direct medical costs.

Third, direct non-medical costs were limited to costs for ambulance runs but other costs such as non-ambulance travel, accommodations and meals may have incurred due to opioid poisoning in a child. The data we analyzed did not allow for inclusion of such costs thus underestimating the total economic costs associated with pediatric opioid poisonings.

Fourth, indirect costs were limited to productivity costs associated with opioid poisonings in children that had a HCF encounter. However, such costs may also have incurred at home. For instance, parents or caregivers may have taken time-off work if they had to observe the child at home for a few hours after a suspected exposure. Lastly, an opioid poisoning event in a young child may have significant intangible costs resulting from stress, anxiety or suffering. Such costs were not included in the current economic burden analyses.

Chapter 5: Specific Aim 3

Aim 3: To examine the characteristics associated with pediatric opioid poisoning-related health care resource use and costs

A. To assess the characteristics associated with pediatric opioid poisoning ED visits

B. To identify factors associated with ED visit costs among children with opioid poisonings

C. To examine the characteristics associated with pediatric opioid poisoning inpatient stays

D. To identify factors associated with inpatient stay costs among children with opioid poisonings

5.1: Methods

Design

A retrospective, cross-sectional study design was implemented for this Specific Aim.

Conceptual framework

Examination of characteristics associated with pediatric opioid poisoning ED visits and inpatient stays can serve as a measure for identifying opioid poisonings in children that are associated with

high HCRU and costs. These characteristics include patient-level predisposing factors such as sociodemographics and clinical factors including severity of poisoning, comorbidities and chronic conditions that may predispose a patient to higher HCRU and costs. Similarly, patient-level enabling factors such as payer source and organizational-level enabling factors such as hospital characteristics can play a role in HCRU and costs associated with pediatric opioid exposures. Payer source influences receipt of care and payment for health care services, whereas hospital-level factors have an impact on practice patterns thereby influencing patient management and care.[131]

Data

The Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS) and Kids' Inpatient Database (KID) were used. These datasets are described in Specific Aim 2.

Sample

Discharge records from NEDS and KID databases were extracted for children under 18 years of age with 1 or more opioid poisoning-related International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes in any-listed diagnosis. Opioid poisoning-related ICD-9-CM codes are listed in Table 16 (Specific Aim 2). The sampling criteria are described in Specific Aim 2.

Variables

Total charges/costs

The HCUP databases provide total charges for ED visits and inpatient stays and not the actual cost of services. The charges reported in NEDS and KID were converted to costs using CCR provided by HCUP. The detailed methodology for implementing these CCR is described in Specific Aim 2.

Clinical variables

Opioid poisonings

Specific opioids involved in poisonings were identified as methadone, other prescription opioids or unspecified opioids, using the ICD-9-CM diagnosis codes listed in Table 16 (Specific Aim 2).

Intentionality

Intentionality of opioid poisonings was identified as unintentional, intentional or undetermined using the ICD-9-CM External Cause of Injury codes (E-codes) listed in Table 16. Data is recorded for up to 4 E-codes for each visit or stay. Records that did not have a specific E-code were initially classified as missing. This resulted in about 7% ED visits with a missing or unknown intentionality in the NEDS. However, NEDS contains certain injury-related variables including intent (self-harm or unintentional) on every record. Information from these injury-related variables was used to impute intentionality to the extent possible. For instance, if the record was classified as undetermined (using E-code 980.0) or missing but had an indicator for self-harm, then the record was reclassified as intentional. Such injury-related variables are not recorded in the KID, inpatient stays that did not have a specific E-code were classified as unknown.

Other clinical variables

Data is recorded for a number of diagnosis and procedure-related variables per visit. About 15 to 25 ICD-9-CM diagnosis codes, Clinical Classification Software (CCS) category codes, CPT procedure codes or ICD-9-CM procedure codes and corresponding CCS categories, and chronic condition indicators are recorded for each visit.

Common first-listed and any-listed diagnosis were examined using the ICD-9-CM and single-level CCS codes. CCS for diagnosis is an HCUP tool that collapses ICD-9-CM codes in 285 mutually exclusive and clinically meaningful categories. CCS for services and procedures categorizes CPT codes or ICD-9-CM procedure codes into distinct categories. Common chronic conditions were identified using the chronic condition indicators and the ICD-9-CM codes. Top primary procedures were identified using the CPT CCS codes in the ED data, and ICD-9-CM procedure CCS codes in the inpatient data. Discharge records with poisonings by other drugs (in addition to opioids) i.e., multi-drug involvement, were identified using the ICD-9-CM codes (960 - 979) in any-listed diagnosis. Detailed description of these codes is provided in Appendix E.

As stated above, information on injury is recorded for every ED visit. HCUP identifies injuries such as burns, fractures, poisonings or others, using ICD-9-CM codes. The multi-injury variable from the NEDS was used to identify ED visits with more than one injury reported.

Further, patient's disposition status at the time of discharge was classified as routine (includes routine discharges or home health care), transfer (includes transfers to short-term hospital, skilled nursing facility (SNF), intermediate care or another type of facility), death, or unknown (not admitted or discharged alive but destination unknown).

In addition to data elements listed above, KID includes information on transferred-in cases which indicates if the patient was a transfer from another HCF. Data is also provided on Elixhauser comorbidities, APR-DRG severity index and mortality risk index, LOS, and Diagnosis-Related Groups (DRGs) for every inpatient stay.

The AHRQ's Elixhauser comorbidity measures identify presence of up to 30 co-existing condition groups such as alcohol abuse, depression, psychoses, that are not directly related to the key reason for admission (or the principal diagnosis), and are likely to have existed preceding the hospital admission.[132] The list of AHRQ Elixhauser comorbidities can be found in Appendix F. The Elixhauser comorbidity measure is a validated tool for risk-adjustment in administrative data.[133] Comorbidity analyses were limited to Elixhauser comorbidities. No further comorbidities were explored because this study was examining outcomes in children so the likelihood of presence of co-existing conditions beyond those included in the HCUP data is low. Also, previous studies have examined other comorbidities in the adult population with opioid poisonings but there is a lack of such literature in the pediatric population.[55]

APR-DRG severity-of-illness index and mortality risk index are provided in the inpatient data to adjust for case-mix complexity and are linked to the intensity of HCRU.[134] These indices classify loss of function and likelihood of mortality into 4 distinct categories, respectively. The LOS and DRG variables were used as recorded in the data. In addition to the two poisoning-related DRGs, DRG 917 (Poisoning and toxic effects of drugs with major complications or comorbidities) and DRG 918 (Poisoning and toxic effects of drugs without major complications or comorbidities), other DRGs were explored in this population.

Payer and hospital-related variables

Data is recorded in the NEDS on the primary payer and hospital location, region, ownership, teaching status and trauma level. Primary payer was classified as Medicaid, private, uninsured or other (includes Medicare). In the NEDS analysis, hospital ownership was grouped as public, private (includes private, non-profit or proprietary), or public/private (includes hospitals that could not be identified as public or private i.e., collapsed category). Hospital location was categorized as urban (includes large or small metropolitans, or micropolitans) or rural (areas that were neither metropolitan nor micropolitan), and hospital teaching status was classified as teaching (includes metropolitan teaching hospitals) or non-teaching (includes metropolitan non-teaching or non-metropolitan hospitals). Hospital trauma-level status was categorized as trauma (includes trauma level I or II centers) or non-trauma (includes non-trauma or trauma level III centers). Hospital region was used as classified in the data.

The KID provides data on primary payer, and hospital region, ownership, bedsize and location/teaching status (combined). All the hospital-related variables were used as categorized in the KID. Classification of payer source was similar to that described above.

Sociodemographic variables

The HCUP provides information on patient's age, gender, residence location and national quartile of median household annual income for patient's ZIP Code, for all ED visits and inpatient stays. Age was primarily categorized into 0 to <1, 1 to 2, 3 to 5, 6 to 12, and 13 to 17 years groups however, the age group of ≤5 years was combined for adjusted analyses. Patient's residence location was classified as urban – mid to large (includes large central, large fringe or medium metropolitans), urban – small to mid (includes medium or small metropolitans, or micropolitans)

or rural (neither metropolitan nor micropolitan areas). Patient's gender and ZIP Code level income information was used as recorded in the data.

In addition to the variables listed above, data is recorded on patient's race in the KID. Race was classified as White, Black, Hispanic or other (includes Asian or Pacific Islander, Native American or other).

Other variables

Discharge-level sampling weight is provided for every discharge record. This along with hospital identifier and sample stratum were used for weighted analyses.

Table 25: HCUP NEDS and KID variables considered for Specific Aim 3

Data Source	Data Variables
NEDS	*Total charges* *Clinical* ▪ Number of diagnosis, procedures and E-codes ▪ Up to 15 ICD-9-CM diagnosis and CCS codes ▪ Up to 4 E-codes ▪ Up to 15 CPT procedure and CCS codes ▪ Up to 9 ICD-9-CM procedure codes ▪ Up to 15 chronic condition indicators ▪ Injury-related variables including number of injuries (multi-injury), intent ▪ Disposition status *Payer and Hospital-related* ▪ Expected primary payment source ▪ Hospital level factors (including location, region, ownership, teaching status, trauma-level) *Patient sociodemographics* ▪ Age, gender, residence location, median household annual income for patient's ZIP Code *Others* ▪ Patient discharge weights
KID	*Total charges* *Clinical* ▪ Number of diagnosis, procedures and E-codes

	▪ Up to 25 ICD-9-CM diagnosis and CCS codes ▪ Up to 4 E-codes ▪ Up to 15 ICD-9-CM procedure and CCS codes ▪ Up to 25 chronic condition indicators ▪ Elixhauser comorbidities ▪ APR-DRG severity index and mortality risk index ▪ LOS, DRGs ▪ Disposition status, transfer-in, ED event on record *Payer and Hospital-related* ▪ Expected primary payment source ▪ Hospital level factors (including ownership, bedsize, region, and location/teaching status) *Patient sociodemographics* ▪ Age, gender, race, residence location, median household annual income for patient's ZIP Code *Others* ▪ Patient discharge weights, hospital-specific CCR

NEDS = Nationwide Emergency Department Sample, KID = Kids' Inpatient Database, ED = Emergency department, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, E-codes = External Cause of Injury codes, CCS = Clinical Classification Software category codes, CPT = Current Procedural Terminology, APR-DRG = All Patients Refined Diagnosis Related Groups, LOS = Length of stay, DRGs = Diagnosis-Related Groups, CCR = Cost-to-charge ratios.

Statistics analyses

Descriptive statistics (frequency, %, mean, SD) were calculated to characterize pediatric opioid poisoning ED visits and inpatient stays. Bivariate analyses using Chi-square tests were performed to examine the association between various characteristics and pediatric opioid poisoning ED visits and inpatient stays by intent of exposure.

Total charges were missing for 182 (17.4%) ED visits in the NEDS, and 20 (1.5%) of inpatient stays in the KID. Mean costs of opioid poisoning-related ED visits and inpatient stays were computed and compared across various sociodemographic and clinical characteristics without imputing the missing cost data. Statistical tests were conducted prior to imputation to avoid any

statistical bias due to imputation of the dependent variable. Additionally, calculation of standard errors of ED and inpatient costs accounted for the sampling design of NEDS and KID respectively.

The distribution of the dependent cost variable(s) was examined. Outliers for ED charges were examined (top/bottom 5%) manually for reasonability. Suspiciously high charges in inpatient data were examined and deleted from cost analyses using the method described by HCUP. This approach is explained in Specific Aim 2.

Bivariate differences in mean ED visit-related costs were tested using t-tests and ANOVA, under the central-limit theorem (CLT) assumption, between the various sociodemographic, clinical, payer and hospital characteristics. Inpatient costs were highly skewed so nonparametric Wilcoxon Rank-Sum test and Kruskal-Wallis tests were used for bivariate comparisons of mean inpatient stay-related costs and the covariates. These analyses were exploratory so all sociodemographic, clinical, payer and hospital-related factors were examined.

Adjusted analyses were performed using generalized linear model (GLM) to estimate the association of independent variables with ED and inpatient costs, respectively. The costs data were skewed and needed to be transformed. Health care costs are non-negative and tend to be skewed to the right with increasing variability with rising mean (heteroscedasticity or unequal variances). Ordinary Least Squares (OLS) regression technique with log transformation of cost can be used for dealing with such skewness and to stabilize variance. However, OLS provides cost results on a log scale and smearing factors have to be applied for retransformation of costs to the original scale. Such retransformation can introduce bias if the unequal variance assumption is violated. Generalized linear model (GLM) is an alternative technique that is widely used for analyzing health care costs data. GLM models do not require cost data to be normally distributed and can correct for heteroscedasticity. GLM allows for a relatively straightforward back transformation

compared to OLS, retaining the original scale. Two important components in a GLM include: (1) the link function (g) which describes the relationship of dependent variable (Y) mean to the predictors, and (2) the family which specifies the distribution or the mean-variance relationship. Log-link function is commonly used for economic cost analyses. Health care cost data typically have log-normal or gamma distribution. The distribution of the GLM model was chosen using the Modified Park test. In this procedure, residuals and predicted value computed from an initial adjusted GLM model are tested. The parameter estimate from the model of residuals and predicted value (obtained from above) provide information on appropriate distribution for the data. For instance, an estimate of 2 corresponds to gamma distribution.[135–137] GLM was performed in SAS using PROC GENMOD with a REPEATED statement, to account for HCUP sampling design using hospital-level clusters. REPEATED statement invokes the generalized estimating equations (GEE) method and gives robust standard errors in the specified model.

For the adjusted ED cost analyses, GLM was initially performed with all covariates (Initial model QIC = 1014.9), and then excluding those that were insignificant in bivariate analyses and the initial model (Final model QIC = 1008). The latter model displayed a better fit and was selected as the final model for analyses. Quasi-likelihood criteria (or QIC) is a goodness of fit statistic and can be used to compare GEE models. QIC can be used for model selection even with non-nested models.[138] Similar approach was followed for the adjusted analyses of inpatient costs. Initial GLM was performed with all covariates (Initial model QIC = 1605.26), and then excluding insignificant covariates (Final model QIC = 1562.13). The latter model displayed a better fit and was selected as the final model for analyses.

All statistical tests were performed with a two-sided significance level of 0.05. All analyses were done in SAS version 9.4 and Microsoft Excel 2013.

5.2: Results

Aim 3A: To assess the characteristics associated with pediatric opioid poisoning ED visits

There were a weighted total of 4,584 ED visits for opioid poisonings among children. Table 26 summarizes various characteristics of pediatric opioid poisoning ED visits. Majority of these ED visits were among teenagers (53.4%) followed by young children, particularly 1 to 2 years of age (28%). Most of these visits were among children from medium to large metropolitan areas (68.6%). About 64.6% of total ED visits were due to unintentional poisonings and 26.1% involved intentional poisonings. Nearly 70% of ED visits resulted from other prescription opioid poisonings, over one-fourth had multi-drug involvement (27.8%) and one-third (32.3%) had a multi-injury. About 35.5% of these visits had one or more chronic condition diagnoses. Nearly three-fourths of the visits were routine discharges (75.3%), while another one-fourth were transfers to a short-term hospital, SNF or intermediate care (24.2%). Medicaid was the most common payer (46.9%) followed by private insurance (41.4%). Most pediatric opioid poisoning ED visits were in hospitals in urban settings (93.2%), commonly in South (36.1%) and West (27.9%) regions of the country, private hospitals compared to public hospitals (33.4% vs. 7.6%), non-teaching (62.7%) and non-trauma institutions (70.2%) (Table 26).

These characteristics were also examined by intent of opioid poisoning-related ED visits as shown in Table 27. Child's age and gender, type of opioid involved, diagnosis of multi-drug poisonings, multi-injuries or chronic conditions, disposition status, payer source and hospital region were significantly associated with the intent of pediatric opioid poisoning ED visits.

Unintentional poisoning-related ED visits were more common among young children (61.2%), while intentional poisoning-related ED visits were common among teenagers (97.1% vs. 33.3%) and girls (69.7% vs. 49.6%). Methadone poisoning-related ED visits were higher among those with unintentional poisonings compared to those with intentional poisoning (5.8% vs. 1.1%), whereas other prescription opioids were more commonly involved in intentional poisoning compared to unintentional poisoning ED visits (79.6% vs. 65.3%).

Compared to ED visits for unintentional poisonings, a higher number of intentional poisoning-related visits were associated with multi-drug involvement (49.3% vs. 17.3%), multi-injuries (55.1% vs. 21.9%), chronic condition diagnosis (63.9% vs. 22.8%), and involved transfers to short-term hospital, SNF or intermediate care facilities (58% vs. 12.3%). Medicaid was the most common payer for unintentional opioid poisoning-related ED visits (50.2% vs. 38%), while private insurance was the common source of payment for intentional opioid poisoning-related ED visits (51.1% vs. 36.3%). Unintentional opioid poisoning-related ED visits were higher than intentional opioid poisoning-related visits in the Northeast hospitals (12.7% vs. 8.8%), while intentional opioid poisoning-related ED visits were more common than unintentional opioid poisoning-related ED visits in the Midwest hospitals (23.4% vs. 17.6%) (Table 27).

Table 28 summarizes the common clinical diagnosis and procedures in opioid poisoning-related ED visits. On average, children with opioid poisoning ED visits had 3 diagnosis (range = 1 to 18) and 6 CPT procedures (range = 0 to 34) recorded. Substance-related disorder (includes diagnosis of opioid poisoning) was the most frequently recorded diagnosis followed by poisoning by other medications and psychotropic drugs, and mood disorders. Depression, tobacco use disorder, drug abuse, asthma and attention-deficit/hyperactivity disorder (ADHD) were common chronic conditions. Aromatic analgesics, benzodiazepines and propionic acid derivatives were commonly

involved in multiple drug poisonings. Most of the procedures in these ED visits were diagnostic (Table 28).

Table 26: Characteristics of pediatric opioid poisoning ED visits

Characteristic	All opioid poisonings[a]	
	Unweighted, N (%) (N = 1,048)	Weighted, N (%) (N = 4,584)
Sociodemographic		
Age group (years)		
0 < 1	48 (4.58)	208 (4.55)
1 - 2	291 (27.77)	1,283 (27.99)
3 - 5	97 (9.26)	424 (9.25)
6 - 12	49 (4.68)	220 (4.81)
13 - 17	563 (53.72)	2,448 (53.41)
Female	564 (53.82)	2,435 (53.11)
Residence		
Urban (Mid to large)	736 (70.23)	3,144 (68.58)
Urban (Small to mid)	237 (22.61)	1,076 (23.48)
Rural	74 (7.06)	360 (7.85)
Unknown	1 (0.1)	4 (0.08)
Median ZIP Code HH income		
$1 - 38,999	267 (25.48)	1,156 (25.22)
$39,000 - 47,999	272 (25.95)	1,157 (25.24)
$48,000 - 62,999	272 (25.95)	1,205 (26.28)
≥ $63,000	216 (20.61)	965 (21.04)
Unknown	21 (2.0)	102 (2.22)
Clinical		
Intent		
Unintentional	675 (64.41)	2,963 (64.64)
Intentional	274 (26.15)	1,196 (26.09)
Undetermined	63 (6.01)	253 (5.52)
Unknown	36 (3.44)	171 (3.74)
Opioid		
Methadone	48 (4.58)	209 (4.56)
Other prescription opioids	726 (69.27)	3,208 (69.97)
Unspecified	274 (26.15)	1,167 (25.47)
Multi-drug poisonings	284 (27.10)	1,275 (27.81)

Multi-injuries	334	(31.87)	1,482	(32.34)
≥ 1 Chronic conditions	377	(35.97)	1,627	(35.49)
Disposition status				
Routine	781	(74.52)	3,452	(75.29)
Transfers	263	(25.10)	1,110	(24.22)
Unknown	4	(0.38)	22	(0.49)
Payer and hospital				
Payer				
Medicaid	492	(46.95)	2,148	(46.86)
Private	422	(40.27)	1,900	(41.44)
Other	53	(5.06)	198	(4.32)
Uninsured	79	(7.54)	329	(7.18)
Unknown	2	(0.19)	9	(0.20)
Hospital location				
Rural	64	(6.11)	310	(6.77)
Urban	984	(93.89)	4,274	(93.23)
Hospital region				
Northeast	116	(11.07)	520	(11.34)
Midwest	219	(20.90)	1,130	(24.65)
South	420	(40.08)	1,654	(36.07)
West	293	(27.96)	1,281	(27.94)
Hospital ownership				
Public	99	(9.45)	347	(7.58)
Private	371	(35.40)	1,533	(33.44)
Public or private	578	(55.15)	2,704	(58.98)
Hospital teaching status				
Non-teaching	669	(63.84)	2,873	(62.67)
Teaching	379	(36.16)	1,711	(37.33)
Hospital trauma level				
Non-trauma or level III	749	(71.47)	3,216	(70.15)
Trauma level I or II	299	(28.53)	1,368	(29.85)

[a]Analyses were limited to ED visits without hospitalization. This may have underestimated the actual number of pediatric opioid poisoning ED visits.
HH = Household.

Table 27: Characteristics of pediatric opioid poisoning ED visits by intent

Characteristic	Unintentional (n = 675), unweighted n (%)		Intentional (n = 274), unweighted n (%)	
Sociodemographic				
Age group (years)*				
0 < 1	44	(6.52)	--	
1 - 2	278	(41.19)	--	
3 - 5	91	(13.48)	--	
6 - 12	37	(5.48)	8	(2.92)
13 - 17	225	(33.33)	266	(97.08)
Female*	335	(49.63)	191	(69.71)
Residence				
Urban (Mid to large)	464	(68.74)	208	(75.91)
Urban (Small to mid)	161	(23.85)	52	(18.98)
Rural	49	(7.26)	14	(5.11)
Unknown	1	(0.15)	--	
Median ZIP Code HH income				
$1 - 38,999	178	(26.37)	61	(22.26)
$39,000 - 47,999	180	(26.67)	67	(24.45)
$48,000 - 62,999	174	(25.78)	70	(25.55)
≥ $63,000	128	(18.96)	71	(25.91)
Unknown	15	(2.22)	5	(1.82)
Clinical				
Opioid*				
Methadone	39	(5.78)	3	(1.09)
Other prescription opioids	441	(65.33)	218	(79.56)
Unspecified	195	(28.89)	53	(19.34)
Multi-drug poisonings*	117	(17.33)	135	(49.27)
Multi-injuries*	148	(21.93)	151	(55.11)
≥ 1 Chronic conditions*	154	(22.81)	175	(63.87)
Disposition status*				
Routine	590	(87.41)	113	(41.24)
Transfers	83	(12.3)	159	(58.03)
Unknown	2	(0.3)	2	(0.73)

Payer and hospital				
Payer*				
Medicaid	339	(50.22)	104	(37.96)
Private	245	(36.30)	140	(51.09)
Other	31	(4.59)	14	(5.11)
Uninsured	58	(8.59)	16	(5.84)
Unknown	2	(0.3)	--	
Hospital location				
Rural	39	(5.78)	15	(5.47)
Urban	636	(94.22)	259	(94.53)
Hospital region*				
Northeast	86	(12.74)	24	(8.76)
Midwest	119	(17.63)	64	(23.36)
South	262	(38.81)	106	(38.69)
West	208	(30.81)	80	(29.20)
Hospital ownership				
Public	61	(9.04)	28	(10.22)
Private	241	(35.70)	100	(36.50)
Public or private	373	(55.26)	146	(53.28)
Hospital teaching status				
Non-teaching	431	(63.85)	168	(61.31)
Teaching	244	(36.15)	106	(38.69)
Hospital trauma level				
Non-trauma or level III	478	(70.81)	194	(70.80)
Trauma level I or II	197	(29.19)	80	(29.20)

*Chi-square $p<.05$. HH = Household.
Results for undetermined or unknown intentionality not shown here.
A total 7 visits had E-code for an adverse effect (E935.1: Methadone causing adverse effects in therapeutic use, or E935.2: Other opiates and related narcotics causing adverse effects in therapeutic use).

Table 28: Clinical conditions and procedures recorded in pediatric opioid poisoning ED visits

Conditions/Procedures	Unweighted, n (%)
Clinical conditions[a,b,c,d]	
Number of diagnoses, mean (SD)	2.77 (2.02)
Primary (first-listed) diagnosis (n = 1,048)	
Substance-related disorders[*]	821 (78.34)
Poisoning by other medications and drugs	78 (7.44)
Poisoning by psychotropic agents	43 (4.1)
Mood disorders	25 (2.39)
Residual codes; unclassified[**]	11 (1.05)
Any-listed diagnosis (n = 2,899)	
Substance-related disorders[*]	1,209 (41.7)
Poisoning by other medications and drugs	283 (9.76)
Mood disorders	161 (5.55)
Poisoning by psychotropic agents	138 (4.76)
Screening and history of mental health and substance abuse	80 (2.76)
Chronic Conditions (n = 1,639)	
Depressive disorder	95 (5.8)
Tobacco use disorder	63 (3.84)
Drug abuse, unspecified	45 (2.75)
Asthma, unspecified	29 (1.77)
Attention-deficit/hyperactivity disorder	27 (1.65)
Multi-drug poisonings (in addition to opioids) (n = 1,237)	
Aromatic analgesics	74 (5.98)
Benzodiazepine-based tranquilizers	67 (5.42)
Propionic acid derivatives	40 (3.23)
Sedative and Hypnotics	23 (1.86)
Antiallergics and antiemetics	20 (1.62)
Hallucinogens	16 (1.29)
Anticonvulsants	15 (1.21)
Antidepressants	14 (1.13)
Clinical procedures[a,b]	
Number of procedures (CPT), mean (SD)[***]	6.42 (6.37)

Primary (first-listed) procedures (n = 1,048)***		
Other diagnostic procedures *(interview, evaluation, consultation)*	472	(45.04)
Other therapeutic procedures	90	(8.59)
Microscopic examination *(bacterial smear; culture; toxicology)*	41	(3.91)
Laboratory - Chemistry and hematology	37	(3.53)
Medications *(Injections, infusions and other forms)*	22	(2.10)

Listed conditions or procedures that were top 5 or those >1%.
*Includes ICD-9-CM codes for opioid poisoning.
**Includes codes for organic sleep disorder, nonspecific abnormal findings, general symptoms and other unclassified ICD-9-CM codes.
***322 (30.4%) visits had CPT codes missing. ICD-9-CM procedure codes were missing for 999 (95.3%) of visits (not shown here).
[a]N represents number of ED visits for primary diagnosis and procedures.
N represents number of diagnosis for any-listed diagnosis.
For chronic conditions and multi-drug poisonings, N represents number of diagnosis for those with ≥1 chronic conditions and ≥1 multi-drug poisonings, respectively.
[b]Primary or any-listed diagnosis were identified using HCUP's single-level CCS. Multi-drugs and chronic conditions were identified using ICD-9-CM diagnosis codes. Primary procedures were identified using single-level CPT CCS.
[c]Total of 73 ED visits had a pain-related diagnosis (i.e., musculoskeletal pain, cancer pain, sickle cell anemia, headache, fracture or abdominal pain) in any-listed diagnosis.
[d]One record had ICD-9-CM code for heroin poisoning.

Aim 3B: To identify factors associated with ED visit costs among children with opioid poisonings

Bivariate comparisons of mean ED hospital cost across various sociodemographic, clinical, payer and hospital characteristics is summarized in Table 29 below. Child's age group and gender; intent of poisoning; diagnosis of one or more multi-drugs, multi-injuries and chronic conditions; total number of diagnoses and procedures; disposition status; hospital ownership and teaching status were found to be significantly associated with the cost of opioid poisoning-related ED visits. The weighted mean cost for a pediatric opioid poisoning-related ED visit was estimated to be $1,288.92

(SE = 54.10). Mean cost was higher for teenagers compared to the young children ($1,712.79 vs. $763.34), and for girls compared to boys ($1,391.02 vs. $1,176.20).

Mean cost of ED visits was significantly higher for intentional opioid poisonings in children ($1,835.24 vs. $1,052.76). However, the mean cost did not vary much by the type of opioid involved. Diagnoses of multi-drug poisonings ($1,567.36 vs. $1,181.33), multi-injuries ($1,563.99 vs. $1,154.45), and chronic conditions ($1,652.52 vs. $1,083.60) were associated with a higher mean ED cost. Mean ED costs were also higher for visits with 3 or more diagnosis or performed procedures ($1732.13 and $1756.62, respectively). ED visits that were transferred to another HCF had higher mean cost compared to those routinely treated and released ($1,989.98 vs. $1,056.07).

Mean ED cost of treatment was higher among private hospitals compared to public centers ($1,597.61 vs. $1,293.86), and non-teaching hospitals compared to teaching institutions ($1,389.29 vs. $1,122.97) (Table 29).

Table 29: Mean ED hospital costs by characteristics (in 2012 USD)

Characteristic	**Unweighted cost, (N = 1,048)**		**Weighted cost, (N = 4,584)**	
	Mean	**SE**	**Mean**	**SE**
Total (original costs)[a]	1,318.57	45.13	1,288.92	54.10
Sociodemographic				
Age group (years)*				
≤ 5	768.19	47.16	763.34	56.57
6 - 12	1,122.03	166.73	1,095.13	191.97
13 - 17	1,757.75	67.65	1,712.79	75.52
Gender*				
Male	1,214.13	61.8	1,176.20	60.87
Female	1,411.19	64.94	1,391.02	75.84

Residence				
Urban (Mid to large)	1,357.34	54.50	1,307.40	60.97
Urban (Small to mid)	1,142.32	73.57	1,173.49	83.06
Rural	1,509.63	226.69	1,460.53	209.94
Unknown	682.50	--	682.50	--
Median ZIP Code HH income				
$1 - 38,999	1,272.79	85.27	1,234.95	81.53
$39,000 - 47,999	1,226.63	90.80	1,242.02	100.56
$48,000 - 62,999	1,392.02	91.09	1,338.32	103.41
≥ $63,000	1,336.75	85.43	1,280.25	104.44
Unknown	1,934.93	529.53	1,895.77	495.87
Clinical				
Intent*				
Unintentional	1,066.13	52.34	1,052.76	64.07
Intentional	1,877.04	82.22	1,835.24	88.96
Undetermined	1,743.46	246.03	1,660.20	196.76
Unknown	926.50	134.66	929.76	133.98
Opioid				
Methadone	1,213.00	134.69	1,157.57	134.49
Other prescription opioids	1,323.19	54.97	1,279.02	60.81
Unspecified	1,324.01	89.44	1,338.05	101.00
Multi-drug poisonings*				
No	1,203.66	53.57	1,181.33	59.74
Yes	1,623.55	80.46	1,567.36	91.17
Multi-injuries*				
No	1,178.21	56.51	1,154.45	62.60
Yes	1,607.72	71.43	1,563.99	84.60
≥ 1 Chronic conditions*				
No	1,098.63	55.39	1,083.60	64.16
Yes	1,695.72	72.81	1,652.52	78.01
Number of diagnoses*				
1	805.28	74.05	776.25	72.44
2	1,182.72	76.40	1,130.70	83.35
≥ 3	1,761.96	69.87	1,732.13	81.98
Number of procedures (CPT)*[b]				
1	401.26	42.66	394.75	49.32
2	462.11	51.50	415.33	43.72
≥ 3	1,788.03	69.84	1,756.62	82.71

Disposition*				
Routine	1,054.21	45.11	1,056.07	53.13
Transfers	2,062.97	101.92	1,989.98	104.75
Unknown	1,037.8	274.23	932.35	254.07
Payer and hospital				
Payer				
Medicaid	1,283.79	71.17	1,252.74	72.01
Private	1,369.39	64.80	1,346.36	80.27
Other	1,434.51	256.68	1,331.67	250.57
Uninsured	1,218.97	108.67	1,200.72	116.15
Unknown	1,121.52	115.62	1,107.87	80.62
Hospital location				
Rural	1,435.19	189.89	1,477.88	197.23
Urban	1,309.58	46.38	1,272.62	50.47
Hospital region				
Northeast	1,233.47	109.61	1,220.39	142.22
Midwest	1,164.82	66.64	1,179.25	75.94
South	1,372.3	73.78	1,306.47	79.19
West	1,500.95	122.67	1,536.79	135.90
Hospital ownership*				
Public	1,207.71	148.03	1,293.86	188.16
Private	1,652.53	101.40	1,597.61	102.35
Public or private	1,152.18	45.98	1,137.61	57.62
Hospital teaching status*				
Non-teaching	1,417.59	64.35	1,389.29	69.77
Teaching	1,150.45	52.54	1,122.97	60.47
Hospital trauma level				
Non-trauma or level III	1,354.92	55.38	1,313.88	57.88
Trauma level I or II	1,218.67	73.6	1,227.19	92.65

*p-value <.05. T-test and ANOVA (under the CLT assumption) were used to examine unweighted mean costs. HH = Household.
[a]Total ED hospital costs were missing for 182 (17.4%) visits.
[b]Number of ED procedures were missing or zero for 30.44% of visits.

For the adjusted analyses of ED-related costs, multiple injuries and multiple drug involvement variables were found to be highly correlated ($|r| \geq 0.8$). Multi-injury covariate was removed from further analyses. Also, patient's residence, median ZIP Code level income, disposition status, and

payer constituted ≤2% of missing data. Since the rate of missing values for these variables was low, the missing observations were dropped from further analyses. The initial adjusted model included all covariates from bivariate analyses. However, characteristics that were found to be insignificant in both the bivariate analyses and the initial model were excluded from the final adjusted analyses. Type of opioid involved was included in the final model irrespective of the statistical significance.

Adjusted analyses exhibited a significant association between age group, number of diagnosis and procedures, disposition status, and ED costs. The results from the adjusted model of ED hospital costs are summarized in Table 30. Other things constant, teenagers had 1.39 (95% CI = 1.15 - 1.68) times higher ED costs compared to the young children. The ED costs for opioid poisoning in children increased by 3% (95% CI = 0% - 6%) and 7% (95% CI = 6% - 8%) for every one additional diagnosis or procedure performed in the ED, respectively. ED visits that resulted in a transfer to another HCF had 1.28 (95% CI = 1.09 - 1.50) times higher costs compared to those routinely treated and released. Although hospital region was not significant, hospitals in the South had significantly lower costs by 0.59 (95% CI = 0.38 - 0.92) times compared to hospitals in the Northeast.

Table 30: Adjusted analyses of ED hospital costs

Characteristic	Estimate (β)	SE	Exp (β) (95% CI)	Z	p-value
Intercept	6.126	0.515	--	11.91	<.0001
Sociodemographic					
Age group (years)*					
≤ 5	--	--	--	--	--
6 - 12	0.081	0.157	1.08 (0.80 - 1.48)	0.52	0.605
13 - 17	0.326	0.097	1.39 (1.15 - 1.68)	3.36	0.0008

Gender						
Male	--	--		--	--	--
Female	0.070	0.072	1.07	(0.93 - 1.24)	0.97	0.3321
Clinical						
Intent						
Unintentional	--	--			--	--
Intentional	-0.053	0.088	0.95	(0.80 - 1.13)	-0.6	0.5503
Undetermined	0.121	0.170	1.13	(0.81 - 1.57)	0.71	0.4754
Unknown	-0.073	0.114	0.93	(0.74 - 1.16)	-0.65	0.5179
Opioid						
Methadone	--	--		--	--	--
Other Rx opioids	0.078	0.146	1.08	(0.81 - 1.44)	0.53	0.5941
Unspecified	0.042	0.145	1.04	(0.79 - 1.39)	0.29	0.771
Multi-drug poisonings						
No	--	--		--	--	--
Yes	-0.090	0.070	0.91	(0.80 - 1.05)	-1.29	0.1982
≥ 1 Chronic conditions						
No	--	--		--	--	--
Yes	-0.141	0.103	0.87	(0.71 - 1.06)	-1.36	0.1737
Number of diagnoses*	0.032	0.014	1.03	(1.00 - 1.06)	2.23	0.0261
Number of procedures*	0.066	0.006	1.07	(1.06 - 1.08)	11.5	<.0001
Disposition status*						
Routine	--	--		--	--	--
Transfers	0.246	0.081	1.28	(1.09 - 1.50)	3.06	0.0022
Hospital						
Hospital region						
Northeast	--	--		--	--	--
Midwest	0.166	0.201	1.18	(0.80 - 1.75)	0.83	0.4078
South	-0.527	0.224	0.59	(0.38 - 0.92)	-2.36	0.0185
West	-0.309	0.382	0.74	(0.35 - 1.55)	-0.81	0.4198
Hospital ownership						
Public	--	--		--	--	--
Private	0.170	0.336	1.19	(0.61 - 2.29)	0.51	0.612
Public or private	0.400	0.397	1.49	(0.69 - 3.25)	1.01	0.3135
Hospital teaching status						
Non-teaching	--	--			--	--
Teaching	-0.009	0.372	0.99	(0.48 - 2.06)	-0.02	0.9806

*Type 3 analyses p-value <.05 (Model QIC = 1008.03). Rx = Prescription.

Aim 3C: To examine the characteristics associated with pediatric opioid poisoning inpatient stays

There were a total of 1,877 weighted inpatient stays for opioid poisonings among children and 56.8% had prior ED-related services on record. Table 31 summarizes various characteristics of pediatric opioid poisoning-related inpatient stays. Majority of inpatient stays involved teenagers (63.7%) followed by children 1 to 2 years of age (18.6%), females (55.3%), and Whites (59.4%). Most of these hospitalizations were in children were from medium to large metropolitan areas (67.6%), and ZIP Code areas with median household income less than $48,000 (56.7%).

About 41.7% of the total inpatient stays were due to unintentional poisonings and another 40.5% were due to intentional poisonings. Nearly 55.8% of inpatient stays resulted from other prescription opioid poisonings and 12.7% from methadone. Multi-drug involvement was recorded in 46.3% of total inpatient stays. Nearly 71.9% of inpatient discharges had one or more chronic condition diagnoses, 66.7% had one or more comorbidities, and 62.7% had moderate-to-extreme loss of function and 24.7% had moderate-to-extreme likelihood of dying.

One-third of inpatient stays were transfers from another acute care hospital or HCF (30.3%). About 67.7% resulted in routine discharges and 30.9% were transferred to a short-term hospital, SNF or intermediate care. Medicaid was the most common payer for these hospitalizations (51.7%). A higher proportion of pediatric opioid poisoning inpatient stays were in hospitals in the southern region (36.5%), private non-profit institutions (77.2%), larger hospitals (68.5%), and urban teaching centers (74.8%) (Table 31).

These characteristics were also examined by intent of opioid poisoning as shown in Table 32. Child's age, gender, race and median household income at ZIP Code level; type of opioid involved; presence of multi-drug poisonings, chronic conditions and comorbidities; severity and mortality indices; disposition status; payer and hospital region, ownership and location/teaching status were significantly associated with the intent of pediatric opioid poisoning hospitalizations.

Unintentional poisoning-related hospitalizations were more common among children under 6 years (65.8%), while intentional hospitalizations were common among teenagers (96.3%), and girls (68.8%). Intentional poisoning-related stays had a higher proportion of Whites (60.7% vs. 56.7%) and Hispanics (12.8% vs. 8.5%), and a lower proportion of Blacks (9.7% vs. 16.3%). Unintentional opioid poisoning-related inpatient stays were more common in children from ZIP Code areas with median household income of less than $48,000 (63.8% vs. 48.8%). Methadone was more commonly involved in unintentional poisoning hospitalizations (19.9% vs. 5%), whereas other prescription opioids were commonly involved in intentional poisonings (65.1% vs. 48.6%).

A higher number of intentional opioid poisoning-related hospitalizations were associated with multi-drug involvement (64.2% vs. 24.8%), chronic condition diagnosis (92.7% vs. 48.6%), comorbidities (80.9 % vs. 50.4%), moderate-to-severe loss of function (70.3% vs. 51.9%), and transfers following hospitalization (54.9% vs. 7.3%). However, moderate-to-major likelihood of mortality was higher for unintentional opioid poisoning-related hospitalizations among children (27.6% vs. 19.3%).

Medicaid was the most common payer for unintentional opioid poisoning-related inpatient stays (61.8% vs. 39.8%), while private insurance was the more common source of payment for intentional opioid poisoning-related stays (51.4% vs. 28.6%). Unintentional poisoning admissions were higher in the Northeast hospitals (18.7% vs. 12.1%), in public hospitals (13.6% vs. 7.9%)

and urban teaching institutions (78.6% vs. 71.6%). Intentional opioid poisoning-related hospitalizations were more common in the Midwest hospitals (29% vs. 21%), in private institutions (92.1% vs. 86.4%), and urban non-teaching hospitals (22.4% vs. 15.8%) (Table 32).

Table 33 summarizes the common DRGs, clinical diagnosis and procedures in opioid poisoning-related hospitalizations. In addition to poisoning DRGs, DRGs related to psychoses and depressive neurosis were most common. Opioid poisoning-related hospitalizations had 6 diagnosis on average (range = 1 to 25), while the number of ICD-9-CM procedures ranged from 0 to 15. Substance-related disorder (includes diagnosis of opioid poisoning) was the most frequently recorded diagnosis followed by poisoning by psychotropic drugs, other medications, and mood disorders. Mental health disorders including depression, ADHD, anxiety and depress psychoses, substance-use disorders including tobacco use disorder, cannabis abuse and drug abuse, and asthma were the most common chronic conditions. Mental health and substance use disorders including psychoses, depression, drug abuse and alcohol abuse, other neurological disorders, fluid and electrolyte disorders, chronic pulmonary disease and obesity were the most common comorbidities. Poisonings by benzodiazepines and aromatic analgesics were frequently involved in multi-drug poisonings. Most of the recorded procedures in these inpatient stays were related to respiratory intubation and mechanical ventilation and other therapeutic procedures such as injections or infusions of therapeutic and prophylactic substances (Table 33).

Table 31: Characteristics of pediatric opioid poisoning inpatient stays

Characteristic	All opioid poisonings	
	Unweighted, N (%) (N = 1,334)	Weighted, N (%) (N = 1,877)
Sociodemographics		
Age group (years)		
0 < 1[a]	102 (7.65)	144 (7.66)
1 - 2	245 (18.37)	349 (18.59)
3 - 5	64 (4.80)	92 (4.90)
6 -12	68 (5.10)	97 (5.16)
13 -17	855 (64.09)	1,196 (63.69)
Female	739 (55.40)	1,038 (55.30)
Race		
White	786 (58.92)	1,114 (59.37)
Black	169 (12.67)	240 (12.78)
Hispanic	135 (10.12)	187 (9.94)
Others	106 (7.95)	146 (7.76)
Unknown	138 (10.34)	190 (10.14)
Residence		
Urban (Mid to large)	909 (68.14)	1,269 (67.61)
Urban (Small to mid)	333 (24.96)	472 (25.13)
Rural	90 (6.75)	132 (7.05)
Unknown	2 (0.15)	4 (0.21)
Median ZIP Code HH income		
$1 - 38,999	406 (30.43)	574 (30.60)
$39,000 - 47,999	345 (25.86)	491 (26.14)
$48,000 - 62,999	306 (22.94)	426 (22.69)
≥ $63,000	239 (17.92)	331 (17.65)
Unknown	38 (2.85)	55 (2.91)
Clinical		
Intent		
Unintentional	552 (41.38)	783 (41.71)
Intentional	545 (40.85)	759 (40.45)
Undetermined	113 (8.47)	160 (8.53)
Unknown	124 (9.30)	175 (9.31)
Opioid		
Methadone	169 (12.67)	238 (12.65)
Other prescription opioids	746 (55.92)	1,048 (55.82)

Unspecified opioids	419	(31.41)	592	(31.53)
Multi-drug poisonings	619	(46.40)	870	(46.32)
≥ 1 Chronic conditions	962	(72.11)	1,350	(71.93)
≥ 1 Elixhauser comorbidities	890	(66.72)	1,252	(66.71)
APR-DRG severity index (loss of function)				
Minor	495	(37.11)	699	(37.25)
Moderate	532	(39.88)	748	(39.84)
Major	225	(16.87)	314	(16.75)
Extreme	81	(6.07)	114	(6.07)
No class specified	1	(0.07)	2	(0.10)
APR-DRG mortality risk index (likelihood of dying)				
Minor	1,004	(75.26)	1,412	(75.25)
Moderate	188	(14.09)	266	(14.16)
Major	87	(6.52)	121	(6.44)
Extreme	54	(4.05)	76	(4.06)
No class specified	1	(0.07)	2	(0.10)
Transfer-In				
Not a transfer	926	(69.42)	1,301	(69.31)
Transfer	403	(30.21)	568	(30.26)
Unknown	5	(0.37)	8	(0.43)
Disposition status				
Routine	902	(67.62)	1,271	(67.71)
Transfer	413	(30.96)	579	(30.86)
Death	9	(0.67)	13	(0.67)
Unknown	10	(0.75)	14	(0.75)
Payer and hospital				
Payer				
Medicaid	686	(51.42)	971	(51.73)
Private	529	(39.66)	740	(39.40)
Other	61	(4.57)	86	(4.57)
Uninsured	52	(3.90)	72	(3.85)
Unknown	6	(0.45)	8	(0.44)
Hospital region				
Northeast	198	(14.84)	277	(14.76)
Midwest	355	(26.61)	481	(25.63)
South	463	(34.71)	685	(36.52)

West	318	(23.84)	433	(23.09)
Hospital ownership				
Public	156	(11.69)	241	(12.83)
Non-profit private	1,047	(78.49)	1,450	(77.24)
Proprietary private	131	(9.82)	186	(9.93)
Hospital Bedsize				
Small	117	(8.77)	175	(9.31)
Medium	293	(21.96)	417	(22.22)
Large	924	(69.27)	1,285	(68.47)
Hospital Location and teaching status				
Rural non-teaching	83	(6.22)	129	(6.85)
Urban non-teaching	252	(18.89)	345	(18.39)
Urban Teaching	999	(74.89)	1,403	(74.76)

[a]89 of these children were neonates and 7 children had neonatal abstinence syndrome diagnosis (ICD-9-CM code 779.5). HH = Household.

Table 32: Characteristics of pediatric opioid poisoning inpatient stays by intent

Characteristic	**Unintentional (n = 552),** unweighted n (%)		**Intentional (n = 545),** unweighted n (%)	
Sociodemographics				
Age group (years)*				
0 < 1	83	(15.04)	--	
1 - 2	221	(40.04)	--	
3 - 5	59	(10.69)	--	
6 -12	35	(6.34)	20	(3.67)
13 -17	154	(27.9)	525	(96.33)
Female*	248	(44.93)	375	(68.81)
Race*				
White	313	(56.70)	331	(60.73)
Black	90	(16.30)	53	(9.72)
Hispanic	47	(8.51)	70	(12.84)
Others	44	(7.97)	40	(7.34)
Unknown	58	(10.51)	51	(9.36)

Residence				
Urban (Mid to large)	381	(69.02)	368	(67.52)
Urban (Small to mid)	129	(23.37)	144	(26.42)
Rural	41	(7.43)	32	(5.87)
Unknown	1	(0.18)	1	(0.18)
Median ZIP Code HH income*				
$1 - 38,999	209	(37.86)	124	(22.75)
$39,000 - 47,999	143	(25.91)	142	(26.06)
$48,000 - 62,999	113	(20.47)	130	(23.85)
≥ $63,000	69	(12.5)	135	(24.77)
Unknown	18	(3.26)	14	(2.57)
Clinical				
Opioid*				
Methadone	110	(19.93)	27	(4.95)
Other prescription opioids	268	(48.55)	355	(65.14)
Unspecified opioids	174	(31.52)	163	(29.91)
Multi-drug poisonings*	137	(24.82)	350	(64.22)
≥ 1 Chronic conditions*	268	(48.55)	505	(92.66)
≥ 1 Elixhauser comorbidities*	278	(50.36)	441	(80.92)
APR-DRG severity index (loss of function) *				
Minor loss of function	265	(48.01)	162	(29.72)
Moderate loss of function	157	(28.44)	276	(50.64)
Major loss of function	92	(16.67)	87	(15.96)
Extreme loss of function	38	(6.88)	20	(3.67)
APR-DRG mortality risk index (likelihood of dying)*				
Minor	400	(72.46)	440	(80.73)
Moderate	92	(16.67)	58	(10.64)
Major	33	(5.98)	34	(6.24)
Extreme	27	(4.89)	13	(2.39)
Transfer-In				
Not a transfer	367	(66.49)	398	(73.03)
Transfer	182	(32.97)	146	(26.79)
Unknown	3	(0.54)	1	(0.18)

Disposition*				
Routine	508	(92.03)	237	(43.49)
Transfer	40	(7.25)	299	(54.86)
Death	3	(0.54)	1	(0.18)
Unknown	1	(0.18)	8	(1.47)
Payer and hospital				
Payer*				
Medicaid	341	(61.78)	217	(39.82)
Private	158	(28.62)	280	(51.38)
Other	26	(4.71)	25	(4.59)
Uninsured	25	(4.53)	21	(3.85)
Unknown	2	(0.36)	2	(0.37)
Hospital region*				
Northeast	103	(18.66)	66	(12.11)
Midwest	116	(21.01)	158	(28.99)
South	194	(35.14)	192	(35.23)
West	139	(25.18)	129	(23.67)
Hospital ownership*				
Public	75	(13.59)	43	(7.89)
Non-profit private	427	(77.36)	436	(80.0)
Proprietary private	50	(9.06)	66	(12.11)
Hospital Bedsize				
Small	46	(8.33)	47	(8.62)
Medium	108	(19.57)	118	(21.65)
Large	398	(72.10)	380	(69.72)
Hospital Location and teaching status*				
Rural non-teaching	31	(5.62)	33	(6.06)
Urban non-teaching	87	(15.76)	122	(22.39)
Urban Teaching	434	(78.62)	390	(71.56)

*Chi-square statistic $p<.05$
Results for undetermined or unknown intentionality not shown here. HH = Household.

Table 33: DRGs, clinical conditions and procedures recorded in pediatric opioid poisoning inpatient stays

DRGs/Conditions/Procedures[a,b,c,d]	Unweighted, n (%)
DRGs (n = 1,334)	
918: Poisoning and toxic effects of drugs without MCC	901 (67.54)
917: Poisoning and toxic effects of drugs with MCC	216 (16.19)
885: Psychoses	88 (6.6)
881: Depressive neurosis	32 (2.4)
208: Respiratory system diagnosis with ventilator support (<96 hours)	8 (0.6)
882: Neuroses (except depressive)	8 (0.6)
Clinical conditions	
Number of diagnoses, mean (SD)	6.34 (3.87)
Primary (first-listed) diagnosis (n = 1,334)	
Substance-related disorders*	805 (60.34)
Poisoning by psychotropic agents	159 (11.92)
Poisoning by other medications and drugs	158 (11.84)
Mood disorders	118 (8.85)
Adjustment disorders	9 (0.67)
Any-listed diagnosis (n = 8,451)	
Substance-related disorders*	1,840 (21.77)
Poisoning by other medications and drugs	675 (7.99)
Mood disorders	628 (7.43)
Poisoning by psychotropic agents	464 (5.49)
Residual codes, unclassified**	407 (4.82)
Number of chronic conditions, mean (SD)	1.84 (1.75)
Chronic Conditions (n = 7,223)	
Depressive disorder, NEC	227 (3.14)
Attention-deficit/hyperactivity disorder	126 (1.74)
Tobacco use disorder	121 (1.68)
Cannabis abuse, unspecified	110 (1.52)
Asthma, unspecified	104 (1.44)
Anxiety state, NOS	98 (1.36)
Drug abuse, unspecified	93 (1.29)
Depress psychoses, unspecified	75 (1.04)
Number of Elixhauser comorbidities, mean (SD)	1.16 (1.11)

Elixhauser comorbidities (n = 1,334)		
Drug abuse	292	(21.89)
Psychoses	259	(19.42)
Other neurological disorders	255	(19.12)
Depression	241	(18.07)
Fluid and electrolyte disorders	158	(11.84)
Chronic pulmonary disease	126	(9.45)
Alcohol abuse	70	(5.25)
Obesity	41	(3.07)
Hypertension (uncomplicated and complicated)	29	(2.17)
Deficiency anemias	17	(1.27)
Multi-drug poisonings (in addition to opioids) (n = 4,742)		
Benzodiazepine-based tranquilizers	192	(4.05)
Aromatic analgesics	157	(3.31)
Propionic acid derivatives	69	(1.46)
Antidepressants	67	(1.41)
Hallucinogens	65	(1.37)
Antiallergics and antiemetics	52	(1.10)
Clinical procedures		
Number of procedures, mean (SD)***	0.49	(1.32)
Primary (first-listed) procedures (n = 1,334) ***		
Respiratory intubation and mechanical ventilation	156	(11.69)
Other therapeutic procedures	26	(1.95)

Listed conditions or procedures that were top 5 or those >1%.
MCC = major complications or comorbidities, NEC = not elsewhere classified, NOS = Not otherwise specified.
*Includes ICD-9-CM codes for opioid poisoning.
**Includes codes for organic sleep disorder, nonspecific abnormal findings, general symptoms and other unclassified ICD-9-CM codes.
***1,044 (78.3%) had ICD-9-CM procedure codes missing.
[a]N represents number of discharges for DRGs, Elixhauser comorbidities and primary diagnosis and procedures. But N represents number of diagnosis for any-listed diagnosis.
For chronic conditions and multi-drug poisonings, N represents number of diagnosis for those with ≥1 chronic conditions and ≥1 multi-drug poisonings, respectively.
[b]Primary or any-listed diagnosis identified using HCUP's single-level CCS. Multi-drugs and chronic conditions were identified using ICD-9-CM diagnosis codes. Primary procedures were identified using CPT codes.
[c]Six records had ICD-9-CM code for heroin poisoning.
[d]Only 10 Elixhauser comorbidities were considered for analyses, other comorbidities were recorded for ≤ 10 inpatient stays.

Aim 3D: To identify factors associated with inpatient stay costs among children with opioid poisonings

Bivariate comparisons of mean inpatient stay cost across various sociodemographic, clinical, payer and hospital characteristics is summarized in Table 34. Child's age group, residence location and median household income at ZIP Code level, intent of poisoning, type of opioid involved, involvement of multiple drugs, diagnosis of chronic conditions and Elixhauser comorbidities, total number of diagnosis and procedures, APR-DRG severity and mortality risk indices, disposition status, payer source, and hospital region, ownership and bedsize were found to be significantly associated with the mean cost of opioid poisoning-related inpatient stays in children.

The mean weighted cost for a pediatric opioid poisoning-related inpatient stay was estimated to be $6,633.41 (SE = 630.21). Mean cost was much higher for children under 6 years compared to teenagers ($8,254.42 vs. $5,846.34), and those living in mid-to-large urban areas ($7,401.2). Although mean cost of pediatric opioid poisoning inpatient stays was lower for children from ZIP Code areas with low median household income ($5,021.91), income did not show a linear trend with hospitalization cost.

Compared to intentional opioid poisonings, mean cost of inpatient stays was significantly higher for unintentional opioid poisonings in children ($7,563.64 vs. 5,083.98). However, the mean costs were higher for those with undetermined or unknown intent as well ($7,448.40 and $8,466.77, respectively). Mean inpatient stay cost for methadone poisonings in children was significantly higher compared to other opioid poisonings ($12,390 vs. $5,555.35). Mean costs were also higher for hospital stays with 3 or more diagnosis or performed procedures ($7270.35 and $41,525, respectively). Surprisingly, the mean inpatient cost of opioid poisonings was not higher for those with multi-drug poisonings compared to stays without such diagnosis ($5,275.14 vs. $7,805.43).

However, diagnosis of one or more chronic conditions ($7,642.33 vs. $4,060.12) and Elixhauser comorbidities ($7,608.18 vs. $4,695.81) were associated with a higher mean hospitalization costs. Inpatient stay costs were significantly higher for children with major or extreme loss of function ($8,611.57 and $40,447, respectively), and moderate, major or extreme likelihood of mortality ($7,558.02, $21,395 and $34,996, respectively). Hospitalizations that resulted in transfer to another HCF had a higher mean cost compared to those routinely discharged ($8,246.33 vs. $5,815.38). Mean cost was significantly higher for children that died in the hospital ($14,937) or those with an unknown disposition ($8,220.81).

Pediatric opioid poisoning inpatient stays with private insurance as a source of payment had higher mean cost compared to Medicaid ($7,611.92 vs. $5,972.72). At hospital-level, mean hospitalization cost of treatment for pediatric opioid poisonings was significantly higher among hospitals in the western region ($10,109), among private non-profit hospitals or private proprietary hospitals ($6,995.39 and $5,801.9, respectively) compared to public centers ($5,099.34), and among large institutions compared to small centers ($6,782.31 vs. $5,822.18) (Table 34).

Inpatient stay costs for pediatric opioid poisonings were also compared across Elixhauser comorbidities. Results are summarized in Appendix G. Presence of drug abuse, other neurological disorders, fluid and electrolyte disorders, deficiency anemias, hypertension and obesity were significantly associated with inpatient costs.

Table 34: Mean inpatient hospital costs by characteristics (in 2012 USD)

Characteristic	Unweighted cost (N = 1,332)		Weighted cost (N = 1,874)	
	Mean	SE	Mean	SE
Total (original costs)[a]	6,624.60	613.53	6,633.41	630.21
Sociodemographic				
Age group (years)*				
≤ 5	8,214.04	1,786.25	8,254.42	1,815.03
6 - 12	6,626.64	891.69	6,593.14	886.66
13 - 17	5,862.79	421.33	5,846.34	435.63
Gender				
Male	7,501.30	1,293.11	7,568.76	1,338.17
Female	5,916.96	373.45	5,875.70	334.88
Race				
White	6,764.01	942.34	6,767.80	951.35
Black	4,658.41	412.57	4,640.42	461.98
Hispanic	7,434.65	2,073.44	7,540.30	2,194.15
Others	6,310.79	883.34	6,314.56	921.12
Unknown	7,640.3	1,170.9	7,664.28	795.58
Residence*				
Urban (Mid to large)	7,348.56	884.66	7,401.20	915.55
Urban (Small to mid)	4,805.79	406.11	4,762.74	398.26
Rural	6,261.44	1,116.82	6,189.75	1,072.16
Unknown	2,179.97	203.97	2,113.45	128.89
Median ZIP Code HH income*				
$1 - 38,999	5,054.54	382.03	5,021.91	379.46
$39,000 - 47,999	6,312.23	883.00	6,314.57	887.26
$48,000 - 62,999	9,287.42	2,249.09	9,414.34	2,357.34
≥ $63,000	6,627.32	1,194.83	6,658.68	1,240.82
Unknown	5,015.01	812.43	4,839.01	801.83
Clinical				
Intent*				
Unintentional	7,563.26	1,327.81	7,563.64	1,367.34
Intentional	5,108.61	281.56	5,083.98	287.58
Undetermined	7,381.03	1,331.89	7,448.40	1,326.72
Unknown	8,437.59	2,361.07	8,466.77	2,384.55

Opioid*				
Methadone	12,344.01	3,942.68	12,390.00	4,014.43
Other prescription opioids	5,556.24	451.90	5,555.35	476.85
Unspecified	6,221.89	788.42	6,233.21	777.79
Multi-drug poisoning*				
No	7,776.83	1,109.14	7,805.43	1,127.88
Yes	5,294.52	321.73	5,275.14	327.11
≥ 1 Chronic conditions*				
No	4,031.2	271.45	4,060.12	286.59
Yes	7,631.77	843.11	7,642.33	847.03
≥ 1 Elixhauser comorbidities*				
No	4,701.98	358.53	4,695.81	374.89
Yes	7,591.41	902.68	7,608.18	917.22
Number of diagnoses*				
1	2,299.29	231.35	2,301.42	230.55
2	2,857.85	209.25	2,855.53	209.88
≥ 3	7,259.02	709.49	7,270.35	721.47
Number of procedures[b]*				
1	6,548.98	483.74	6,561.19	490.39
2	10,877.48	1,286.44	10,808.00	1,288.07
≥ 3	40,586.1	8,753.77	41,525.00	8,828.69
APR-DRG severity index (loss of function)*				
No class specified	2,075.64	--	2,075.64	--
Minor	3,140.85	125.76	3,122.97	138.83
Moderate	4,204.38	214.74	4,188.76	225.18
Major	8,617.03	607.72	8,611.57	623.67
Extreme	39,936.31	9,538.57	40,447.00	9,132.29
APR-DRG mortality index (likelihood of dying)*				
No class specified	2,075.64	--	2,075.64	--
Minor	3,805.75	126.09	3,783.16	143.82
Moderate	7,507.92	723.85	7,558.02	761.41
Major	21,007.09	7,497.64	21,395.00	7,900.55
Extreme	34,940.58	7,748.13	34,996.00	7,896.15
Transfer-In				
Not a transfer	6,723.41	822.23	6,734.83	852.71
Transfer	6,432.34	764.62	6,442.92	800.50
Unknown	4,196.75	1,441.09	4,005.52	1,414.78

Disposition*				
Routine	5,823.48	423.58	5,815.38	410.29
Transfer	8,188.41	1,740.5	8,246.33	1,827.45
Death[c]	15,048.13	3,468.5	14,937.00	3,024.70
Unknown	8,223.89	2,607.64	8,220.81	2,202.55
Payer and hospital				
Payer*				
Medicaid	5,966.27	514.85	5,972.72	510.54
Private	7,567.92	1,391.47	7,611.92	1,457.21
Other	7,327.17	1,503.38	7,223.21	1,405.39
Uninsured	5,251.82	1,171.45	5,139.36	1,296.22
Unknown	4,909.94	2,081.8	5,064.08	2,005.40
Hospital region*				
Northeast	6,228.38	558.41	6,222.25	562.46
Midwest	5,988.44	533.02	5,983.36	519.75
South	5,157.01	711.99	5,140.49	706.16
West	9,844.77	2,302.52	10,109.00	2,385.32
Hospital ownership*				
Public	5,275.5	622.73	5,099.34	415.85
Non-profit private	6,925.45	730.77	6,995.39	756.07
Proprietary private	5,826.87	2,132.82	5,801.90	2,192.38
Hospital Bedsize*				
Small	5,938.29	864.63	5,822.18	884.74
Medium	6,420.98	973.82	6,489.36	987.55
Large	6,769.01	817.37	6,782.31	846.05
Hospital Location and teaching status				
Rural non-teaching	3,831.86	395.86	3,782.37	373.20
Urban non-teaching	5,666.92	1,082.68	5,719.06	1,146.96
Urban Teaching	7,104.46	772.74	7,126.32	789.46

*p-value <.05. Wilcoxon rank sum and Kruskal-Wallis tests were used to examine unweighted mean costs. HH= Household.

[a]Total inpatient hospital costs were missing for 20 (1.5%) discharges and these were not included in the mean cost calculation.

[b]These are ICD-9-CM inpatient procedures. The number of procedures were zero or missing for 78.23% of the total stays.

[c]Deaths were recorded for 9 discharges.

For the adjusted analyses of inpatient stay costs, APR-DRG severity index and mortality index were highly correlated ($|r| \geq 0.7$). APR-DRG mortality index was removed from further analyses. Also, patient's residence, median ZIP Code level income, disposition status, severity index and payer constituted ≤2% of missing data. Since the rate of missing values for these variables was low, the missing observations were dropped from further analyses. Race was unknown for 10.4% (138 observations) of the total observations. Race was included in the initial GLM model (making 'unknown race' as one level of the variable), but excluded from the final model due to statistical insignificance. The initial adjusted model included all covariates from bivariate analyses however, characteristics that were found to be insignificant in both the bivariate analyses and the initial model were excluded from the final adjusted analyses. Also, Elixhauser comorbidities were not included in this final model for two reasons. First, presence of one or more chronic conditions was included as an independent variable in the model which allows for risk adjustment. Second, Elixhauser comorbidities and presence of one or more chronic conditions were highly collinear.

Adjusted analyses showed a significant association of inpatient stay costs with ZIP Code level median household income, multi-drug poisonings, number of diagnosis and procedures, severity index, disposition status, payer and hospital region. The results from the adjusted model of inpatient hospital costs are summarized in Table 35.

ZIP Code level median household income of $48,000 to $62,999 was associated with 1.32 (95% CI = 1.08 - 1.61) times higher inpatient stay costs compared to low area-level income. Compared to children under 6 years of age, children 6 to 12 years had 0.38 (95% CI = 0.21 - 0.69) times lower hospitalization costs for opioid poisoning but age was not a significant factor. Also child's residence location was not significant but opioid poisoning-related hospitalization costs of children

in rural areas was 1.64 (95% CI = 1.24 - 2.17) times higher compared to that of children from medium to large urban areas.

Surprisingly, diagnosis of multiple drug poisonings was associated with 0.79 (95% CI = 0.67 - 0.94) times lower inpatient stay costs compared to those without such diagnosis. The inpatient costs for opioid poisoning in children increased by 6% (95% CI = 4% - 8%) and 24% (95% CI = 19% - 29%) for every additional diagnosis or procedure performed during the stay, respectively. Inpatient stays of children with major or extreme loss of function were associated with 2.02 (95% CI = 1.60 - 2.57) times and 3.32 (95% CI = 2.53 - 4.35) times higher costs, compared to minor loss of function. Transfer was associated with 1.24 (95% CI = 1.01 - 1.51) times higher inpatient costs while death had 0.43 (95% CI = 0.27 - 0.69) times significantly lower costs compared to inpatient stays with routine discharge. Death was documented for a small number of discharge records (n = 9), hence this finding should be interpreted with caution.

Private insurance was associated with 1.52 (95% CI = 1.29 - 1.80) times and other insurance had 1.59 (95% CI = 1.14 - 2.20) times higher hospitalization costs for pediatric opioid poisonings compared to Medicaid. Lastly, hospitals in the West had 0.56 (95% CI = 0.37 - 0.86) times significantly lower costs compared to hospitals in the Northeast (Table 35).

Table 35: Adjusted analyses of inpatient hospital costs

Characteristic	Estimate (β)	SE	Exp (β) (95% CI)	Z	p-value
Intercept	8.927	0.531	--	16.81	<.0001
Sociodemographics					
Age group (years)**					
≤5	--	--	--	--	--
6 -12	-0.968	0.109	0.38 (0.21 - 0.69)	-8.88	<.0001
13 -17	-0.267	0.055	0.77 (0.57 - 1.03)	-4.83	<.0001

Residence						
Urban (Mid to large)	--	--		--	--	--
Urban (Small to mid)	0.021	0.053	1.02	(0.83 - 1.25)	0.40	0.6909
Rural	0.495	0.080	1.64	(1.24 - 2.17)	6.18	<.0001
Median ZIP Code HH income*						
$1 - 38,999	--	--		--	--	--
$39,000 - 47,999	-0.221	0.058	0.81	(0.64 - 1.03)	-3.62	0.0003
$48,000 - 62,999	0.275	0.053	1.32	(1.08 - 1.61)	5.19	<.0001
≥ $63,000	0.049	0.075	1.05	(0.84 - 1.32)	0.66	0.5166
Clinical						
Intent						
Unintentional	--	--		--	--	--
Intentional	-0.188	0.060	0.83	(0.64 - 1.08)	-3.15	0.0017
Undetermined	-0.020	0.069	0.98	(0.70 - 1.37)	-0.28	0.7764
Unknown	0.235	0.067	1.27	(0.94 - 1.69)	3.49	0.0005
Opioid						
Methadone	--	--		--	--	--
Other Rx opioids	-0.168	0.049	0.85	(0.70 - 1.03)	-3.41	0.0006
Unspecified opioids	-0.192	0.058	0.83	(0.65 - 1.05)	-3.31	0.0009
Multi-drug poisonings*						
No	--	--		--	--	--
Yes	-0.233	0.056	0.79	(0.67 - 0.94)	-4.13	<.0001
≥ 1 Chronic conditions						
No	--	--		--	--	--
Yes	-0.050	0.071	0.95	(0.73 - 1.24)	-0.70	0.4869
Number of diagnoses*	0.059	0.006	1.06	(1.04 - 1.08)	10.51	<.0001
Number of procedures *	0.217	0.009	1.24	(1.19 - 1.29)	25.14	<.0001
APR-DRG severity index (loss of function)*						
Minor	--	--		--	--	--
Moderate	0.371	0.094	1.45	(1.15 - 1.83)	3.95	<.0001
Major	0.705	0.092	2.02	(1.60 - 2.57)	7.70	<.0001
Extreme	1.199	0.097	3.32	(2.53 - 4.35)	12.32	<.0001
Disposition status*						
Routine	--	--		--	--	--
Transfer	0.214	0.043	1.24	(1.01 - 1.51)	4.94	<.0001
Death	-0.842	0.150	0.43	(0.27 - 0.69)	-5.60	<.0001
Payer and hospital						

Payer*						
Medicaid	--	--		--	--	--
Private	0.420	0.045	1.52	(1.29 - 1.80)	9.32	<.0001
Other	0.461	0.071	1.59	(1.14 - 2.20)	6.46	<.0001
Uninsured	0.260	0.144	1.30	(0.89 - 1.90)	1.80	0.0724
Hospital region*						
Northeast	--	--		--	--	--
Midwest	0.010	0.103	1.01	(0.66 - 1.55)	0.10	0.9242
South	-0.089	0.100	0.92	(0.65 - 1.29)	-0.88	0.3779
West	-0.572	0.093	0.56	(0.37 - 0.86)	-6.17	<.0001
Hospital ownership						
Public	--	--		--	--	--
Non-profit private	-0.293	0.108	0.75	(0.50 - 1.11)	-2.72	0.0065
Proprietary private	-1.735	0.910	0.18	(0.09 - 0.36)	-1.91	0.0567
Hospital Bedsize						
Small	--	--		--	--	--
Medium	0.162	0.086	1.18	(0.74 - 1.86)	1.89	0.0584
Large	-0.449	0.101	0.64	(0.38 - 1.06)	-4.43	<.0001
Hospital Location and teaching status						
Rural non-teaching	--	--		--	--	--
Urban non-teaching	0.219	0.512	1.25	(0.62 - 2.50)	0.43	0.6682
Urban Teaching	-0.377	0.487	0.69	(0.41 - 1.15)	-0.77	0.4391

*Type 3 analysis p-value <.05 (Model QIC = 1562.13).
**Type 3 analysis of age group p-value = 0.0512.
HH = Household and Rx = Prescription.

5.3: Discussion

Characteristics associated with pediatric opioid poisoning ED visits and inpatient stays

After examining the prevalence of pediatric opioid exposures and poisonings and estimating its economic costs to the society, the next step was to explore the characteristics associated with two major components of direct medical costs i.e., ED visits and inpatient stays. The second part of this section highlighted the factors associated with costs of ED visits and hospital stays. To our knowledge, no previous study has examined factors associated with costs of opioid poisonings in

children. Evaluation of pediatric opioid poisonings that result in high costs can help to plan interventions from clinical and economic perspectives.

It is important to note two points before discussing these results. First, ED visits and inpatient stays for Specific Aims 2 and 3 were identified using ICD-9-CM and ICD-10 codes and represent opioid poisonings. Specific Aim 1 characterized all opioid exposures in children including those that did not result in poisonings (i.e., a clinical effect following an exposure). Second, unintentional and intentional opioid poisonings in Specific Aims 2 and 3 were identified using the ICD-9-CM or ICD-10 codes. In Specific Aim 1, intent of exposure was identified using AAPCC definitions which vary from those obtained by ICD codes. For example, assume a teenager misused opioids not with an intent to suicide but to get a high and had subsequent poisoning. This scenario would be recorded as unintentional using ICD codes. However, the same situation would be recorded as intentional in the NPDS by the PC specialist.

There were about 4,584 annual ED visits and 1,877 annual inpatient stays for pediatric opioid poisonings. This indicates that nearly 41% of ED visits for opioid poisonings in children resulted in hospitalization. This finding is similar to another study that examined opioid exposures and poisonings in children.[31] Opioid poisoning-related ED visits and inpatient stays mostly involved teenagers and children 1 to 2 years of age. This validates our results from Specific Aim 1 wherein we found high prevalence of opioid exposures and poisonings in these age groups. Furthermore, hospitalizations related to pediatric opioid poisonings were higher among Whites. Rates of opioid prescribing in adults and use and misuse of opioids in adolescents and adults is reported to be higher among Whites compared to other racial groups.[139–141] Hence it can be postulated that there is higher availability of opioids in these households resulting in more exposures in children at home. Interestingly, opioid poisoning-related hospitalizations occurred more frequently among

children from areas with low income. Two prior studies that examined drug poisoning ED visits reported similar results but these studies were not specific to children.[56,57] This finding indicates some association of severe opioid poisonings and socioeconomic status among children and should be investigated further.

Pediatric opioid poisoning-related ED visits and inpatient stays were more frequently in hospitals located in the South and in private institutions. Similar hospital characteristics were reported by some previous studies that examined drug or opioid poisoning-related ED visits across all age groups.[50,56,57,67] Opioid poisoning-related inpatient stays in children were also more commonly treated in large hospitals and teaching institutions. These hospital characteristics coincide with the national pattern of hospital stays. All-stay hospital admissions are reported to be higher in the South, in large hospitals, and in private and teaching institutions.[142–144]

Three out of every 5 opioid poisoning hospitalizations in children were recorded to have moderate-to-extreme loss of function i.e., high severity-of-illness. Respiratory intubation and mechanical ventilation were performed in about 12% of inpatient stays. Although there is no direct comparison for these results, Burghardt et al. found that about 70% of children with admissions following opioid exposures and poisonings had a significant injury (i.e., moderate-to-severe effects).[31] The current results reiterate our previous findings (from Specific Aim 1) that opioid poisoning in children is associated with significant morbidity. Additionally, over one-fourth of ED visits and inpatient stays related to opioid poisonings in children resulted in transfer to short-term stay facilities. We found that over 20% of children with opioid poisoning hospitalizations had major-to-extreme loss of function which may have necessitated transfer to short-term or intermediate care. Also, psychiatric care admissions frequently occur after an opioid poisoning among teenagers, particularly after a suspected suicide.[43] We found that 15.3% of teenagers were admitted

to psychiatry care service following an opioid exposure (Specific Aim 1) while Zosel et al. reported that 35.3% of teenagers had psychiatric admission after a suspected suicidal drug exposure.[43]

We found that intentional opioid poisoning-related ED visits and admissions were more common among teenagers and females. Teenagers often intentionally use opioids to self-harm and have severe opioid poisonings leading to ED visits and subsequent hospital admissions.[43] Adolescent girls particularly are shown to be involved in such drug-taking behavior.[42,43,57] One study using recent data from NSDUH reported that among adolescents more females were nonmedical users of opioids during the past year.[139] Previous research has also found female predominance in intentional opioid exposures resulting from suicide attempts.[43] These gender differences among adolescents can partly be attributed to the high prevalence of behavioral health conditions such as depression among teenage girls.[66]

Multiple drugs, particularly benzodiazepines and aromatic analgesics, were involved in 49.3% and 64.2% of intentional opioid poisoning-related ED visits and inpatient stays in children. One study that examined opioid exposures and poisonings in teenagers reported that over half had involvement of more than one substance.[43] Another study found benzodiazepines as the commonly involved substance in prescription opioid poisoning-related ED visits and inpatient stays but these analyses were not limited to children.[55] Poisonings by aromatic analgesics include acetaminophen poisonings. Hence, the ED visits or inpatient stays with diagnosis of poisonings by opioids and poisonings by aromatic analgesics may suggest involvement of combination opioids. Past studies have reported that co-diagnosis of poisonings by aromatic analgesics for such cases is not completely recorded since the opioid effects are more acute and prominent.[145] Additionally, 80.9% of hospital discharges for intentional pediatric opioid poisonings in the current analyses indicated presence of comorbidities such as depression, psychoses, drug abuse and other neurological

disorders. Co-occurrence of these mental health conditions with substance use disorders is reported to be common among teenagers. Kline-Simon et al. reported that among adolescents with substance use disorders, 58.2% had at least one psychiatric comorbidity diagnosis in the electronic health record.[66]

Interestingly, Medicaid was the more common payer for unintentional opioid poisoning ED and hospital visits while private insurance was more common among intentional opioid poisoning ED and hospital visits in children. The literature on payer source for opioid or drug related poisonings has been inconclusive, and none of the past studies have inspected the source of payment for children by intent of poisoning. These findings may indicate that unintentional opioid poisoning-related hospitalizations were higher among children from lower socioeconomic status as most of these children had Medicaid coverage. Moreover, opioid poisoning-related hospitalizations especially for unintentional poisonings were found to be higher among children from lower area-level income (above). Access to private insurance may indicate higher socioeconomic status among children with intentional opioid poisonings.

Factors associated with ED and inpatient costs among children with opioid poisonings

Next, the association of various factors with mean ED and inpatient costs for pediatric opioid poisonings was examined. A few other studies have investigated ED or inpatient costs of opioid poisonings. However, these studies have not specifically examined factors that are associated with high cost of treatment or they were not limited to the pediatric population. This makes it harder to compare cost results from the current study.

Teenagers had significantly greater ED costs compared to children under the age of 6 years. Such age-specific cost differences were not significant for inpatient stays. Teenagers presenting to the

ED may have medically more complicated opioid poisonings requiring more treatment and services. In the earlier part of the study, we found that teenagers frequently engaged in intentional opioid exposures and poisonings, had multiple product involvement and often presented with mental health-related comorbidities and severe poisonings. These factors may have contributed to the high costs of emergency treatment. However, it is possible that the management of opioid poisonings may not vary by age once an ED visit reaches the threshold for subsequent admission.

Children from areas with higher income had higher hospitalization costs for opioid poisonings. It would be expected that children from low income areas would have lower health outcomes and consequently high cost of care but such an association was not observed for opioid poisonings in children. We found more intentional opioid poisoning-related inpatient stays among children from high income areas. It can be postulated that children from high income areas presented with more severe or medically complicated opioid poisonings thus resulting in higher costs of care.

Severity-of-illness showed a significant linear trend with inpatient costs for opioid poisonings in children. This is an expected finding as high severity-of-illness corresponds to higher loss of body function which may necessitate more care and management in the hospital resulting in higher costs. Surprisingly, children with involvement of multiple drugs had lower hospitalization costs. Similar findings were reported by another study that found inpatient costs of opioid poisonings with benzodiazepines to be lower than costs of opioids only hospitalizations.[55] Involvement of co-ingestants in opioid poisonings would be expected to result in more medical complications and consequently higher cost of care. One possible explanation for this unexpected finding is that the association of multi-drug opioid poisonings with treatment costs may depend on the potency of the opioid agent itself. Future costs studies should further investigate opioid poisonings with multiple drug involvement. Additionally, children transferred to short-term stay facilities had

significantly greater ED and inpatient costs. Transfer to short-term or intermediate care facilities may indicate that these poisonings were medically complicated or severe and have high cost of care during ED visit or inpatient stay.

Inpatient costs were greater for children with private or other insurance compared to those with Medicaid. Although not specific to pediatric opioid poisonings, the mean cost per hospital stay was found to be higher for patients with private insurance compared to those with Medicaid.[143] This may point towards higher costs of care for non-public insurance beneficiaries.

As for hospital characteristics, hospitals in the West had higher mean inpatient costs for pediatric opioid poisonings. This same pattern has been observed for all-stay hospitalizations nationally.[144] Interestingly, after controlling for disposition status and number of diagnoses in the adjusted analyses, hospitals in the West were associated with lower inpatient costs compared to the Northeast. At least one prior study has reported a significant association between hospital region and disposition status.[146] We found that opioid poisoning-related hospitalizations in the West had a higher proportion of transfers (34.2%) compared to hospitals in the Northeast (26.5%). Moreover, opioid poisoning-related discharges in the West also had a slightly higher mean number of diagnoses compared to hospitals in the Northeast. Lastly, larger hospitals had significantly lower inpatient stay costs for opioid poisonings in children compared to smaller hospitals. Although literature on the association of hospital bedsize and costs has been inconclusive, in theory hospitals with a higher number of beds are thought to have lower average cost per patient due to economies of scale.[69]

Several limitations exist, particularly the biases and confounding integral to a retrospective study design. First, summary CCR data were used for ED analyses from the 2003 HCUP preliminary

report. These CCRs may have changed since 2003 but there is no other updated data for converting ED charges to costs. Second, some limitations are inherent with the use of administrative databases. Opioid poisonings and intentionality were identified using the ICD-9-CM codes. Although ICD-9-CM poisoning diagnosis codes are reported to have a high positive predictive value for identifying opioid poisonings cases,[147] potential coding errors are possible with the use of secondary databases. Third, HCUP data are discharge-level and not patient-level hence repeated ED visits or admissions could not be linked in the databases used. Such readmissions may be common among teenagers with intentional poisonings, therefore it is possible that children may be counted more than once in the current analyses. But the goal was to estimate the economic costs of opioid poisonings and examine the factors associated with costs. So repeated admissions, if any, should have a small impact on the results.

Chapter 6: Conclusions and Future Research

Conclusions

Our study examined the epidemiology of medicinal opioid poisonings in children using PC data and the associated economic burden to society using national ED, hospital admission and mortality data. We conclude that opioid exposures and poisonings in children continue to occur. Although the prevalence of pediatric opioid exposures and poisonings has declined over the 5-year study period, the magnitude of annual decreases has been low. Morbidity associated with opioid exposures and poisonings in children remains high. We documented a total of 83,418 opioid exposures in children and about 39,202 ED visits and hospital admissions from 2010 to 2014. We also identified 123 opioid poisoning-related deaths in children annually.

One common theme across the study results using different data sources was that the epidemiology of opioid exposures and poisonings differs significantly by age. Opioid exposures and poisonings were more prevalent, but less severe and mainly accidental in younger children. Exposures in adolescents were more likely to be intentional and severe, and were more common in girls. Adolescents also had higher health care use and greater ED costs. Exposures to buprenorphine and methadone in children were more likely to result in negative medical outcomes. Development of educational efforts and targeted prevention strategies particularly those that are age- and agent-specific is warranted.

Quantifying health care resource use and costs associated with pediatric opioid poisonings can help decision makers to understand the economic trade-offs in planning interventions. Our study estimated a total economic burden of pediatric opioid poisonings at $230.8 million of which $21 million were attributed to direct medical costs annually. Given such societal spending on opioid poisonings in children, investment in primary prevention strategies such as education and counselling of providers and caregivers in order to promote adoption of safe use, storage and disposal of opioids may be worthwhile.

Naloxone was the common antidote used for severe opioid poisonings in children. Take-home naloxone programs have increased access to naloxone and have shown to be a successful strategy to prevent opioid poisoning-related morbidity and mortality among adults.[148] Opioid poisoning in children is acute and can be fatal if not treated promptly. Exploring a similar naloxone distribution strategy for children may be valuable. To provide rough estimates of one such strategy from an economic perspective, consider distribution of naloxone to adults on long-term opioid therapy. Assuming that about 9.6 to 11.5 million adults are prescribed long-term opioid therapy based on a prior CDC report[149] and the price of prescription naloxone injection at $18.7 (average wholesale price (AWP) obtained from Lexicomp online resource), the cost of distributing naloxone would be approximately at $179 to $215 million per year. This could roughly result in cost-savings of $15 to $51 million to society.

Our study reported a high prevalence of opioid exposures and poisonings among young children. We also found buprenorphine and methadone pediatric exposures to be highly associated with negative medical outcomes. These findings may provide a good starting point for exploring clinically and economically feasible strategies that would benefit children from such naloxone distribution program.

Future Research

In addition to addressing the weaknesses of the current study, future research can use results from this exploratory study to generate hypotheses related to individual-level sociodemographic and clinical factors as well as area-level socioeconomic factors that were found to be associated with opioid exposures and poisonings in children. The current study could not examine the correlation of opioid exposures in children and opioid use and misuse in the family. Past research has established a link between pediatric opioid exposures and poisonings and adults' opioid availability.[31,38] But literature on the correlation of opioid exposures in children and parental or caregiver opioid misuse, abuse or addiction is sparse. One study conducted in Iran reported that a history of addiction in the family was indirectly correlated with drug exposures in children.[150] Future studies can examine such association of adults' opioid use and misuse with opioid exposures in children. This would aid in identifying children at risk for future opioid exposures and poisonings. It would also be interesting to explore the impact of CDC's new pain management guidelines on the prevalence of pediatric opioid exposures and poisonings. We also found differences in the rate of pediatric opioid exposures by state. Further research can investigate the factors related to such differences at state-level. Lastly, future work can incorporate a complete assessment of health care resource use and economic burden associated with opioid poisonings in children by monitoring long-term outcomes and costs.

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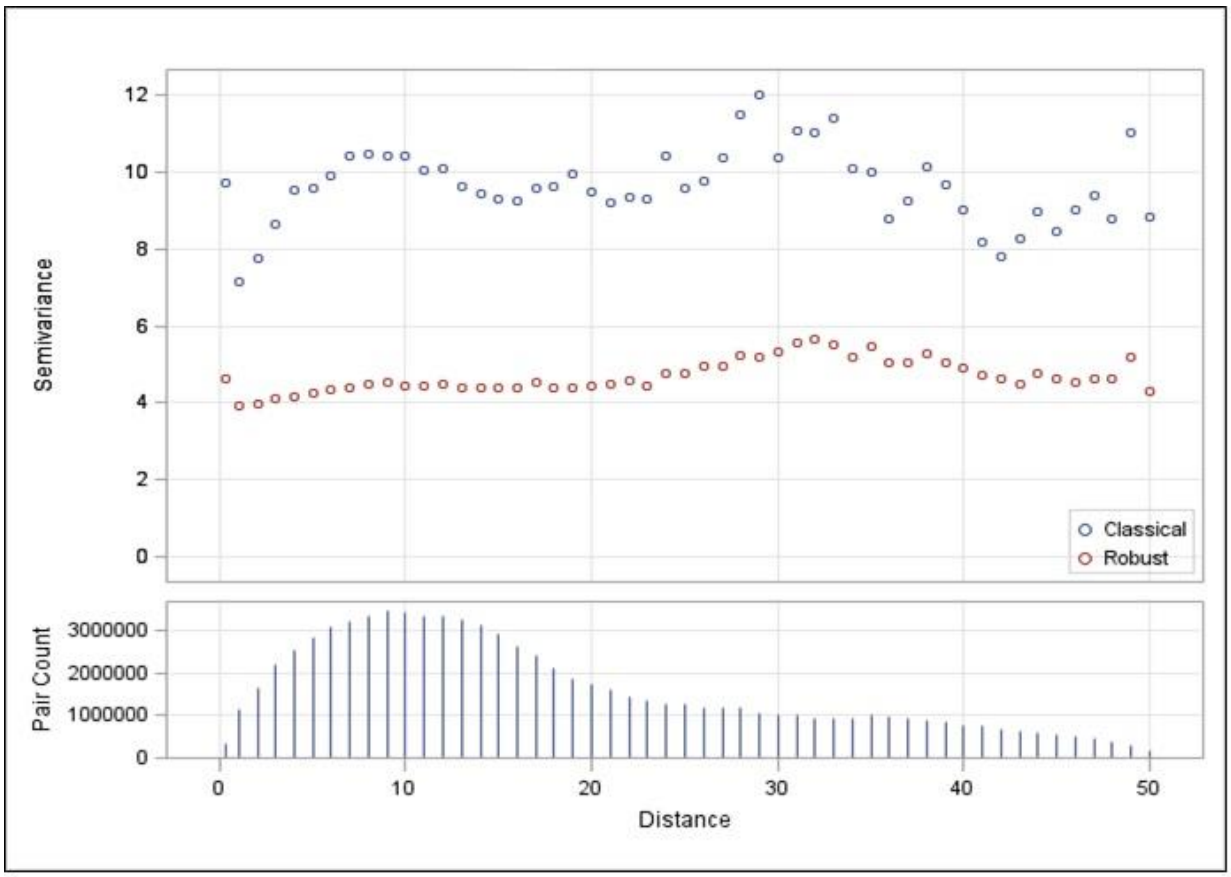
Appendix A

Table 36: List of Opioids included in Specific Aim 1 analyses

Acetaminophen (APAP) combinations
Acetaminophen with codeine
Acetaminophen with hydrocodone
Acetaminophen with other narcotics or narcotic analogs
Acetaminophen with oxycodone
Acetaminophen with propoxyphene
Acetylsalicylic acid (ASA) combinations
Acetylsalicylic acid with codeine
Acetylsalicylic acid with other narcotics or narcotic analogs
Acetylsalicylic acid with oxycodone
Acetylsalicylic acid with propoxyphene
Nonsteroidal anti-inflammatory drug (NSAIDs) combinations
Ibuprofen with hydrocodone
Opioids
Alfentanil
Buprenorphine
Butorphanol
Codeine
Difenoxin
Dihydrocodeine
Fentanyl
Hydrocodone alone or in combination (excluding combination products with APAP, ASA or ibuprofen)
Hydromorphone
Levorphanol
Meperidine
Methadone
Morphine
Nalbuphine
Oxycodone alone or in combination (excluding combination products with APAP or ASA)
Oxymorphone
Pentazocine

Propoxyphene
Remifentanil
Sufentanil
Tapentadol
Tramadol
Other or unknown narcotics
Cough and cold (CNC) products
APAP and codeine combinations with decongestant and/or antihistamine without phenylpropanolamine (PPA)
APAP and other opioid combinations with decongestant and/or antihistamine without PPA
APAP, ASA and opioid combinations with decongestant and/or antihistamine without PPA
APAP, PPA, and codeine combinations with decongestant and/or antihistamine
APAP, PPA, and other opioid combinations with decongestant and/or antihistamine
APAP, ASA, PPA and opioid combinations with decongestant and/or antihistamine
ASA and codeine combinations with decongestant and/or antihistamine without PPA
ASA and other opioid combinations with decongestant and/or antihistamine without PPA
ASA, PPA and codeine combinations with decongestant and/or antihistamine
ASA, PPA and other opioid combinations with decongestant and/or antihistamine
Antihistamine and/or decongestant with PPA and codeine
Antihistamine and/or decongestant with PPA and other opioid
Antihistamine and/or decongestant with codeine without PPA
Antihistamine and/or decongestant with other opioid without PPA
Non-ASA salicylates, PPA and opioid combinations with decongestant and/or antihistamine
Non-ASA salicylates and opioid combinations with decongestant and/or antihistamine without PPA
Gastrointestinal (GI) agents
Antidiarrheals: diphenoxylate and atropine containing
Antidiarrheals: paregoric containing
Antidiarrheals: other narcotic containing

Appendix B



Y-axis represents semivariance in observed pairs of 5-digit ZIP Code areas and X-axis represents distance bins.

Figure 11: Semivariogram for 5-digit ZIP Code data (Specific Aim 1D)

Appendix C

Cost-to-Charge Ratios (CCR) for ED visits

HCUP 2003 preliminary report provides ED CCR based on certain hospital characteristics including hospital ownership, location and volume (or bedsize) as listed in Table 37. However, the 2012 NEDS has different categories for hospital ownership and location as listed in Tables 38 and 39. Additionally, hospital bedsize is not included in the NEDS. Hence certain mean CCR provided in the HCUP report were combined for the current analyses. For example, CCR for hospital in urban areas with private, collapsed (i.e., proprietary or PNFP) ownership was calculated using the mean CCR and the sample size provided in the HCUP report as shown below. Table 40 lists the CCR used for the current analyses.

CCR for Urban, private collapsed (proprietary or PNFP):

$$\left[\frac{185}{185+46}\right] * 0.552 \quad + \quad \left[\frac{46}{185+46}\right] * 0.395 \quad = \quad 0.521$$

Table 37: ED hospital mean CCR provided by HCUP

	N of hospitals	Weighted mean CCR
Rural, low volume, Government	41	0.570
Rural, low volume, PNFP or Prof	33	0.571
Rural, Non-low volume, Government	70	0.527
Rural, Non-low volume, PNFP	110	0.529
Rural, Non-low volume, Prof	42	0.361
Urban, Government	30	0.457

Urban, PFNP	185	0.552
Urban, Prof	46	0.395
All hospitals	556	0.514

PFNP= Private not-for-profit, Prof = for profit (proprietary)

Table 38: Hospital ownership categories provided in NEDS 2012

Hospital ownership
Government or private (collapsed)
Government
Private, not-for-profit
Private, proprietary
Private, not-for-profit or proprietary (collapsed)

Table 39: Hospital location categories provided in NEDS 2012

Hospital Location
Large metropolitan (urban)
Small metropolitan (urban)
Micropolitan (urban)
Small metropolitan and micropolitan, collapsed (urban)
Large and small metropolitan, collapsed (urban)
Not metropolitan or micropolitan (rural)
Micropolitan and non-urban, collapsed (rural)

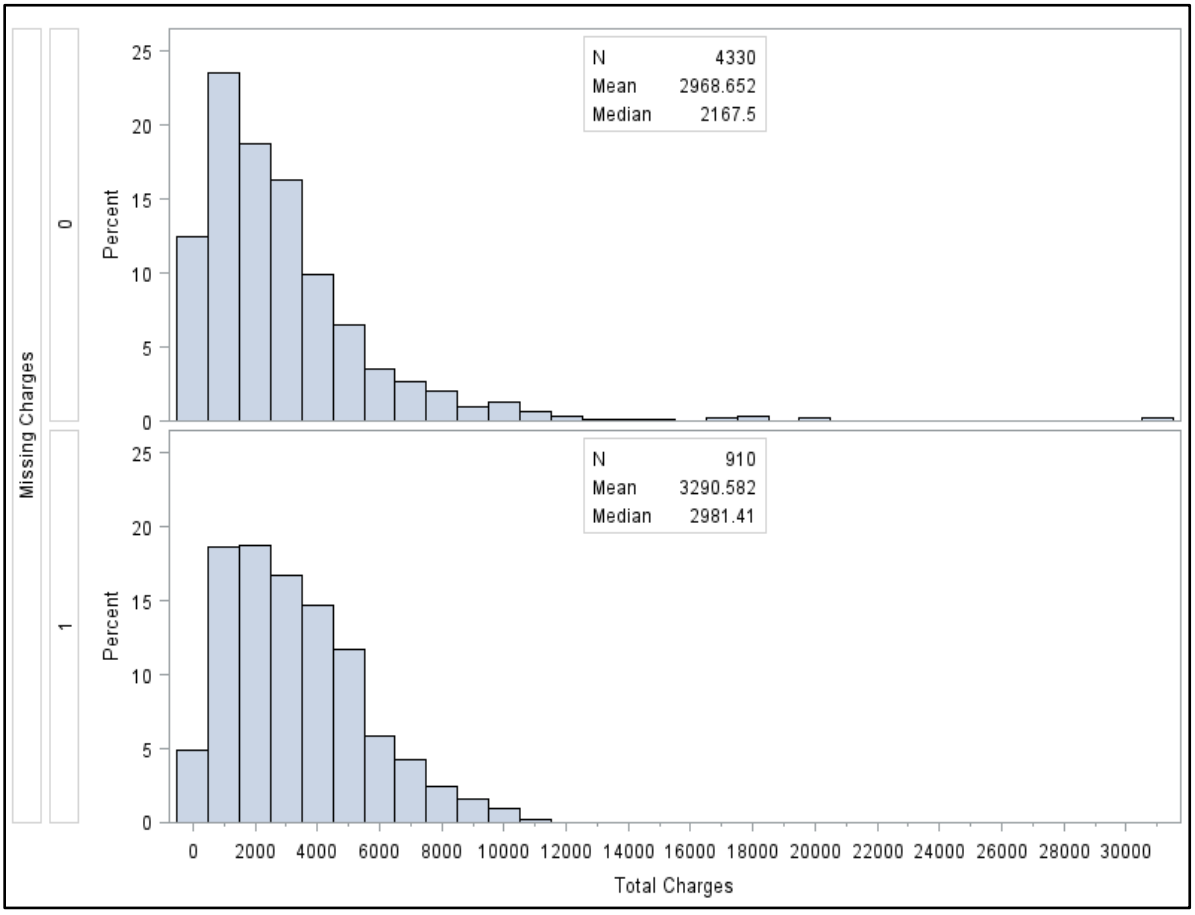
Table 40: ED CCR used in the current analyses

	Weighted mean CCR
Rural, Government*	0.543
Rural, PNFP	0.529
Rural, Proprietary	0.361
Rural, PNFP or proprietary (collapsed)	0.571
Rural, Government or private (collapsed)*	0.570
Urban, Government	0.457
Urban, PFNP	0.552
Urban, Proprietary	0.395
Urban, PNFP or proprietary (collapsed)*	0.521
Urban, Government or private (collapsed)*	0.419

*Calculated CCR

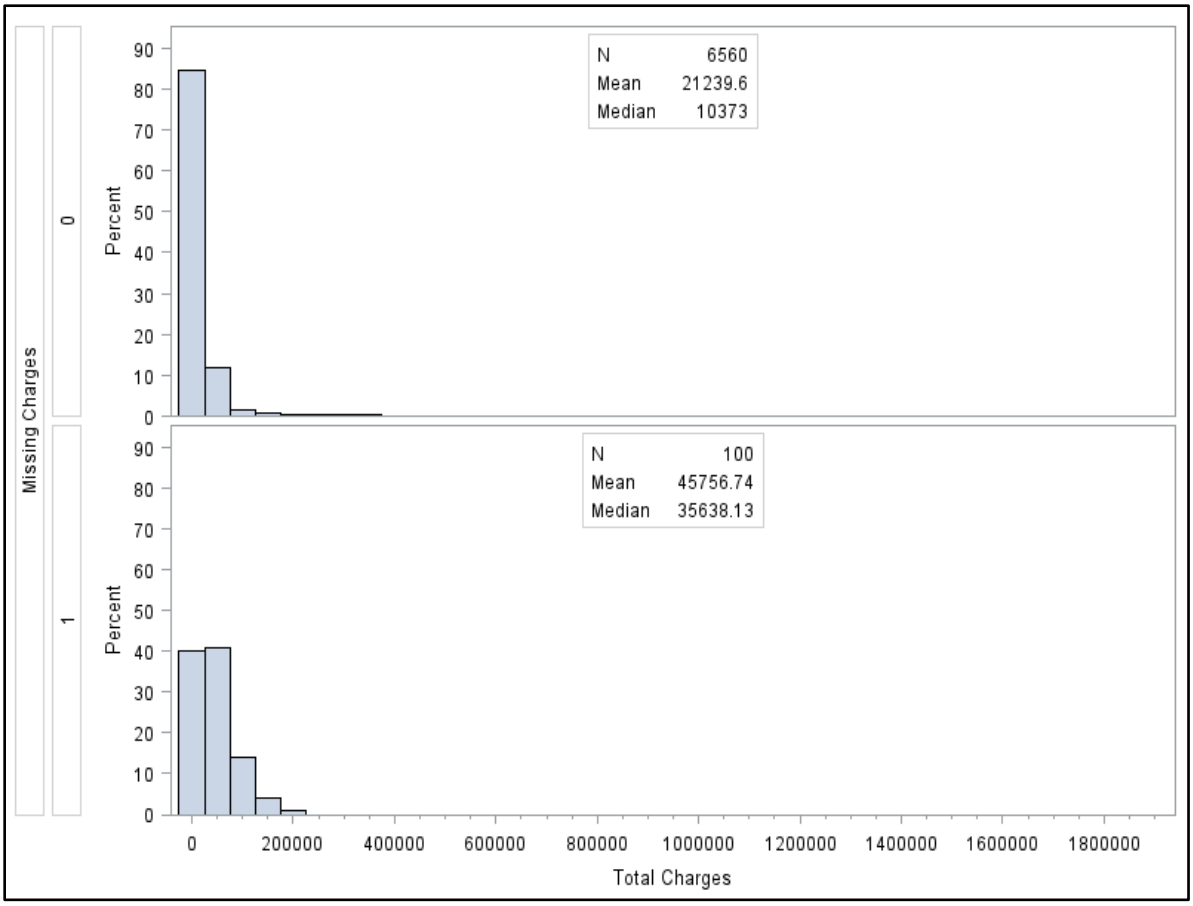
PFNP= Private not-for-profit.

Appendix D



N represents sample size from 5 imputed datasets.
Missing charges = 0 correspond to non-missing observations.
Missing charges = 1 correspond to missing observations that were imputed.

Figure 12: Distribution of ED missing and non-missing charges



N represents sample size from 5 imputed datasets.
Missing charges = 0 correspond to non-missing observations.
Missing charges = 1 correspond to missing observations that were imputed.

Figure 13: Distribution of inpatient missing and non-missing charges

Appendix E

Table 41: ICD-9-CM codes for identifying multi-drug involvement

ICD-9-CM code	Description
960	Poisoning by antibiotics
961	Poisoning by other anti-invectives
962	Poisoning by hormones and synthetic substitutes
963	Poisoning by primarily systemic agents
964	Poisoning by agents primarily affecting blood constituents
965	Poisoning by analgesics antipyretics and antirheumatics
966	Poisoning by anticonvulsants and anti-parkinsonism drugs
967	Poisoning by sedatives and hypnotics
968	Poisoning by other central nervous system depressants and anesthetics
969	Poisoning by psychotropic agents
970	Poisoning by central nervous system stimulants
971	Poisoning by drugs primarily affecting the autonomic nervous system
972	Poisoning by agents primarily affecting the cardiovascular system
973	Poisoning by agents primarily affecting the gastrointestinal system
974	Poisoning by water mineral and uric acid metabolism drugs
975	Poisoning by agents primarily acting on the smooth and skeletal muscles and respiratory system
976	Poisoning by agents primarily affecting skin and mucous membrane ophthalmological otorhinolaryngological and dental drugs
977	Poisoning by other and unspecified drugs and medicinal substances
978	Poisoning by bacterial vaccines
979	Poisoning by other vaccines and biological substances

Appendix F

Table 42: List of Elixhauser comorbidities

Acquired immune deficiency syndrome (AIDS)
Alcohol abuse
Deficiency anemias
Rheumatoid arthritis/collagen vascular diseases
Chronic blood loss
Congestive heart failure
Chronic pulmonary disease
Coagulopathy
Depression
Diabetes, uncomplicated
Diabetes with chronic complications
Drug abuse
Hypertension, uncomplicated and complicated
Hypothyroidism
Liver disease
Lymphoma
Fluid and electrolyte disorders
Metastatic cancer
Other neurological disorders
Obesity
Paralysis
Peripheral vascular disorders
Psychoses
Pulmonary circulation disorders
Renal failure
Solid tumor without metastasis
Peptic ulcer disease excluding bleeding
Valvular disease
Weight loss

Appendix G

Table 43: Mean inpatient hospital costs (in 2012 USD) by Elixhauser comorbidities

Selected Elixhauser comorbidity	Weighted cost (N = 1,874)	
	Mean	SE
Psychoses		
No	6939.53	769.61
Yes	5365.91	447.61
Alcohol abuse		
No	6648.09	656.77
Yes	6356.30	981.10
Deficiency anemias*		
No	6321.44	602.05
Yes	31206.00	16102.00
Chronic pulmonary disease		
No	6749.20	688.03
Yes	5512.05	615.46
Depression		
No	7042.11	758.63
Yes	4778.48	298.63
Drug abuse*		
No	6626.71	790.63
Yes	6657.45	535.69
Hypertension[a]*		
No	6431.81	640.19
Yes	16026.00	5025.38
Fluid and electrolyte disorders*		
No	5194.58	309.34
Yes	17820.00	4861.85
Other neurological disorders*		
No	6649.19	764.17
Yes	6567.47	811.32

Obesity*		
No	6582.94	642.33
Yes	8217.44	1295.08

*p-value <.05.
[a]Includes uncomplicated & complicated.

Appendix H

Table 44: Sociodemographic and clinical characteristics of sample for Aim 1D

Characteristic, n (%)	Total opioid exposures (N = 83,418)	Sample for Aim 1D (n = 43,701)
Age group		
0 < 1	5,042 (6.04)	2,881 (6.59)
1 - 2	32,204 (38.61)	18,736 (42.87)
3 - 5	13,744 (16.48)	9,370 (21.44)
6 - 12	8,819 (10.57)	6,361 (14.56)
13 - 17	23,245 (27.87)	6,130 (14.03)
Unknown (child)	364 (0.44)	223 (0.51)
Gender		
Female	42,022 (50.38)	20,859 (47.73)
Male	41,081 (49.25)	22,692 (51.93)
Unknown	315 (0.38)	150 (0.34)
Opioid type involved		
Single substance	40,651 (48.73)	19,620 (44.90)
APAP combinations	37,472 (44.92)	19,555 (44.75)
CNC combinations	5,406 (6.48)	4,182 (9.57)
Other combinations	1,028 (1.23)	554 (1.27)
Route		
Ingestion	82,322 (98.69)	43,371 (99.24)
Other	1,602 (1.92)	382 (0.87)
Unknown	375 (0.45)	71 (0.16)
Chronicity		
Acute	77,602 (93.03)	41,396 (94.73)
Non-acute	4,609 (5.53)	2,111 (4.83)
Unknown	1,207 (1.45)	194 (0.44)

Reason		
Unintentional	61,206 (73.37)	38,989 (89.22)
Intentional	20,064 (24.05)	3,723 (8.52)
Adverse reaction	1,088 (1.3)	702 (1.61)
Other	227 (0.27)	33 (0.08)
Unknown	833 (1)	254 (0.58)
Scenario		
Therapeutic error	15,666 (18.78)	12,570 (28.76)
Storage/Access	2,917 (3.5)	1,917 (4.39)
Other	778 (0.93)	419 (0.96)
Unknown	64,458 (77.27)	29,014 (66.39)
Related effect		
Any	27,846 (33.38)	8,039 (18.40)
Neurological	21,544 (25.83)	5,890 (13.48)
Gastrointestinal	7,751 (9.29)	2,438 (5.58)
Cardiovascular	5,136 (6.16)	297 (0.68)
Ocular	3,126 (3.75)	527 (1.21)
Respiratory	2,863 (3.43)	352 (0.81)
Other	4,275 (5.12)	1,180 (2.7)
Performed therapy		
Decontamination	19,571 (23.46)	11,748 (26.88)
Naloxone	5,300 (6.35)	548 (1.25)
Other therapy	14,591 (17.49)	2,608 (5.97)
HCF		
None	30,093 (36.07)	26,121 (59.77)
T/E and R	25,983 (31.15)	8,573 (19.62)
Critical care	7,097 (8.51)	778 (1.78)
Non-critical care	6,122 (7.34)	1,090 (2.49)
Psychiatric care	3,658 (4.39)	232 (0.53)
Other	9,836 (11.79)	6,491 (14.85)
Unknown	629 (0.75)	416 (0.95)
Outcome		
No effect	32,944 (39.49)	18,912 (43.28)
Minor	32,443 (38.89)	17,907 (40.98)
Moderate	7,709 (9.24)	971 (2.22)
Major	1,368 (1.64)	47 (0.11)
Death	111 (0.13)	6 (0.01)
Unknown	8,843 (10.6)	5,858 (13.4)
Poisoning	43,503 (52.15)	19,990 (45.74)

Vita

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