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Prevalence of polypharmacy and associated adverse outcomes and risk factors among children with asthma in the USA: a cross-sectional study

Luyu Xie ,[1,2] Andrew Gelfand,[3] Caitlin C Murphy,[4] M Sunil Mathew,[1,2] Folefac Atem ,[2,5] George L Delclos,[6] Sarah Messiah [1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Sarah Messiah;
Sarah.E.Messiah@uth.tmc.edu

ABSTRACT

Objective To estimate the prevalence of polypharmacy, identify risk factors and examine related adverse outcomes in the US children with asthma.

Design, setting and participants This population-based, cross-sectional study included 1776 children with asthma from the 2011–2020 National Health and Nutrition Examination Surveys.

Exposures Polypharmacy is defined as taking ≥2 medications concurrently for ≥1 day over the past 30 days.

Main outcomes and measures (1) Weighted prevalence estimates of polypharmacy in children with asthma; (2) asthma attacks and emergency department (ED) visits.

Results The estimated prevalence of polypharmacy in the US children with asthma was 33.49% (95% CI 31.81% to 35.17%). 15.53% (95% CI 14.31% to 16.75%), 12.63% (95% CI 11.37% to 13.88%) and 5.33% (95% CI) of participants were taking 2, 3–4, and 5 prescription medications, respectively. In addition to asthma medications, the most common sources of polypharmacy included antihistamines (20.17%, 95% CI 16.07% to 24.28%), glucocorticoids (16.67%, 95% 12.57% to 20.78%), and anti-infectives (14.28%, 95% CI 10.29 to 18.28). Risk factors for the increased number of medications included age 5–11 years old (vs 1–4 years: adjusted incidence rate ratio (aIRR) 1.38, 95% CI 1.10 to 1.72), fair-to-poor health (vs excellent or very good: aIRR 1.42, 95% CI 1.05 to 1.92), or ≥6 healthcare utilisation encounters over the last year (vs 0–5 encounters: aIRR 1.45, 95% CI 1.26 to 1.66). Polypharmacy increased the odds of an asthma attack (adjusted OR (aOR) 2.80, 95% CI 1.99 to 3.93) and ED visit (aOR 2.41, 95%1.59–3.63) after adjusting for demographics, insurance and health status.

Conclusions Every one in three US children with asthma experienced polypharmacy. Although it may reflect the treatment guidelines that various asthma medications are needed for maintenance therapy, our results suggested that polypharmacy increased the odds of asthma attacks or ED visits. This may be due to the concurrent use with other non-asthma medications indicating that there is an opportunity to improve medication management in children with asthma.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This population-based study used the most recent nationally (USA) representative data from the 2011–2020 National Health and Nutrition Examination Survey (NHANES).
⇒ The sample weights provided by NHANES allow for nationally representative estimates.
⇒ A quality control process, including showing containers and matching drug names in the Lexicon Plus drug database, was in place to reduce recall or reporting bias of medication use.
⇒ Because the study design is cross sectional, it cannot be used to establish a temporal relationship or make causal inferences.

INTRODUCTION

Asthma is a common chronic disease in the paediatric population.[1] More than five million US children suffer from asthma resulting in over US$80 billion in healthcare expenditure, 1.6 million emergency department (ED) visits, and about 200 deaths in the US each year.[1 2] Medications are often needed to control asthma symptoms and prevent asthma exacerbations. Specifically, clinical guidelines recommend a stepwise approach for asthma management based on the patient's age and severity of illness.[3] Children with intermittent asthma may take a single short-acting beta agonist as needed, while older children with persistent, severe asthma may take up to three asthma medications (eg, inhaled corticosteroids, long-acting beta-agonist, and oral steroids) for maintenance therapy.[3] Moreover, children with asthma may also frequently take medications for complex health conditions, such as allergies, infection and behaviour disorders.[4 5]

The common definition of polypharmacy in children is the concurrent use of two or more medications for at least 1 day.[6–8] However, understanding the degree and

depth of polypharmacy is also essential because there may be a positive association between the total number of medications and adverse outcomes.[9] Although the prevalence of polypharmacy generally increases with age, the US Center for Disease Control and Prevention (CDC) reported that about 2.5 million (3.5%) and 0.7 million (1%) US children took more than two or five concurrent drugs, respectively, in 2018.[10] Additionally, as the number of children with complex health conditions has increased,[11] polypharmacy is an emerging concern in the paediatric population because it often leads to adverse outcomes, including poor medication adherence, drug–drug interactions and adverse drug events.[6–8]

Preventing polypharmacy is a top priority for the US healthcare,[12] yet limited research has been conducted on patients with paediatric asthma. A hospital-based retrospective medical chart review (n=163) suggested more than 20% of children with asthma had polypharmacy.[13] The most frequently used drugs included asthma medications (eg, nebulised salbutamol, ipratropium), antiinfectives (eg, macrolides, penicillins) and antipyretics.[13] Exposure to multiple drugs was also associated with longer hospital stay and adverse outcomes such as fever.[13] Another retrospective cohort study showed that US hospitalised children with various chronic health conditions, including asthma, can receive more than 10 medications at admission, with an increase to nearly 30 medications after 7 days of hospitalisation.[14] While these studies have been conducted among hospitalised children with asthma, no study has characterised the prevalence of polypharmacy or identified potential risk factors in US non-hospitalised children with asthma.

To address this gap in the literature, we used population-based data from the National Health and Nutrition Examination Surveys (NHANES) to: (1) estimate the prevalence of polypharmacy and therapeutic drug class use in children with asthma with polypharmacy; (2) identify risk factors of increasing prescription medication use; (3) examine the association between polypharmacy and asthma attack or ED visit.

METHODS

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. The Institutional Review Board at the University of Texas Health Science Center ruled this study to be exempt from review and informed consent because of the use of publicly available, deidentified data for analysis.

DATA SOURCE AND PARTICIPANTS

The most recent NHANES (2011–2012, 2013–2014, 2015–2016, and 2017–March 2020 cycles) data were used to estimate the prevalence of polypharmacy in children with asthma. NHANES is a cross-sectional, publicly accessible and continuous survey conducted in a 2-year cycle by the National Center for Health Statistics of the CDC to monitor the health and nutrition status of the US population residing in all 50 states and Washington D.C. NHANES uses various survey methods to collect relevant information.[15] For instance, face-to-face household interviews are conducted by trained interviewers using the Computer-Assisted Personal Interview system to gather information on demographics, medical conditions and prescription medication use, whereas physical examinations, including body measures, are conducted in the Mobile Examination Center by trained health workers. All participants 18 years or older had written consent, while parental permission was obtained for children and adolescents younger than 18 year old; documentation of assent was also obtained among those aged 7–17 years. Due to interruptions in data collection related to the COVID-19 pandemic in 2020, the NHANES 2019–March 2020 data cycle was combined with 2017–2018 cycle data to produce a nationally representative sample.[16]

As mentioned above, medical conditions were self-reported and collected during a household interview. Participants who were 16 years or older answered for themselves; those younger than 16 years had proxy-assisted interviews. A childhood asthma diagnosis is reported by the child or guardian who answers the following two questions: (1) 'Has a doctor or other health professional ever told you that you have asthma?' 2) 'Do you still have asthma?' Children/guardians who answered 'yes' to both questions were categorised as having asthma. Participants aged≤19 years who reported asthma were included in the final sample.

Data were obtained and downloaded from the NHANES website and were stored in secure servers managed by UTH Information Technology. These servers are part of UTH's Datacenter, which stores sensitive research and clinical data. The Datacenter Operations team manages data centre services, including servers that support mission-critical systems for UTH and collaborating research and clinical organisations. Data from different survey instruments were merged by the unique identifier for each sample person. Data from each survey cycle were appended into a final master dataset. The research team performed data cleaning in SAS V.9.4 (SAS Institute).

MEASUREMENT AND ASSESSMENT

Prescription medication use

The Prescription Medications Questionnaire (RXQ) was also disseminated to participants during the household interview to obtain information on prescription drug use. Participants were first asked if they have taken any medications in the past 30 days for which they needed a prescription. If they answered 'yes', the interviewer asked to see medication containers and then recorded the generic drug names on the containers. When the containers were unavailable, the interviewer recorded the self-reported medication names and matched them to medication names in the Lexicon Plus drug database. All reported drug names were converted to standard generic names

in the released data. Two additional questions were also asked: (1) how long they have been taking the medication and (2) the main reason for use. The total count of all prescription medications for each participant was also released in the data file.

Polypharmacy

Polypharmacy was defined using the number of prescription medications reported by participants as taking two or more medications in the past 30 days. Although two or more medications are commonly used in the literature to define polypharmacy in children, the estimated prevalence of taking 2, 3–4, and≥5 medications were also reported to help understand the depth and extent of polypharmacy. Asthma medication combinations were treated as a single medication based on patients' self-reported data. For example, the combination of albuterol/ipratropium was counted as one medication when defining polypharmacy.

Prescription classes

The Lexicon Plus drug database provided a nested three-level of classification[17] and was used to categorise medications into different therapeutic classes. The prevalences of using the following major therapeutic classes were reported: 'asthma medications', 'attention-deficit/hyperactivity disorder (ADHD) medications', 'anti-infectives', 'antineoplastics', 'anticonvulsants', 'antidepressants', 'antidiabetic agents', 'antihistamines', 'antipsychotics', 'anxiolytics, sedatives, and hypnotic', 'cardiovascular agents', 'contraceptives', 'glucocorticoids', 'analgesics', and 'gastrointestinal agents'. The above drug classes were selected because they are highly relevant to child and adolescent health as described by Hales *et al*.[18] Because medical conditions in children commonly vary by age, the use of prescription medications was further stratified by age group. Therapeutic subclasses or individual prescription medications were also reported when the sample size was adequate.

Risk factors

We examined potential risk factors including sociodemographic factors (age (1–4, 5–11, 12–19 years), sex (male or female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other/multirace), payer status (insured or no insurance), and family income-to poverty ratio (<1, 1–1.99. 2–2.99, 3–3.99, and ≥4)); body mass index (BMI) categories for children (underweight (<5th percentile), normal weight (5–84.99th percentile), overweight (85–94.99th percentile), and obese (95–99th percentile))[19]; general health (excellent or very good, good, fair or poor); and the number of healthcare utilisation over the last year (0–5 times, and ≥6 times). Those risk factors were chosen because previous studies suggested that they were associated with behaviours surrounding medication use in children.[6–8 18]

Asthma-related adverse outcomes/events

Two adverse outcomes, asthma attack and ED visit for asthma, were measured with two yes/no questions: 'During the past 12 months, have you had an episode of asthma or an asthma attack?' and '[During the past 12 months], have you had to visit an emergency room or urgent care center because of asthma?'

STATISTICAL ANALYSIS

For descriptive analysis, categorical variables were presented as weighted percentages (SE), and continuous variables were summarised as weighted means (SE). To compare demographic characteristics, insurance and health indicators between patients with or without polypharmacy, two-sample t-tests with equal or unequal variance and Rao-Scott χ^2 analysis were used to analyse continuous and categorical variables, respectively.

The estimated prevalence of polypharmacy (≥ 2 medications) in the US asthma children was reported using aggregated four cycles (2011–2020). We also reported the prevalence of using 2, 3–4, and ≥5 medications. Taylor series linearisation was used to construct SEs of prevalence estimates and the method of Korn and Graubard was used to estimate the 95% CI.[20] Prevalence of therapeutic classes and individual drug among participants with polypharmacy were also generated, as mentioned above.

Negative binomial regression was used to estimate incidence rate ratios (IRR) to identify risk factors of prescription medication use, defined as the total number of prescription medications taken over the past 30 days. We treated prescription medication use as a type of count data and entered as the dependent variable in the model. Risk factors included: age (1–4 years as the reference group), sex (male as the reference group), race/ethnicity (non-Hispanic White as the reference group), family income-to-poverty ratio (<1 as the reference group), BMI (normal weight as the reference group), health insurance (insured as the reference group), general health (excellent or very good as the reference group), healthcare utilisation (0–5 times as the reference group). The goodness-of-fit tests were performed to assess the model fitting of negative binomial regression in comparison with Poisson regression and zero-inflated negative binomial models.

Two sets of survey logistic regression models were used to examine the association between asthma attacks and ED visits (dependent variables) and polypharmacy (independent variables) adjusting for covariates mentioned above.

A complex 3-step weighting method is designed for each survey cycle to represent the US non-institutional, civilian population. Notably, because the 2017-March 2020 data represent a 3.2-year period instead of a 2-year period in previous cycles, the survey weights were adjusted to reflect the longer period and larger population represented by the 2017–March 2020 files.[16] All analyses included appropriate stratum-specific weights, clusters and strata using SURVEYMEANS, SURVEYFREQ, SURVEY LOGISTICS or GENMOND procedure,[21] and were performed using

SAS V.9.4 (SAS Institute) and R V.4.0.5 (R core team, 2021). Two-sided p value<0.05 was considered significant.

SENSITIVITY ANALYSIS

We conducted a sensitivity analysis to examine the temporal trends of polypharmacy (≥2 and ≥5 medications) across NHANES cycles by conducting a survey logistic regression analysis. The temporal trends were further stratified by: (1) age groups (1–4, 5–11, and 12–17 years): the age groups are defined based on the asthma treatment guideline[3 22]; (2) sex (male and female); and (3) race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other).

PATIENT AND PUBLIC INVOLVEMENT

Besides being involved as participants of this study, patients or the public were not involved in the design or conduct of our research. However, the public was welcome to provide feedback during the dissemination process.

RESULTS

Our analytical sample comprised 1776 children with asthma (mean age 11.2 (0.1) years, 54.0% (95% CI 50.5% to 58.9%) of whom were boys, and 48.6% (95% CI 43.3% to 53.9%) non-Hispanic white). In total, one-third (33.5% (95% CI 31.8% to 35.2%)) took at least two drugs concurrently over the past 30 days (hereafter 'polypharmacy group'). Compared with the no polypharmacy group, children in the polypharmacy group were younger (mean age 10.7 (0.2) vs 11.4 (0.2) years, p<0.001) and less likely to be girls (40.8% vs 47.6%, p=0.005). About one-third of children who had polypharmacy were obese, while 22.8% of children without polypharmacy were obese (p=0.046). In addition, more children in the polypharmacy group reported having fair/poor health (15.4% vs 9.1%, p<0.001) and more healthcare utilisation (47.3% used≥6 times vs 16.7%, p<0.001) than those in the no polypharmacy group. Table 1 also summarises the sample's characteristics by using 2, 3–4, or ≥5 medications. The estimated prevalence of taking 2, 3–4, and >5 prescription medications were 15.5% (95% CI 14.3% to 16.7%), 12.6% (95% CI 11.4% to 13.9%) and 5.3% (95% CI 3.7% to 6.9%), respectively.

A total of 83.4% (95% CI 79.0% to 87.7%) children took at least one common asthma medication with the majority using bronchodilators (67.4%, 95% CI 61.7% to 73.0%) and inhaled corticosteroids (48.0%, 95% CI 43.3% to 52.6%). Antihistamines (20.2%, 95% CI 16.1% to 24.3%), systematic glucocorticoids (16.7%, 95% CI 12.6% to 20.8%), anti-infectives (14.3%, 95% CI 10.3% to 18.3%), and ADHD medications (13.9%, 95% CI 9.2% to 18.7%) were the top 4 most commonly prescribed medications in children with asthma. In addition, variations were found in the utilisation patterns of medications by age group. For example, 19.2% of children aged 5–11 years took ADHD medications, with none in children younger than 4 years. Moreover, about one in five (18.4%) adolescents with asthma were prescribed antidepressants, versus 4.0% (95% CI 0.3 to 7.6%) in children aged 5–11 years and 0% in children younger than 4 years (table 2).

Crude and adjusted negative binomial regression analysis were used to identify risk factors of polypharmacy. In the fully adjusted model, we found several risk factors increased the number of prescription medication use, including 5–11 years of age (vs 1–4 years: adjusted incidence rate ratio (aIRR) 1.38, 95% CI 1.10 to 1.72), having fair-to-poor health (vs excellent or very good: aIRR 1.42, 95% CI 1.05 to 1.92), or ≥6 healthcare utilisation encounters over the last year (vs 0–5 encounters: aIRR 1.45, 95% CI 1.26 to 1.66) (table 3).

The adjusted odds of asthma attack were almost three times (aOR=2.80, 95% CI 1.99 to 3.93) higher in children with polypharmacy than those without polypharmacy, adjusting for age, gender, race/ethnicity, insurance status, family income-to-poverty ratio, BMI categories, general health, and healthcare utilisation. Moreover, polypharmacy was also significantly associated with an ED visit for asthma (aOR=2.41, 95% CI 1.59 to 3.63). Notably, the odds of an asthma attack (aOR 3.26, 95% CI 1.63 to 6.52) and ED visit (aOR 3.00, 95% CI 1.23 to 7.29) were the highest among children who took≥5 medications compared with those who took one or less medication (no polypharmacy) (table 4).

The sensitivity analysis identified no increasing or decreasing polypharmacy trends (All p trend>0.05). However, the estimated prevalence of polypharmacy (≥ 2 medications) in children with asthma remained above 30% from 2011 to 2020. Likewise, no identifiable trend of polypharmacy was found for those who used 2, 3–4, or ≥5 medications for subgroups including sex, age, and race/ethnicity. (online supplemental figures 1-3)

DISCUSSION

Polypharmacy in children with asthma

About 1 in 5 US children takes at least one prescription medication to prevent and treat various health conditions.[10] Although polypharmacy is generally considered less prevalent in children compared with adults, attention to polypharmacy among the paediatric population has been rising. Feinstein *et al*[9] reported that 35% of paediatric patients enrolled in a Colorado Medicaid sample had polypharmacy. Similarly, our study showed one in three outpatient children with asthma received two or more medications concurrently from the 2011–2020 NHANES data, which is concerning given the potential adverse health outcomes. While it is well known that asthma has multifactorial triggers, these findings suggest that polypharmacy should be considered a modifiable risk factor and could be controlled to improve asthma health risks.

In March 2017, the WHO initiated the 3rd Global Patient Safety Challenge: Medication Without Harm,

Table 1 Participant characteristics by polypharmacy status among children with asthma, NHANES, 2011–2020* (N=1776)

	Polypharmacy				No polypharmacy	P value†
Number of Rx	2	3–4	≥ 5	Total (≥ 2)	0–1	
N (%)	283 (15.5)	221 (12.6)	81 (5.3)	585 (33.5)	1191 (66.5)	
Duration of taking Rx, days, mean (SD)	1078.0 (66.9)	1092.4 (47.8)	990.39 (83.1)	1056.99 (45.0)	1252.87 (72.5)‡	<0.001
Age, mean (SD)	10.7 (0.4)	10.5 (0.3)	11.4 (0.9)	10.7 (0.2)	11.4 (0.2)	<0.001
1–4, n (%)	43 (11.1)	37 (11.6)	5 (6.0)	85 (10.5)	207 (12.2)	0.008
5–11, n (%)	133 (44.7)	111 (43.9)	43 (41.2)	287 (43.9)	502 (34.4)	
12–19, n (%)	107 (44.2)	73 (44.5)	33 (52.7)	213 (45.7)	482 (53.5)	
Female, n (%)	105 (37.9)	85 (42.2)	35 (45.6)	225 (40.8)	542 (47.6)	0.006
Race/ethnicity						0.859
NHW	69 (47.8)	57 (47.2)	26 (61.4)	152 (49.8)	265 (48.0)	
NHB	108 (22.7)	80 (19.8)	29 (19.2)	217 (21.1)	488 (23.1)	
Hispanics	68 (21.1)	55 (21.6)	15 (14.1)	138 (20.2)	278 (19.5)	
Other	38 (8.3)	29 (11.5)	11 (5.4)	78 (9.0)	160 (9.4)	
Family income-to-poverty ratio§						0.733
<1	101 (30.5)	81 (26.7)	26 (22.1)	208 (27.7)	443 (30.3)	
1–1.99	55 (21.6)	54 (26.0)	28 (30.2)	137 (24.7)	300 (25.5)	
2–2.99	41 (16.8)	29 (16.2)	12 (25.8)	82 (17.9)	130 (14.2)	
3–3.99	23 (12.1)	21 (10.4)	2 (1.8)	46 (9.8)	73 (9.3)	
≥ 4	37 (19.0)	24 (20.7)	7 (20.2)	68 (19.9)	135 (20.7)	
BMI category¶						0.046
Underweight	10 (3.7)	4 (1.2)	1 (0.3)	15 (2.3)	31 (3.2)	
Normal weight	141 (54.3)	100 (50.0)	32 (49.7)	273 (52.0)	598 (58.4)	
Overweight	38 (16.4)	37 (17.4)	10 (9.1)	85 (15.6)	177 (15.5)	
Obese	74 (25.6)	61 (31.3)	31 (40.9)	166 (30.2)	266 (22.8)	
Health insurance						0.095
Insured	271 (95.7)	212 (96.1)	79 (94.9)	562 (95.7)	1118 (93.2)	
No insurance	12 (4.3)	9 (4.0)	2 (5.1)	23 (4.3)	70 (6.8)	
General Health						<0.001
Excellent or very good	130 (48.8)	96 (49.6)	21 (31.7)	247 (46.0)	685 (62.1)	
Good	113 (39.3)	77 (34.0)	34 (47.2)	224 (38.5)	380 (28.8)	
Fair or poor	40 (11.9)	48 (17.4)	26 (21.1)	114 (15.4)	126 (9.1)	
Healthcare utilisation over last year						<0.001
0–5 times	139 (63.6)	86 (49.7)	21 (28.3)	246 (52.7)	773 (83.3)	
≥ 6 times	72 (36.4)	70 (50.3)	39 (71.7)	181 (47.3)	152 (16.7)	

All percentages and means are weighted.
*2020 data only included January to March due to the COVID-19 pandemic.
†χ^2 analysis or t-test with equal or unequal variance to compare polypharmacy (total) versus no polypharmacy.
‡Only calculated among participants with one prescription.
§Total family income divided by the poverty threshold.
¶BMI category for children and youth.
BMI, body mass index; NHANES, National Health and Nutrition Examination Survey; Rx, prescription medication.

aiming to decrease severe, preventable harm related to medications by 50% by 2023.[23] Polypharmacy is sometimes clinically indicated and reflects a standard of care (eg, inhaled corticosteroid combined with long-acting beta agonist is highly recommended for asthma control), but inappropriately managed polypharmacy can cause harmful health consequences and increase healthcare visits due to drug–drug interaction, medication nonadherence and ADEs, accounting for a total of 18 billion dollars avoidable healthcare cost worldwide.[23]

Table 2 Estimated prevalence with 95% CI of selected prescription medications among children with asthma polypharmacy by age group, NHANES 2011–2020*

Therapeutic class	1–4 years	5–11 years	12–19 years	Total
Asthma medications	96.7 (93.5–100)	88.3 (82.6–93.9)	75.6 (68.3–82.9)	83.4 (79.1–87.7)
Bronchodilators	83.4 (73.4–93.5)	68.5 (60.0–76.9)	62.6 (54.5–62.0)	67.4 (61.7–73.0)
Adrenergic bronchodilators	83.4 (73.4–93.5)	67.7 (59.2–76.3)	62.6 (54.5–70.7)	67.0 (61.3–72.7)
Inhaled corticosteroids	71.2 (57.4–85.0)	55.0 (47.3–62.6)	36.0 (28.1–43.9)	48.0 (43.3–52.6)
Montelukast	25.4 (14.4–36.4)	32.3 (25.5–39.1)	29.5 (20.2–38.7)	30.3 (25.1–35.5)
Asthma combinations	7.7 (0–16.9)	14.8 (10.4–19.3)	14.4 (8.1–20.8)	13.9 (10.3–17.6)
ADHD medications	0 (0)	19.2 (9.4–29.1)	12.1 (6.0–18.1)	13.9 (9.2–18.7)
CNS stimulants†	0 (0)	19.1 (9.3–28.9)	9.7 (5.0–14.4)	12.8 (7.9–17.8)
SNRI (atomoxetine)	0 (0)	0.9 (0–2.0)	2.4 (0–6.2)	1.5 (0–3.4)
Anti-infectives	17.7 (6.6–28.7)	14.1 (7.8–20.4)	13.7 (8.6–18.7)	14.3 (10.3–18.3)
Antibiotics	16.7 (5.8–27.7)	13.2 (6.8–19.5)	11.2 (6.8–15.5)	12.6 (8.7–16.5)
Antiviral/antifungals /antimalarial/ antituberculosis agents	0.9 (0–2.7)	2.1 (0–4.3)	3.0 (0–6.2)	2.42 (0.7–4.1)
Antineoplastics	0 (0)	0.2 (0–0.6)	2.1 (0–4.7)	0.8 (0–2.3)
Anticonvulsants	1.7 (0–5.2)	4.0 (0.3–7.6)	9.0 (3.5–14.4)	6.0 (3.1–8.9)
Antidepressants	0 (0)	3.4 (0.9–5.9)	18.4 (9.4–27.4)	9.9 (5.1–14.6)
SSRI	0 (0)	2.8 (0.4–5.3)	17.3 (8.4–26.2)	9.2 (4.4–12.9)
Antidiabetic agents	0 (0)	0 (0)	1.1 (0–2.1)	1.1 (0–2.1)
Antihistamines	12.7 (5.8–19.6)	23.0 (16.1–29.9)	19.2 (13.2–25.1)	20.2 (16.1–24.3)
Antipsychotics	0 (0)	3.2 (1.1–5.3)	4.9 (1.6–8.2)	3.6 (2.0–5.3)
Anxiolytics, sedatives, and hypnotic	0.5 (0–1.6)	3.4 (1.5–5.3)	7.3 (2.4–12.1)	4.9 (2.5–7.2)
Cardiovascular agents	0 (0)	6.8 (2.3–11.4)	8.6 (4.5–12.8)	6.9 (4.3–9.5)
Antihypertensive agents	0 (0)	0.2 (0–0.7)	3.5 (0.1–6.8)	1.7 (0.1–3.3)
Contraceptives	0 (0)	0 (0)	3.4 (0.7–6.2)	1.6 (0.3–2.9)
Glucocorticoids	34.6 (20.5–48.8)	16.0 (9.3–22.6)	13.2 (7.3–19.2)	16.7 (12.6–20.8)
Analgesics	3.4 (0–11.5)	1.7 (0–3.7)	13.9 (8.4–19.5)	7.6 (4.8–10.4)
Gastrointestinal agents	7.2 (1.6–12.8)	4.4 (1.6–7.3)	9.3 (3.9–14.8)	6.9 (4.1–9.8)
Proton pump inhibitors	0.9 (0–2.7)	1.7 (0.3–3.1)	6.1 (1.9–10.4)	3.6 (1.6–5.7)
H_2 antagonists	2.1 (0–4.8)	0.4 (0–1.1)	3.6 (0–7.6)	2.1 (0.2–3.9)

*2020 data only included January–March due to the COVID-19 pandemic.
†Include amphetamine, dexmethylphenidate, dextroamphetamine, methylphenidate and lisdexamfetamine.
ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; NHANES, National Health and Nutrition Examination Survey; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Our results here showed that polypharmacy doubled the odds of asthma attack, or an ED visit compared with no polypharmacy after rigorously controlling for potential confounders. Although we could not examine the exact causes for the increased likelihood of adverse asthma outcomes in the present study, it may be explained by the following possible mechanisms: (1) increased medication count is associated with decreased medication adherence, which in turn, results in reduced symptoms control[24]; (2) the adverse effects of certain medications, such as non-selective beta-blockers for treating hypertension, may cause bronchospasm and asthma attack[25]; (3) asthma medication may interact with other medications, such as protease inhibitors or antifungal agents, through Cytochrome P450 3A4 (CYP3A4) enzymes, which leads to toxicity and increased healthcare visits.[26]

Source of polypharmacy: asthma medications

The majority (83.4%) of the sample had medications to treat asthma. There may be two main reasons that not all children need asthma medications. First, our data show the prevalence of using asthma medications decreased slightly with age, which aligns with other studies that show that asthma symptoms and severity typically decline with age.[27] In those with mild, intermittent asthma, daily maintenance medications may not be needed for asthma control. Second, some children may be treated with novel biologics, which were not captured in the NHANES

Table 3 Crude and adjusted negative binomial regression to identify predictors for prescription medication use, NHANES 2011–2020*

	IRR (95% CI)†	P value†	aIRR (95% CI) ‡	P value‡
Age group				
1–4	1 (ref)	–	1 (ref)	–
5–11	**1.34 (1.06 to 1.71)**	**0.017**	**1.38 (1.10–1.72)**	**0.005**
12–19	1.08 (0.82 to 1.42)	0.603	1.08 (0.84–1.38)	0.555
Sex				
Male	1 (ref)	–	1 (ref)	–
Female	0.97 (0.79 to 1.19)	0.539	0.90 (0.73–1.10)	0.292
Race/ethnicity				
Non-Hispanic white	1 (ref)	–	1 (ref)	–
Non-Hispanic black	0.89 (0.71 to 1.11)	0.302	0.88 (0.68–1.12)	0.289
Hispanic	0.93 (0.77 to 1.13)	0.469	0.90 (0.72–1.13)	0.370
Other	0.91 (0.65 to 1.28)	0.598	1.01 (0.80–1.28)	0.905
Family income-to-poverty ratio				
<1	1 (ref)	–	1 (ref)	–
1–1.99	1.20 (0.94 to 1.53)	0.140	1.21 (0.95–1.54)	0.118
2–2.99	1.35 (0.94 to 1.95)	0.108	1.28 (0.94–1.76)	0.120
3–3.99	1.00 (0.77 to 1.31)	0.976	1.19 (0.86–1.65)	0.291
≥ 4	1.15 (0.87 to 1.52)	0.332	1.32 (0.96–1.81)	0.081
Body mass index category				
Underweight	0.91 (0.67 to 1.24)	0.549	0.90 (0.63–1.29)	0.565
Normal weight	1 (ref)	–	1 (ref)	–
Overweight	1.03 (0.81 to 1.30)	0.841	1.13 (0.91–1.42)	0.268
Obese	**1.38 (1.05 to 1.82)**	**0.021**	1.17 (0.93–1.47)	0.165
Health insurance				
Insured	1 (ref)	–	1 (ref)	–
No insurance	0.76 (0.48 to 1.19)	0.229	0.71 (0.44–1.15)	0.165
General health				
Excellent or very good	1 (ref)	–	1 (ref)	–
Good	**1.52 (1.26 to 1.86)**	**<0.001**	**1.30 (1.10–1.53)**	**0.002**
Fair or poor	**1.85 (1.41 to 2.42)**	**<0.001**	**1.42 (1.05–1.92)**	**0.021**
Healthcare utilisation over the last year				
0–5 times	1 (ref)	–	1 (ref)	–
≥ 6 times	**2.59 (2.04 to 3.28)**	**<0.001**	**1.45 (1.26–1.66)**	**<0.001**

Bold-face indicates statistical significance (P< 0.05).
*2020 data only included January to March due to the COVID-19 pandemic.
†Crude negative binomial regression.
‡Multivariate negative binomial regression adjusting for age, gender, race/ethnicity, insurance status, family income-to-poverty ratio, BMI categories, general health, and healthcare utilisation.
BMI, body mass index; NHANES, National Health and Nutrition Examination Surveys.

household interview because currently, the majority of biologics are administered subcutaneously or intravenously in a doctor's office. It also should be noted that about 14% of children reported using asthma medication combinations, which is lower than 67% on single bronchodilators and 48% on inhaled corticosteroids. Previous studies suggested the use of combination asthma therapy is associated with better adherence, outcomes, and cost-effectiveness compared with the concurrent use of single medications.[28 29] Hence, there is an opportunity to improve clinical and public health awareness and message to reduce unnecessary polypharmacy when we can.

Table 4 Comparison of asthma outcomes between polypharmacy users and non-polypharmacy users, NHANES, 2011–2020*

Number of prescription medications	Asthma attacks in the past year			Emergency department visits for asthma in the past year		
Polypharmacy	N (%)†	OR (95% CI)‡	aOR (95% CI)§	N (%)†	OR (95% CI)‡	aOR (95% CI)§
2	184 (64.75)	2.60 (1.74 to 3.88)	2.79 (1.77 to 4.40)	88 (26.02)	1.90 (1.26 to 2.88)	2.14 (1.32 to 3.48)
3–4	151 (64.72)	2.60 (1.66 to 4.07)	2.64 (1.63 to 4.26)	80 (29.36)	2.25 (1.52 to 3.34)	2.56 (1.53 to 4.27)
≥ 5	50 (63.56)	2.47 (1.43 to 4.26)	3.26 (1.63 to 6.52)	30 (29.55)	2.27 (1.17 to 4.39)	3.00 (1.23 to 7.29)
Total (≥ 2)	385 (64.55)	2.58 (1.90 to 3.51)	2.80 (1.99 to 3.93)	198 (27.84)	2.09 (1.51 to 2.89)	2.41 (1.59 to 3.63)
No polypharmacy	502 (41.37)	1 (ref)	1 (ref)	246 (15.59)	1 (ref)	1 (ref)

*2020 data only included January–March due to the COVID-19 pandemic.
†Percentage is weighted.
‡Univariate logistic regression.
§Multivariate logistic regression controlling for age, gender, race/ethnicity, insurance status, family income-to-poverty ratio, BMI categories, general health, and healthcare utilisation.
BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

Source of polypharmacy: non-asthma medications

Children with asthma disproportionately suffer from other comorbidities, such as allergies and infection. Not surprisingly, our results showed that the anti-infectives, antihistamines and systemic glucocorticoids were the three most commonly coprescribed medications. Nevertheless, previous studies[17 30–32] suggested that the overall use of these mediations was significantly decreasing in the general paediatric population. Specifically, the most recent data showed less than 5% of US children took any antibiotics, 2% took antihistamines, and 0.9% took glucocorticoids.[18] However, in children with asthma, the percentage of using these three medications was substantially higher (12.6% antibiotics, 20.2% antihistamines and 16.7% systemic glucocorticoids). This is not only indicating the difference in medication use profiles for patients with various diseases, but also suggests individualised medication management is needed to improve patient care. Most importantly, these three types of medications are highly recommended to take as a short course to avoid long-term side effects including antibiotic resistance and many oral corticosteroids dependent side effects. It is also important to prioritise medication management in children with asthma and ADHD as the prevalence of taking ADHD medications was also high in children aged 4 years and above.

In addition, adolescents with asthma who were prescribed with antidepressants were much greater than the general US paediatric population (18.4% vs 3.4%).[33] The mental health of patients with asthma has received recent increased attention because depression may not only be a consequence resulting from asthma, but these two conditions may also be linked due to shared physiological mechanisms. A randomised control trial supported using antidepressants to help control asthma and treat depression simultaneously.[34] However, it is well known that common antidepressants, such as selective serotonin reuptake inhibitors interact with many other medications causing severe adverse events and are associated with weight gain.[35 36] Hence, the appropriateness of antidepressants in patients with asthma should be closely monitored.

In sum, clinicians may focus on non-respiratory medications when deprescribing given the concurrent use of different asthma medications is usually clinically indicated and recommended by clinical guidelines for those with persistent asthma. Specifically, medication reconciliation at the transition of care, discontinuing duplicate medications, evaluating drug–drug interaction, assessing adverse drug events, and reviewing dosages can be conducted in children with chronic conditions to reduce potential harms from polypharmacy.

Risk factors for polypharmacy among children with asthma

The expected mean count of prescription medications was 1.38 times higher in children with asthma aged 5–11 years compared with preschool-aged children. However, the prevalence of using asthma medication decreased with

age (1–4 years: 96.7% vs 5–11 years: 88.3% vs 12–19 years: 75.6%). This implies that more comprehensive medication review is needed for children with asthma in primary school as they are likely to get multiple medications for different diseases.

In addition, our results also suggested that poor health and increased healthcare utilisation were significantly and positively associated with polypharmacy. Although few studies evaluated outpatient polypharmacy in children with asthma, this finding aligns with a recent study by Feinstein *et al* suggesting medication regimen complexity is associated with increased acute visits among children with neurological impairment.[37] Our results are also similar to the risk factors of polypharmacy among adults including multiple commodities and seeing multiple medical providers.[38] Furthermore, another cross-sectional study suggested that adults with respiratory conditions had a lower prevalence of polypharmacy compared with other chronic condition groups, but prevalence increased as the number of comorbidities increased, including musculoskeletal or cardiometabolic diseases.[39]

LIMITATIONS

Balancing the potential therapeutic benefits and risks of multiple drug therapy needs to receive more attention. In the present study, the number of medications was used to define polypharmacy. Although it was commonly used and accepted in the literature,[6–8] it fails to consider the benefits received from necessary medications. Future studies should use a prospective study design to further examine the association between polypharmacy and adverse asthma outcomes after excluding necessary maintenance asthma therapy.

This study also has other limitations. First, a temporal or causal relationship cannot be established because of the cross-sectional nature of our study. Second, although there was a quality control process in place, including showing containers and matching drug names in the Lexicon Plus drug database to reduce recall or reporting bias, under-reporting of medication use may still be possible. Third, we could not examine the impact of dosages, formulations, scheduled versus as-needed medications, or medications only available as over-the-counter products because NHANES does not collect this information. Fourth, asthma combination therapy was counted as a single medication in the present study, which may underestimate the prevalence of polypharmacy. Fifth, as children with one condition may be more likely to be diagnosed with a concurrent condition, medical surveillance bias may be present. Finally, selection bias may exist as evidenced by the modest response rates (52%–73%)[40]; however, the NHANES assigned sample weights in order to decrease possible sampling bias.

CONCLUSION

Approximately every one in three US children with asthma experienced polypharmacy, which may reflect the standard of care recommending multiple medications as part of maintenance therapy. However, our results suggested that polypharmacy increased the odds of asthma attacks and ED visits. Future studies are needed to explore the mechanisms. Specific efforts, such as developing screening tools or deprescribing criteria, are needed to decrease the medication burden in the US children with asthma to improve asthma health risks, especially among those without healthy weight, having poorer health and frequently visiting physician offices.

Author affiliations
[1]Deparment of Epidemiology, Human Genetics & Environmental Sciences, University of Texas Health Science Center at Houston, Dallas, Texas, USA
[2]Center for Pediatric Population Health, UTHealth School of Public Health, Dallas, Texas, USA
[3]Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas, Texas, USA
[4]Department of Health Promotion & Behavioral Sciences, University of Texas Health Science Center at Houston, Houston, Texas, USA
[5]Department of Biostatistics & Data Science, University of Texas Health Science Center at Houston, Dallas, Texas, USA
[6]Deparment of Epidemiology, Human Genetics & Environmental Sciences, University of Texas Health Science Center at Houston, Houston, Texas, USA

Twitter Sarah Messiah @sarahmessiah

Contributors Conceptualisation: LX; Methodology: LX, CCM, FA, and SM; Software: MSM; Formal analysis: LX; Writing–original draft: LX and SM; Writing–review and editing: AG, GLD, CCM, and SM; Supervision: SM; Project administration: MSM; Guarantor for the overall content: LX and SM.

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ORCID iDs
Luyu Xie http://orcid.org/0000-0003-4499-0555
Folefac Atem http://orcid.org/0000-0002-1142-7806

Sarah Messiah http://orcid.org/0000-0001-6685-2175

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