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Polypharmacy among Medicaid-Insured Children with and without Documented Obesity

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Abstract

OBJECTIVE: Polypharmacy increases the risk of drug-drug interactions and adverse drug events. As obesity and rates of obesity comorbid chronic conditions continue to rise, an improved

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Author Contributions:

Dr. Kyler led overall conceptualization and design of the study, analyzed and interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Hall led acquisition and analysis of the data and contributed to conceptualization and design of the study, and drafting and critical review of the manuscript.

Drs. Feinstein, Antoon, Shah, Tang Girdwood, Goldman, Grijalva and Williams contributed to the overall conceptualization and design of the study, analysis and interpretation of data, and critical review of the manuscript.

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understanding of whether children with obesity experience higher risk of polypharmacy is needed. This study aimed to compare chronic medication polypharmacy prevalence among children with and without a diagnosis of obesity.

METHODS: We performed a cross-sectional examination of prescription data for children aged 2–18 years prescribed ≥1 chronic medication using the 2019 Marketscan Medicaid database. Children with documented obesity were identified using medical visit diagnosis codes. Chronic medications included any ≥30-day prescription with ≥2 dispensed refills. Polypharmacy was defined as the prescription of ≥2 chronic medications for ≥1 overlapping days. Chi square tests compared polypharmacy prevalence and the distribution of chronic medication classes between children with and without obesity. Logistic regression determined the adjusted odds ratio (aOR) of polypharmacy for children with obesity, adjusting for relevant demographic and clinical differences.

RESULTS: Of 634,671 included children, 12.2% had documented obesity. More than one-half (52.7%) of children with obesity experienced polypharmacy compared with 47.6% of children without obesity (aOR 1.06 [95% confidence interval 1.04–1.06]). Chronic medication prescriptions, particularly for psychiatric and asthma medications, were more commonly prescribed among children with obesity than those without obesity.

CONCLUSIONS: Children with documented obesity have higher polypharmacy prevalence than children without obesity. Clinicians must be aware of this risk and minimize inappropriate polypharmacy whenever possible. Future work should examine the consequences of polypharmacy, including drug-drug interactions and adverse drug events in children with obesity.

Keywords

Polypharmacy; obesity; drug interactions; chronic conditions

Introduction

Polypharmacy, defined as the prescription of ≥2 medications for 1 or more overlapping days[1], is common among the general pediatric population in the United States (US), occurring in an estimated 30–35% of children in the outpatient setting.[2,3] Although sometimes necessary for treatment of acute and chronic conditions, polypharmacy increases the risk of drug-drug interactions, adverse drug events, difficulty with medication adherence, and even hospitalizations.[4,5]

Obesity increases the risk of developing chronic health conditions that often require multiple medications for management.[6,7] Such polypharmacy places obese children at risk of medication-related adverse drug events, including drug-drug interactions.[1] Obesity itself may also increase the risk of experiencing adverse drug events as a result of altered pharmacokinetic and pharmacodynamic drug responses.[8] Although obesity affects 1 in 5 American children[9] and increases the risk of many chronic medical problems, the frequency of polypharmacy in children with obesity in the US is unknown. While a few studies have focused on psychotropic medication polypharmacy and obesity[10,11,12], little is known about other medication classes. Additionally, the results of work defining polypharmacy

prevalence varied due to the use of different study methodologies and definitions of polypharmacy.[2]

Obesity and polypharmacy may present additive risks for adverse drug events. This risk, coupled with evidence of more frequent polypharmacy associated with certain clinical factors or diagnoses (e.g., medical complexity), necessitate an examination of how children with obesity experience polypharmacy. We aimed to determine the prevalence of chronic medication polypharmacy among Medicaid-insured children with and without documented obesity. We also sought to determine whether clinical factors aside from weight status augmented the risk of experiencing polypharmacy in children.

Methods

Study Design

We conducted a cross-sectional study using the 2019 MarketScan Multi-state Medicaid Database (IBM Watson Health, Armonk, NY). This de-identified dataset contains detailed claims data from 11 geographically diverse states, including inpatient, outpatient, and pharmacy claims, and provides patient demographic and clinical characteristics. This study was deemed non-human subjects research by the Children's Mercy Hospital Institutional Review Board.

Study Definitions

Chronic medications were identified from dispensed pharmacy claims for all unique medication prescriptions meeting the following accepted definition: any ≥30-day prescription fill with ≥2 subsequent dispensed refills.[13] Chronic medications were categorized based on therapeutic class using the 2019 American Hospital Formulary Service classification compilation.

Children with documented obesity (hereafter referred to as children with obesity) were identified based on the presence of any International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) obesity diagnosis code associated with an encounter in the 2019 database (Supplemental Table 1). Having an ICD-10-CM code for obesity has been found to be highly specific and generally has a positive predictive value of >90%.[14]

Polypharmacy was defined as the prescription of ≥2 chronic medications for 1 or more overlapping days.[1] This is the expert recommended definition provided by a scoping review published in 2018. The short overlap period of 1 or more days is recommended for children as adverse drug events may occur with even very short overlaps of drug pairs. We identified overlapping drug pairs using drug dispensed dates coupled with the length of the prescription and number of refills reported in the Marketscan database.

Study Population

We included children 2–18 years of age who were prescribed at least 1 chronic medication and were continuously enrolled in Medicaid fee-for-service and managed care plans for ≥11

months of 2019. Continuously enrollment was required to enable examination of annual prescription fill data.

Children with no chronic medication prescriptions and those without any Medicaid utilization during the study period were excluded. Children younger than 2 years of age were excluded because the Centers for Disease Control and Prevention definition of obesity does not include children younger than 2 years. Children with complex chronic conditions (CCCs) were also excluded using a prior developed algorithm[15], as they are known to experience higher rates of polypharmacy.[3]

Study Outcomes and Measures

The primary outcome was the prevalence of polypharmacy in children with and without obesity. To determine if obesity was independently associated with risk of polypharmacy, we also examined the following demographic and clinical factors, determined *a priori*: patient age, race/ethnicity, sex, type and number of common obesity comorbid conditions, number of non-complex chronic diseases (excluding obesity), and number of mental health conditions. Obesity-associated comorbid conditions included: hypertension, polycystic ovarian syndrome (PCOS), pre-diabetes, diabetes mellitus, obstructive sleep apnea (OSA), and asthma.[7] Dyslipidemia and non-alcoholic fatty liver disease were excluded from the list of obesity comorbid conditions for this study because they are considered CCCs. Non-complex chronic diseases, identified using the Agency for Healthcare Research and Quality (AHRQ) Chronic Condition Indicator, are conditions expected to last 12 months or longer and result in the need for ongoing intervention with medical products/services/equipment or place limitations on self-care, independent living, and social interactions.[16] Obesity was excluded from the list of non-complex chronic diseases for this study. Mental health conditions were identified through ICD-10-CM codes for mental health conditions, and included diagnoses such as depression and anxiety, as well as autism spectrum disorder, neurocognitive conditions, and intellectual disability.[17]

Statistical Analysis

Demographic and clinical characteristics, as well as number and classes of chronic medications and polypharmacy prevalence, were summarized using frequencies and percentages overall and by weight category. These were compared across weight categories using Chi-square tests. Logistic regression was used to measure the association between obesity and polypharmacy, accounting for the demographic and clinical factors identified above. All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC), and $p<0.05$ was considered statistically significant.

Results

Study population

We included the 634,671 children who were prescribed at least 1 chronic medication in the analysis (Figure 1). Most children were adolescents (46.8% age 12–18 years), male (56.3%), and non-Hispanic White (52.5%) (Table 1). Most children had 1 (43.9%) or 2–3 (40.3%)

non-complex chronic diseases. A majority (61.4%) of the cohort had at least 1 mental health condition.

The prevalence of documented obesity was 12.2% (Table 1). Compared with children without obesity, those with obesity were more likely to be adolescents, non-Hispanic Black or Hispanic, and female. Approximately one-half of children with obesity (52.3%) had at least 1 obesity-associated comorbid condition. Asthma and mental health conditions were the most common chronic conditions among children with and without obesity, though the prevalence of these conditions was higher among children with obesity.

Chronic Medication Utilization

Children with obesity were more likely to have at least 1 chronic medication prescription during the study period compared to those without obesity (Table 2). Children with obesity more often received 5+ chronic prescriptions compared to those without obesity.

The top 10 most frequently prescribed classes of chronic medications were the same for both groups. Children with obesity received higher proportions of prescriptions for asthma/allergy medications, sympathomimetics, antidepressants, antipsychotics, ear/nose/throat anti-inflammatory medications, adrenals, and anti-convulsants (Figure 2). The most common classes of medications co-prescribed differed between children with and without obesity. Children with obesity were most likely to have co-prescriptions of allergy and asthma medications (e.g., antihistamines-leukotriene modifiers), whereas those without obesity had more co-prescriptions for stimulants and hypotensive agents (Table 3).

Factors Associated with Chronic Medication Polypharmacy

Polypharmacy occurred in 52.7% of children with obesity compared to 47.6% of those without obesity ($p<0.001$). After accounting for other demographic and clinical differences, obesity was independently associated with an increased risk of polypharmacy (adjusted odds ratio [aOR] 1.06, 95% confidence interval [CI] 1.04–1.08; Figure 3).

Other factors associated with an increased risk of polypharmacy included male sex, increasing age, and increasing medical and mental health complexity (Figure 3). As the number of non-complex chronic diseases increased, the risk of polypharmacy increased substantially. For example, children with 6+ non-complex chronic diseases had more than 7 times higher odds of experiencing polypharmacy compared to children with no non-complex chronic diseases (aOR 7.71, 95% CI 6.9–8.62). Children with increasing mental health complexity also experienced significantly higher odds of polypharmacy (6+ mental health conditions aOR 4.41, 95% CI 4.25–4.57).

Discussion

In this large, multicenter study of children 2–18 years, we found that children with obesity had increased odds of experiencing polypharmacy of chronic medications compared to children without obesity. Children with obesity were also more likely to receive chronic medication prescriptions in general and more often received medication prescriptions for asthma/allergies and mental health conditions.

Our study fills an important gap for children with obesity, with 52.7% of this group having polypharmacy, significantly more than children without obesity. Our findings align with prior work describing other clinical factors associated with risk of polypharmacy including: male sex, increasing age, and increasing medical complexity (in terms of number of chronic medical and mental health problems).[3] In one prior study examining Medicaid-insured children from a single state, 35% of children experienced polypharmacy. However, the study cohort differed in important ways from ours which may partially explain difference in results, particularly the inclusion of children younger than 2 years of age and analysis of acute and chronic medication prescriptions.[3] Prior work has shown that the type and depth of polypharmacy differs between early childhood and later in adolescence[3,18], which our results confirm with adolescents experiencing 2x higher odds of polypharmacy compared to preschool aged children. Keast et. al. found that overweight or obese foster children in Oklahoma were more likely than foster children with a healthy weight to experience multi-class psychotropic medication polypharmacy.[12] Our results add to these findings and provide a more comprehensive description of polypharmacy among a multi-state cohort of children with obesity.

Greater polypharmacy in children with obesity may be partially attributed to the presence of obesity-associated comorbid conditions, many of which may require pharmacotherapy. One-third of our cohort with obesity had asthma, and other prevalent obesity-associated comorbid conditions included mental health conditions like depression (19%) and anxiety (17%). The higher prevalence of these conditions is reflected in the classes of medications prescribed most frequently to this group. For example, antidepressants made up more than 18% of chronic medication prescriptions for children with obesity, compared to < 15% for those without obesity. Drugs used to treat obesity comorbid conditions (e.g., selective serotonin reuptake inhibitors, antihypertensives), are implicated in some of the most frequently encountered potential drug-drug interactions in outpatient populations, placing patients at risk for adverse drug events including serotonin syndrome and serious cardiac arrhythmias.[19] Additionally, some drugs used to treat obesity-associated comorbid conditions, particularly antidepressants and antipsychotics, may predispose patients to developing obesity, highlighting the bidirectional nature of obesity and chronic medication prescriptions in some cases. Providers must be aware of contraindicated and high-risk drug combinations when prescribing treatment for common obesity comorbid conditions.

The increased odds of polypharmacy for children with obesity found in our study is alarming, as it may be putting this group at disproportionate risk of adverse drug events. While the observed differences in polypharmacy prevalence between children with and without obesity were relatively small, the rates of obesity, severe obesity[9], and obesity-associated comorbid conditions continue to increase in the US.[20,21] Therefore, clinicians must remain cognizant of risks posed by polypharmacy in children with obesity. In addition to higher risk of polypharmacy, children with obesity have physiologic differences that may result in alterations in how drugs are absorbed, distributed, metabolized, and eliminated. For example, altered organ blood flow, higher levels of systemic inflammation, and differences in liver metabolic enzyme activity, are likely responsible for known pharmacokinetic differences for a number of drugs used commonly in children with obesity.[8,22,23] These pharmacokinetic differences, coupled with medical complexity of children with obesity

experiencing polypharmacy, confer a potential for increased adverse drug events that requires further investigation.

Our results should be considered in the context of several limitations. We used ICD-10 codes to identify children with a diagnosis of obesity. Just over 12% of our study cohort had a diagnosis code for obesity, a smaller proportion than expected in a large group of Medicaid-insured children.[9] While ICD-10 codes have a very high specificity (>99%) and positive predictive value, they have a relatively low sensitivity for capturing individuals with obesity.[24,25] Thus, we likely underestimated the prevalence of obesity in our study, which would bias our results toward a null finding. Second, we did not include children with private or supplementary insurance and our findings generalize best to Medicaid-only insured children. In our analysis of chronic medications, we could not account for over-the-counter prescriptions, leading us to underestimate the proportion of polypharmacy in our cohort. It is unclear whether such misclassification would disproportionately affect children with obesity. We also did not include information regarding acute medication prescriptions, which would add to the risk of polypharmacy, and is an area in need of further study. Finally, our analysis was based on dispensed pharmacy claims, and we were unable to account for actual use of dispensed drugs. Despite these limitations, our findings advance knowledge of polypharmacy in children with obesity by providing a comprehensive analysis of polypharmacy prevalence, frequently prescribed drug classes, and factors associated with polypharmacy and obesity.

Conclusions

Children with obesity have a higher prevalence of polypharmacy compared to children without obesity. Children with obesity were more often prescribed medications for mental health conditions and asthma, both obesity-associated comorbid conditions. As obesity rates continue to climb, clinicians must be cognizant of the risks of polypharmacy for children with obesity. Future work should evaluate the relationship between polypharmacy, drug-drug interactions, and adverse drug events in children with obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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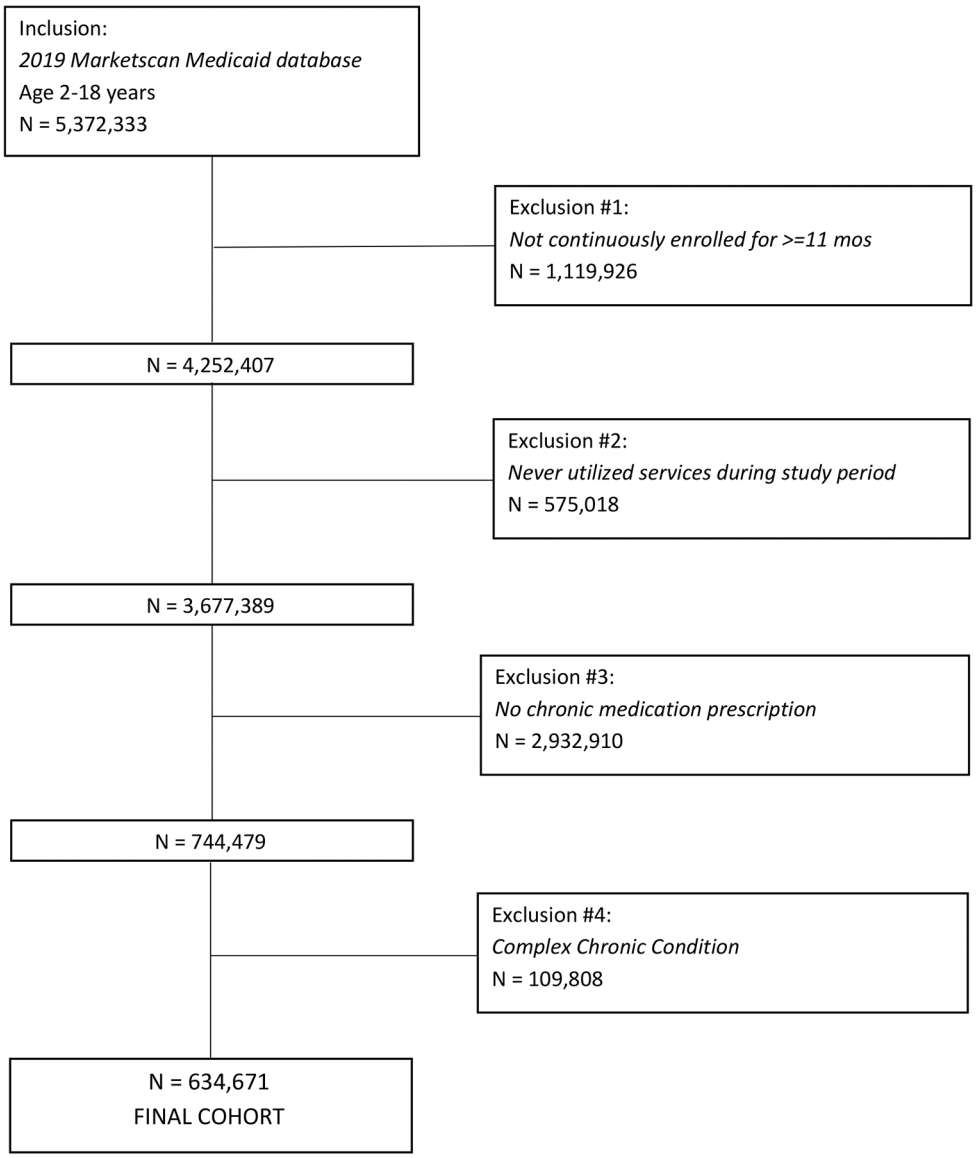

Figure 1.
STROBE diagram

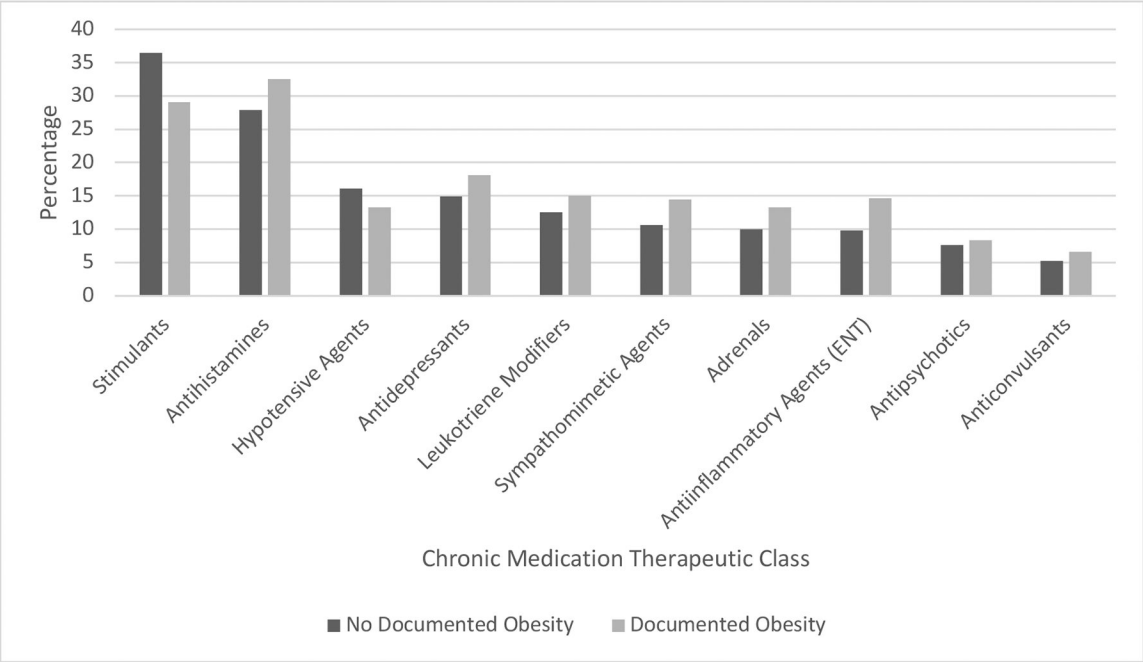

Figure 2.

Proportions of most frequently prescribed chronic medication classes by weight category*

*All comparisons statistically significant with $p<0.001$

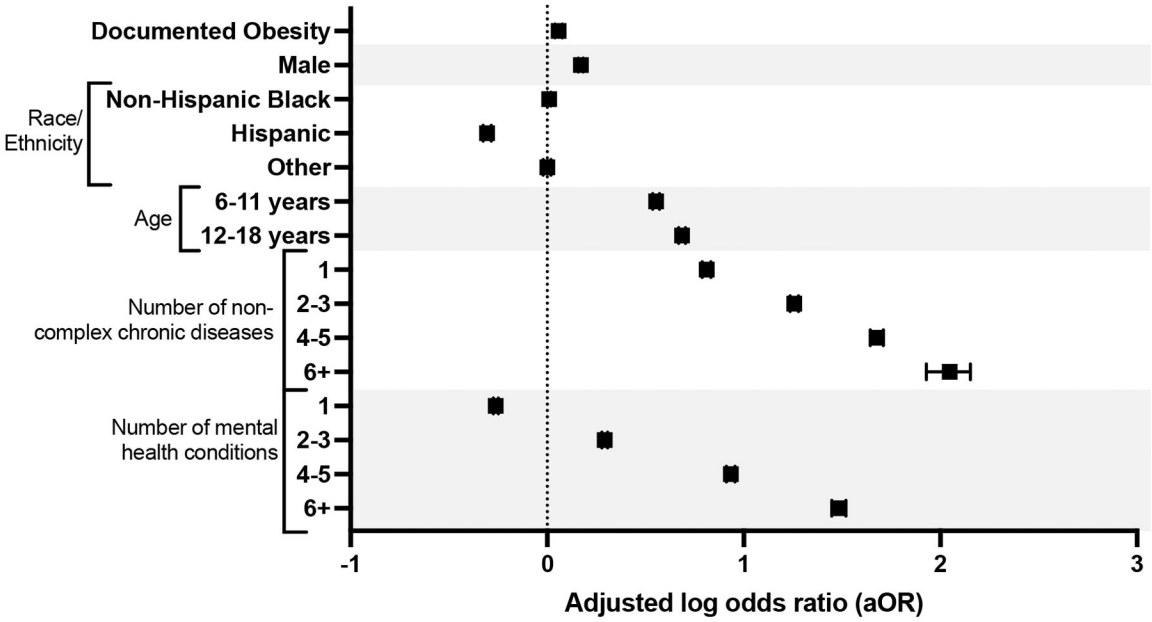

Figure 3.

Adjusted odds of polypharmacy

*Adjusted for: age, sex, race/ethnicity, number of non-complex chronic conditions and number of mental health conditions. With 95% confidence intervals.

Table 1.

Demographic and Clinical Characteristics of study population[†]

		Overall	No Documented Obesity	Documented Obesity
N Children		634671	557556 (87.8)	77115 (12.2)
Age	2–5 years	84655 (13.3)	77827 (14)	6828 (8.9)
	6–11 years	252921 (39.9)	224761 (40.3)	28160 (36.5)
	12–18 years	297095 (46.8)	254968 (45.7)	42127 (54.6)
Race/ethnicity	Non-Hispanic White	333240 (52.5)	295070 (52.9)	38170 (49.5)
	Non-Hispanic Black	183861 (29)	159139 (28.5)	24722 (32.1)
	Hispanic	44996 (7.1)	38076 (6.8)	6920 (9)
	Other	72574 (11.4)	65271 (11.7)	7303 (9.5)
Sex	Male	357320 (56.3)	317026 (56.9)	40294 (52.3)
Number of non-complex chronic diseases (except obesity)	0	67768 (10.7)	62391 (11.2)	5377 (7)
	1	278812 (43.9)	251078 (45)	27734 (36)
	2–3	256078 (40.3)	219320 (39.3)	36758 (47.7)
	4–5	29962 (4.7)	23363 (4.2)	6599 (8.6)
	6+	2051 (0.3)	1404 (0.3)	647 (0.8)
Number of mental health conditions	0	244986 (38.6)	214549 (38.5)	30437 (39.5)
	1	150552 (23.7)	133597 (24)	16955 (22)
	2–3	159684 (25.2)	141140 (25.3)	18544 (24)
	4–5	56318 (8.9)	49087 (8.8)	7231 (9.4)
	6+	23131 (3.6)	19183 (3.4)	3948 (5.1)
Number of Obesity comorbid conditions	0	386672 (60.9)	349921 (62.8)	36751 (47.7)
	1	222248 (35)	189737 (34)	32511 (42.2)
	2	23883 (3.8)	17177 (3.1)	6706 (8.7)
	3+	1868 (0.3)	721 (0.1)	1147 (1.5)
Obesity comorbid conditions	Hypertension (Idiopathic)	5400 (0.9)	2918 (0.5)	2482 (3.2)
	PCOS	1527 (0.2)	643 (0.1)	884 (1.1)
	Prediabetes	3324 (0.5)	1337 (0.2)	1987 (2.6)
	Diabetes (Type II)	2584 (0.4)	1514 (0.3)	1070 (1.4)
	OSA	7954 (1.3)	5208 (0.9)	2746 (3.6)
	Asthma	163797 (25.8)	138131 (24.8)	25666 (33.3)
	Depression	91291 (14.4)	76538 (13.7)	14753 (19.1)
	Anxiety	92923 (14.6)	79511 (14.3)	13412 (17.4)

[†]All comparisons statistically significant with $p<0.001$

PCOS – polycystic ovarian syndrome; OSA – obstructive sleep apnea

Table 2.

Number of Chronic Medications[†] by Weight Category

		Overall	No Documented Obesity	Documented Obesity	p value
Number chronic medications	1	321827 (50.7)	286201 (51.3)	35626 (46.2)	<.001
	2–4	265536 (41.8)	232347 (41.7)	33189 (43)	
	5–9	45366 (7.1)	37583 (6.7)	7783 (10.1)	
	10+	1942 (0.3)	1425 (0.3)	517 (0.7)	

[†]Number of chronic medications does not factor in element of prescription overlap; therefore, this is not equivalent to polypharmacy

Table 3.

Most Common Co-Prescribed Chronic Medication Classes

No Documented Obesity			
Medication Class 1†	**Medication Class 2†**	**N**	**%**
Hypotensive Agents	Stimulants	67020	12.0
Antihistamines	Leukotriene Modifiers	38547	6.9
Antidepressants	Stimulants	38279	6.9
Antihistamines	Anti-inflammatory Agents (ENT)	36791	6.6
Antihistamines	Stimulants	33856	6.1
Hypotensive Agents	Antidepressants	29799	5.3
Adrenals	Antihistamines	28488	5.1
Antipsychotics	Stimulants	26431	4.7
Adrenals	Leukotriene Modifiers	25997	4.7
Adrenals	Sympathomimetic Agents	25212	4.5

Documented Obesity			
Medication Class 1†	**Medication Class 2†**	**N**	**%**
Antihistamines	Anti-inflammatory Agents (ENT)	8737	11.3
Antihistamines	Leukotriene Modifiers	7837	10.2
Hypotensive Agents	Stimulants	7344	9.5
Adrenals	Antihistamines	6467	8.4
Antidepressants	Stimulants	6171	8.0
Adrenals	Leukotriene Modifiers	5665	7.3
Antihistamines	Sympathomimetic Agents	5580	7.2
Hypotensive Agents	Antidepressants	5495	7.1
Adrenals	Sympathomimetic Agents	5411	7.0
Antidepressants	Antipsychotics	5331	6.9

†Common examples of drugs in each class: Stimulants (methylphenidate); Leukotriene modifiers (montelukast); Hypotensive agents (clonidine); Antihistamines (cetirizine); Antidepressants (sertraline); Sympathomimetic agents (albuterol, pseudoephedrine); Adrenals (budesonide, other steroids); Anti-inflammatory agents ENT (fluticasone); Antipsychotics (risperidone); Anticonvulsants (levetiracetam)