Trends in characteristics of the recipients of new prescription stimulants between years 2010 and 2020 in the United States: An observational cohort study

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Summary

Background Stimulant prescriptions increased by 250% in the United States from 2006-2016 while diagnoses for ADHD minimally increased. There is insufficient data regarding who may be the recipients of these new stimulant prescriptions and safety of stimulants have come under scrutiny in some populations. We aim to describe trends in stimulant prescriptions across biopsychosocial patient level factors between 2010 and 2020.

Methods We applied a retrospective observational cohort design utilizing electronic health records from 52 healthcare organizations sourced from the TriNetX research network database in the United States. We assessed new stimulant prescriptions across biopsychosocial variables for recipients of prescriptions. We utilized linear regression to assess longitudinal trends of all participants and also conducted an age stratified logistic regression analysis.

Findings There was an increase in stimulants to people categorized as white (OR 1.24 CI 1.20-1.28), female (OR 1.28 CI 1.23-1.31), and to those with diagnosed anxiety disorders (OR 1.39 CI 1.35-1.44) as well as obesity (OR 1.34 CI 1.28-1.41). The average age of recipients increased throughout the study, and among people sixty-five and older, there was an increase in prescriptions to people with multiple cardiovascular risk factors.

Interpretation Prescription stimulant dispensing may have liberalized during the study period in some demographics as a greater number of new prescriptions were dispensed to individuals with risk of adverse outcomes (i.e. older individuals, obese individuals, and geriatric patients with CV risk factors) between 2010 and 2020. Similar trends in prescription medications were witnessed through the opioid epidemic and warrant attention given concerning trends with illicit stimulants. Additional research that investigates patient and provider motivation for stimulant prescriptions, as well as risk perception of stimulants, may be warranted.

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Keywords: Amphetamines; Stimulants; ADHD; Cardiovascular outcomes

Introduction

Stimulants are sympathomimetic drugs with FDA approval to treat Attention Deficit Hyperactivity Disorder (ADHD), as well as narcolepsy.[1] They are also prescribed off-label as an adjunct in the treatment of depression[2–5] and obesity. ADHD affects 11% of all children ages four to seventeen and is the most common reason for stimulant prescriptions. Among the individuals with ADHD, approximately 69.3% are prescribed medication.[6] Additionally, the CDC estimates that 42.4% of all Americans qualify as obese,[7] and phentermine is the most commonly prescribed drug for weight loss.[8,9] While their mechanism of action is not fully elucidated, stimulants freely cross the blood-brain barrier and exert their effects via elevation of synaptic concentrations of norepinephrine and dopamine.[10,11] Their stimulation of mesolimbic and mesocortical neural pathways improve concentration, increase energy,

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Research in context

Evidence before this study

Stimulant prescriptions are controlled substances with a black box warning for cardiovascular events as well as potential for diversion, yet prescriptions for these medications increased by 250% from 2006-2016 in the United States. Meanwhile, diagnoses for ADHD and narcolepsy have not seen concordant increases. The purpose of this study is to determine which patient groups are receiving stimulant prescriptions and whether individuals receiving these prescriptions carry diagnoses that elevate risk of negative outcomes. Given that multiple studies have demonstrated increased risk of cardiovascular events among older adults, this study assesses trends in prescription stimulants among age stratified cohorts.

Added value of this study

This study suggests that prescriptions for stimulants may be increasing for individuals at risk of negative outcomes including those with anxiety and those at risk factors for cardiovascular disease. This highlights a shift in provider prescribing practices that may be attributed to increased leniency with stimulant prescriptions for some demographics over the past two decades.

Implications of all the available evidence

The risk of stimulants in healthy pediatric populations are well established, however data is accumulating that certain sub-populations with risk factors for cardiovascular disease and mental illness may experience harm from these medications. Still, these data align with other studies that demonstrate practitioners have increased the total number prescription stimulants over the past decade, and many of those prescriptions have been dispensed to individuals at risk of negative outcomes. These trends in prescription stimulants, amidst a growing stimulant epidemic, mirror trends in prescription opioids in the early stages of the opioid epidemic. Additional research that investigates patient and provider motivation for stimulant prescriptions, as well as risk perception of stimulants, may be warranted.

and decrease appetite.[12] While they are effective in alleviating aforementioned symptoms, their impact on the reward system potentiates the possibility for dependence and misuse.[13–16] Young adults are at particularly high risk of stimulant misuse.[17] Moreover, stimulants also produce effects on other organ systems, and safety of stimulants have come under scrutiny in some populations. Animal models have demonstrated potentially adverse epigenetic changes related to repeated substance exposure, including FDA-approved stimulant medications such as stimulants,[18,19] and concern for cardiovascular risks among older adults has been raised.[20,21] This is relevant given prescriptions for stimulants increased by 250% in the United States from 2006-2016 while diagnoses for ADHD have increased by just 4%.[22,23] As such, it remains unclear who might be the primary recipient of these new stimulant prescriptions. Previous studies have demonstrated that ADHD diagnoses in children correlate with certain demographic factors, including male sex, Black or White race, income below 200% of the federal poverty line, and public health insurance coverage.[24] Additionally, National Center for Health Statistics data has shown that obesity rates among Black and Hispanic children and adults are higher than their White and Asian counterparts.[25] Still, there is a paucity of data regarding the actual dispensing of prescription stimulants within those groups. In this retrospective cohort study, we aim to describe trends in stimulant prescriptions across biopsychosocial patient level factors between 2010 and 2020.

Methods

Study design

The analysis applied a retrospective observational design utilizing electronic health records from 52 healthcare organizations sourced from the TriNetX research network database in the United States (Cambridge, MA). TriNetX is a federated health research network that provides researchers with access to de-identified, aggregated EHR data (demographics, diagnoses, procedures, medications, and laboratory tests) of more than 70 million patients from participating healthcare organizations. The platform is compliant with the security and confidentiality regulations of the Health Insurance Portability and Accountability Act of 1996. Because these are aggregate data and there was no patient-level identifiable data involved or accessed in the analysis, missingness could not be assessed. For these same reasons, this research was determined to be exempt from the Institutional Review Board oversight and patient consent was not possible or required.

Study population

The study population consisted of pediatric and adult patients who were prescribed stimulants between January 1, 2010 and December 31, 2020, but had no history of stimulant prescriptions prior to 2010. Each eligible patient was attributed to a yearly cohort, which corresponded to the year when they were first prescribed stimulant. Data collected included patient demographics (age, sex, race/ethnicity), medical conditions (acute myocardial infarction, arrhythmias, atherosclerotic heart disease, cerebral infarction, hypertension, narcolepsy, obesity), psychiatric history (ADHD, anxiety, bipolar, depression, schizophrenia), and substance

use disorders (alcohol, cannabis, cocaine, nicotine, opioid, stimulant) that were documented in patients' EHRs before the initial stimulant prescription. The population characteristics consisted of binary variables (1=yes, 0=no), indicating the presence of demographics and clinical conditions. Detailed information for diagnosis codes are provided in the Appendix.

Data analysis

The number of patients who were newly prescribed stimulants each year was calculated representing the incidence of new patients starting stimulant treatment in that year. Patients who had prior history of stimulant prescriptions were excluded from the incidence calculation. The percentage of the incidence of new patients on prescription stimulants was also computed by demographic and clinical characteristic. The age stratified analysis involved the following age groups: ≤17, 18-25, 26-44, 45-64 and ≥65. To better characterize the pattern of the incidence of new patients on stimulant treatment over year, we utilized logistic regression modeling to assess the change of population characteristics among patients newly prescribed stimulants from 2010 to 2020, by each of the aforementioned age groups. Contrast analysis also was performed to calculate odds ratios and confidence intervals for the likelihood of a population characteristic among patients receiving initial stimulant prescription in 2010 compared to patients receiving initial stimulant prescription in 2020. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc).

Role of the funding source

The funding source did not have any role in the study design, data collection, analysis, or interpretation of data. They did not participate in the writing of the report nor in the decision to submit the paper for publication Curtis Bone, Wen Jan Tuan, and Shannon Brumbaugh had full access to the data, which they were able to access and verify. All authors agreed to submit for publication.

Results

When considering all ages, there were 23,677 individuals who received a stimulant prescription in 2010 and there were 107,756 individuals with documented stimulant prescriptions in 2020.

The characteristics of patients receiving new stimulant prescriptions changed across multiple biopsychosocial domains over these ten years.

Linear trends

When we assessed year to year variability in prescriptions with best fit lines, we observed that trends were not linear in all cases however there was a consistent increase in the average age of people who received prescription stimulants, an increase in BMI among prescription recipients, and an increase in prescriptions to people with anxiety disorders as well as ADHD. There was a decreased trend in prescriptions to people with cannabis use disorder and opioid use disorder (Figure 1).

Demographics

When we compare 2010 to 2020, there was an increase in prescriptions delivered to people categorized as Female (46% to 52% OR 1.28 CI 1.23-1.31), Asian (0.55% to 1.34% OR 2.25 CI 2.05-2.94) and White (71% to 75% OR 1.24 CI 1.20-1.28) (Table 1 and Figure 2). When we assess these trends by age group, we witness an increase in prevalence of stimulant prescriptions to those identified as female for all age groups with the exception of 26-44 year olds (OR 0.93 CI 0.87-0.98) and those who are 65 and older (OR 1.00 CI 0.87-1.16). Although we observe an increase in prevalence of prescriptions to American Indian or Alaska Natives in all age groups (OR 2.25 CI 1.88-2.69) Asian individuals (OR 2.46 CI 2.05-2.94) and people identified as White (OR 1.24 CI 1.20-1.28), the only group that had a significant increase in prescriptions to individuals 65 and older is people identified as white (OR 1.48 CI 1.24-1.76).

Medical comorbidities

When we consider biological comorbidities for all age groups, there were fewer prescriptions dispensed in 2020 compared to 2010 among people with history of myocardial infarction (OR 0.77 CI 0.64-0.92), atherosclerotic heart disease (OR 0.76 CI 0.69-0.85), diabetes (OR 0.89 CI 0.83-0.95), and hypertension (OR 0.91 CI 0.87-0.95) while there was a higher prevalence of people with diagnosis of obesity who received stimulant prescriptions in 2020 (OR 1.34 CI 1.28-1.41) when compared to 2010. However, there was variability by age group in some of these domains. For example, there was an increase in prevalence of stimulants in 2020 among people 65 and older with diagnosis of cardiac arrythmia, cerebral infarction, diabetes, and essential hypertension. Moreover, the only age groups with an increase in stimulant prescriptions among people with BMI greater than 30 were ages 18-25, 26-44, and 45-64. Individuals 17 and younger had the lowest percentages of prescriptions with a diagnosis of myocardial infarction (0.66%), atherosclerotic heart disease (2.0%), obesity (11.9%), arrhythmia (2.7%), cerebral infarction 0.90%) and hypertension (11.5%). They remained the least likely to receive stimulant prescriptions after these diagnoses in 2020 and were

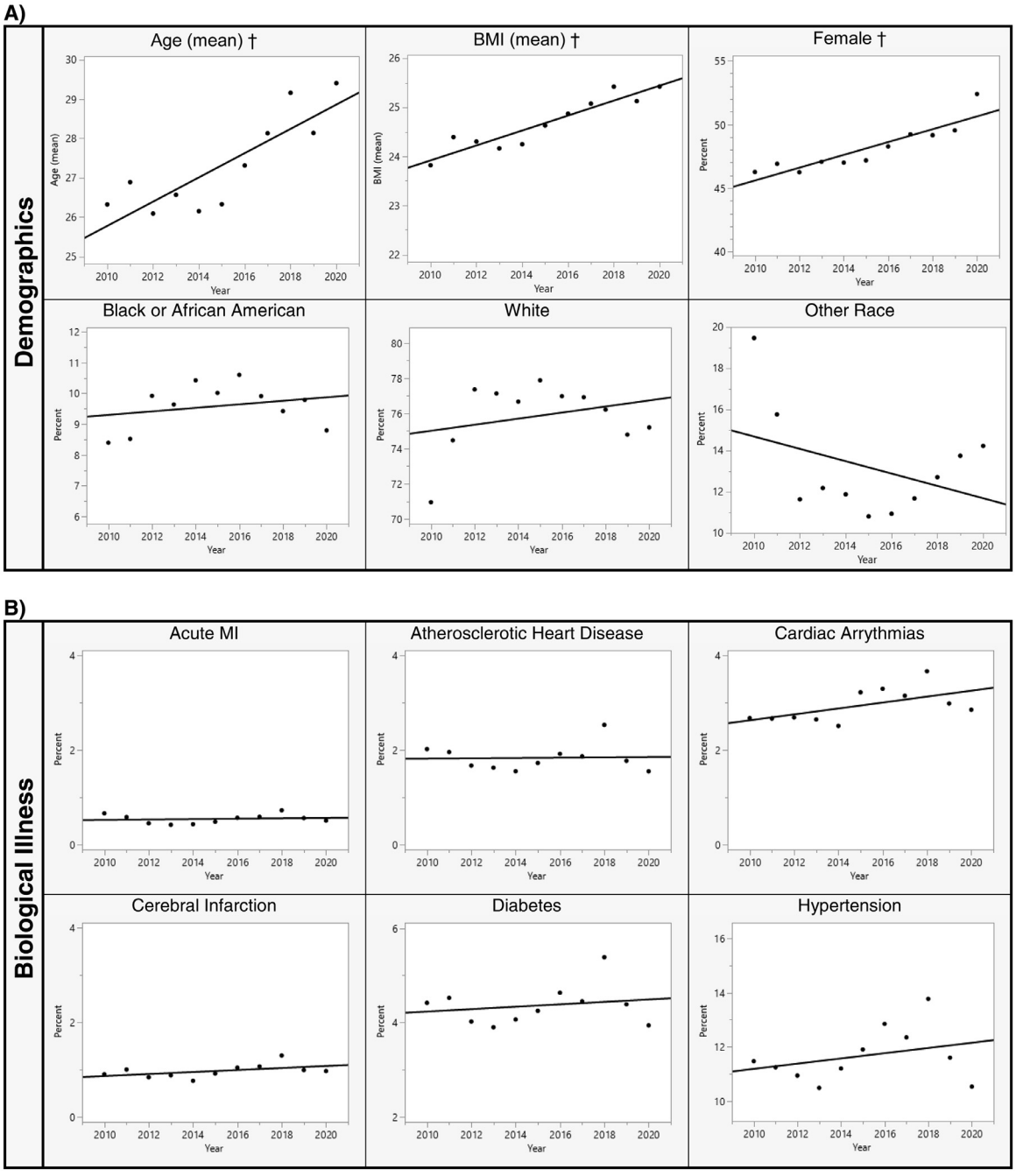
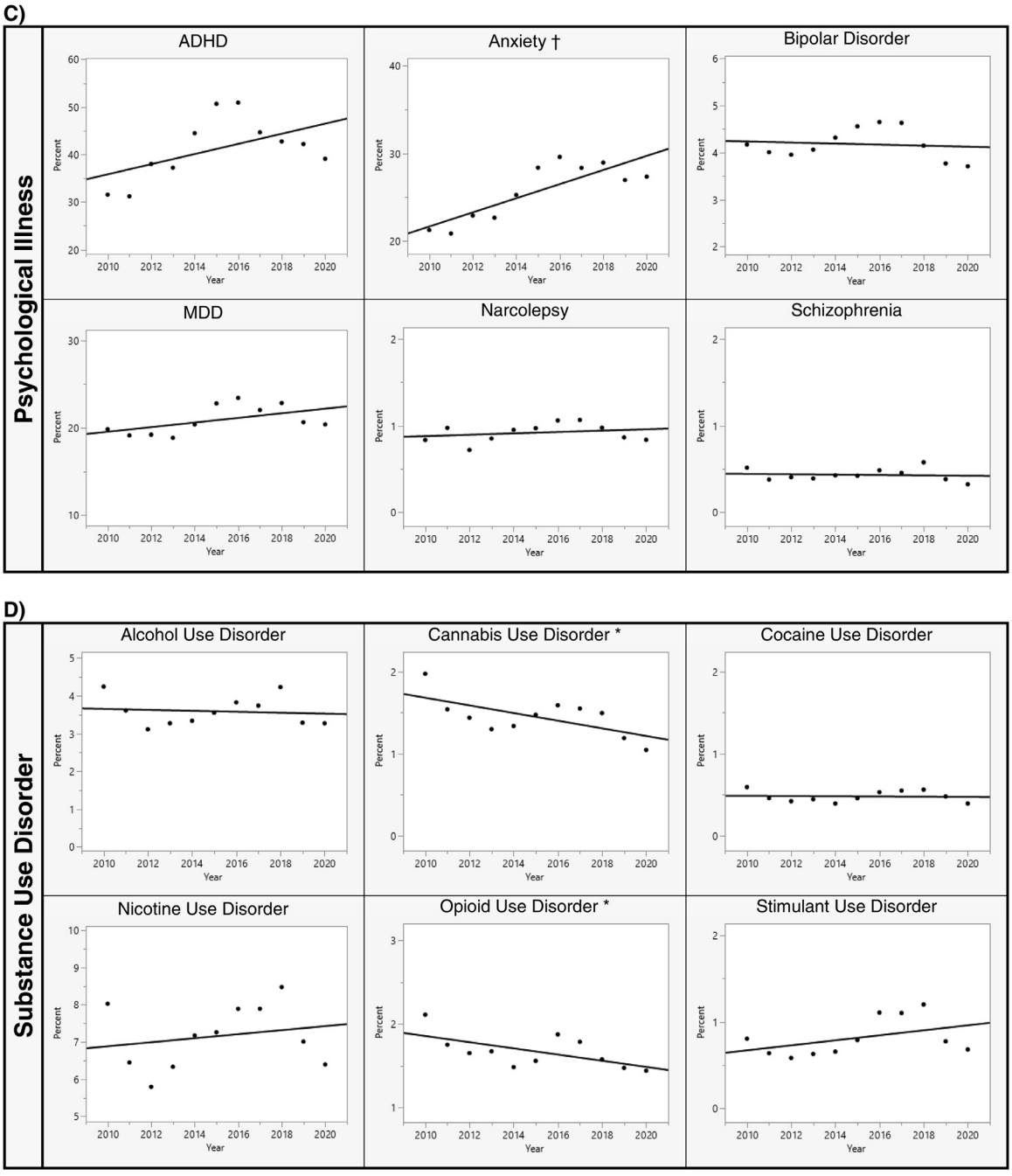


Figure 1. Trends in biopsychosocial characteristics of patients newly prescribed an amphetamine in the United States from years 2010-2020.

* Statistical significance ($p < 0.05$) AND Slope <1.0.

† Statistical significance ($p < 0.05$) AND Slope >1.0.



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	All Ages	<17 years old	18-25 years old	26-44 years old	45-64 years old	65+ years old
2010 N (%)	23667	10414 (44.00)	3592 (15.18)	4850 (20.49)	3795 (16.03)	876 (3.70)
2020 N (%)	107756	35028 (32.51)	16125 (14.96)	34356 (31.88)	17525 (16.26)	4635 (4.30)
	2010 vs. 2020 OR (95% CI)	**2010 vs. 2020 OR (95% CI)**	**2010 vs. 2020 OR (95% CI)**	**2010 vs. 2020 OR (95% CI)**	**2010 vs. 2020 OR (95% CI)**	**2010 vs. 2020 OR (95% CI)**
Demographics						
Female	1.28 (1.24-1.31)†	1.29 (1.23-1.36)†	1.27 (1.18-1.36)†	0.93 (0.87-0.98)*	1.09 (1.01-1.17)†	1.00 (0.87-1.16)
Male	0.78 (0.76-0.81)*	0.77 (0.74-0.81)*	0.79 (0.73-0.85)*	1.08 (1.01-1.15)†	0.92 (0.86-0.99)*	1.00 (0.87-1.16)
American Indian or Alaska Native	2.25 (1.88-2.69)†	2.70 (1.93-3.79)†	2.02 (1.45-2.83)†	2.40 (1.68-3.43)†	1.40 (0.87-2.26)	1.37 (0.49-3.86)
Asian	2.46 (2.05-2.94)†	2.87 (2.03-4.04)†	1.94 (1.39-2.72)†	2.56 (1.79-3.66)†	1.80 (1.11-2.90)†	1.90 (0.68-5.32)
Black or African American	1.05 (1.00-1.11)	1.11 (1.04-1.18)†	1.45 (1.22-1.73)†	1.80 (1.54-2.12)†	1.20 (1.02-1.42)†	0.72 (0.53-0.98)*
White	1.24 (1.20-1.28)†	1.11 (1.06-1.16)†	1.21 (1.12-1.31)†	1.16 (1.08-1.25)†	1.26 (1.16-1.38)†	1.48 (1.24-1.76)†
Other Race	0.69 (0.66-0.71)*	0.77 (0.73-0.81)*	0.65 (0.59-0.71)*	0.64 (0.59-0.69)*	0.67 (0.61-0.74)*	0.68 (0.56-0.83)*
Medical Comorbidities						
Acute myocardial infarction	0.77 (0.64-0.92)*	0.07 (0.01-0.66)*	0.74 (0.20-2.70)	0.58 (0.37-0.92)*	0.56 (0.44-0.72)*	1.11 (0.77-1.60)
Atherosclerotic heart disease	0.76 (0.69-0.85)*	0.45 (0.13-1.58)	0.31 (0.10-0.98)*	0.33 (0.24-0.46)*	0.55 (0.48-0.64)*	1.19 (0.97-1.46)
Cardiac arrhythmias	1.07 (0.98-1.17)	1.06 (0.90-1.27)	1.67 (1.27-2.19)†	0.84 (0.70-1.02)	0.69 (0.59-0.81)*	1.76 (1.34-2.31)†
Cerebral infarction	1.08 (0.93-1.25)	1.19 (0.59-2.38)	0.67 (0.31-1.42)	0.58 (0.41-0.82)*	0.85 (0.68-1.06)	1.76 (1.28-2.42)†
Diabetes	0.89 (0.83-0.95)*	0.56 (0.46-0.68)*	0.90 (0.66-1.23)	0.56 (0.49-0.65)*	0.82 (0.74-0.92)*	1.70 (1.37-2.11)†
Essential (primary) hypertension	0.91 (0.87-0.95)*	0.37 (0.32-0.44)*	0.48 (0.40-0.57)*	0.60 (0.55-0.66)*	0.84 (0.78-0.91)*	2.16 (1.85-2.52)†
BMI Normal (<24.9)	0.74 (0.71-0.77)*	0.89 (0.82-0.96)*	0.82 (0.74-0.91)*	0.81 (0.74-0.88)*	0.76 (0.68-0.85)*	0.85 (0.70-1.05)
BMI Overweight (25.0-29.9)	1.15 (1.10-1.21)†	1.13 (1.02-1.25)†	1.01 (0.90-1.14)	1.09 (1.00-1.20)	0.91 (0.82-1.01)	1.08 (0.88-1.33)
BMI Obese (>30.0)	1.34 (1.28-1.41)†	1.09 (0.98-1.23)	1.33 (1.17-1.51)†	1.13 (1.04-1.24)†	1.36 (1.23-1.51)†	1.09 (0.88-1.35)
Psychological Diagnoses						
Anxiety disorders	1.39 (1.35-1.44)†	1.04 (0.98-1.10)	1.73 (1.59-1.89)†	1.31 (1.22-1.40)†	1.33 (1.23-1.45)†	2.21 (1.81-2.70)†
Attention-deficit hyperactivity disorders	1.39 (1.35-1.44)†	1.64 (1.57-1.72)†	1.89 (1.74-2.05)†	1.50 (1.40-1.60)†	1.21 (1.10-1.32)†	1.75 (1.31-2.34)†
Bipolar disorder	0.89 (0.82-0.95)*	0.39 (0.33-0.46)*	0.87 (0.73-1.05)	0.75 (0.67-0.84)*	1.07 (0.91-1.25)*	1.93 (1.20-3.11)†
Major depressive disorder	1.04 (1.00-1.07)	0.72 (0.67-0.76)*	1.47 (1.33-1.61)†	0.88 (0.82-0.94)*	0.85 (0.79-0.92)*	1.62 (1.37-1.92)†
Narcolepsy	1.00 (0.86-1.17)	1.66 (0.90-3.07)	1.52 (1.00-2.32)	0.72 (0.56-0.93)*	0.68 (0.51-0.89)*	0.80 (0.47-1.34)
Schizophrenia	0.63 (0.51-0.77)*	0.22 (0.14-0.36)*	0.51 (0.31-0.84)*	0.62 (0.43-0.90)*	0.93 (0.57-1.52)	1.58 (0.48-5.24)
Comorbid Substance Use						
Alcohol Use Disorder	0.76 (0.71-0.82)*	0.09 (0.07-0.12)*	0.40 (0.34-0.47)*	0.97 (0.86-1.09)	1.05 (0.88-1.25)	1.39 (0.82-2.36)
Cannabis Use Disorder	0.52 (0.47-0.58)*	0.20 (0.16-0.24)*	0.74 (0.59-0.94)*	0.68 (0.55-0.85)*	1.16 (0.75-1.79)	N/A
Cocaine Use Disorder	0.66 (0.54-0.80)*	0.09 (0.04-0.19)*	0.36 (0.22-0.58)*	0.50 (0.38-0.65)*	1.54 (0.94-2.53)	N/A
Nicotine Use Disorder	0.78 (0.74-0.83)*	0.08 (0.07-0.10)*	0.51 (0.44-0.58)*	0.76 (0.69-0.83)*	1.22 (1.08-1.37)†	1.97 (1.40-2.77)†
Opioid Use Disorder	0.68 (0.61-0.75)*	0.12 (0.08-0.18)*	0.16 (0.12-0.21)*	0.66 (0.57-0.77)*	0.94 (0.75-1.18)	1.52 (0.65-3.56)
Other stimulant Use Disorder	0.84 (0.72-0.99)*	0.11 (0.06-0.19)*	0.37 (0.26-0.53)*	0.89 (0.69-1.14)	1.62 (1.04-2.53)†	N/A

***Table 1*: Age stratified logistic regression of baseline characteristics in 2020 vs. 2010.**

* Statistical significance ($p < 0.05$) AND OR <1.0.

† Statistical significance ($p < 0.05$) AND OR >1.0.

Lack of a star indicates that difference between point estimates in 2010 and 2020 were not statistically significant.

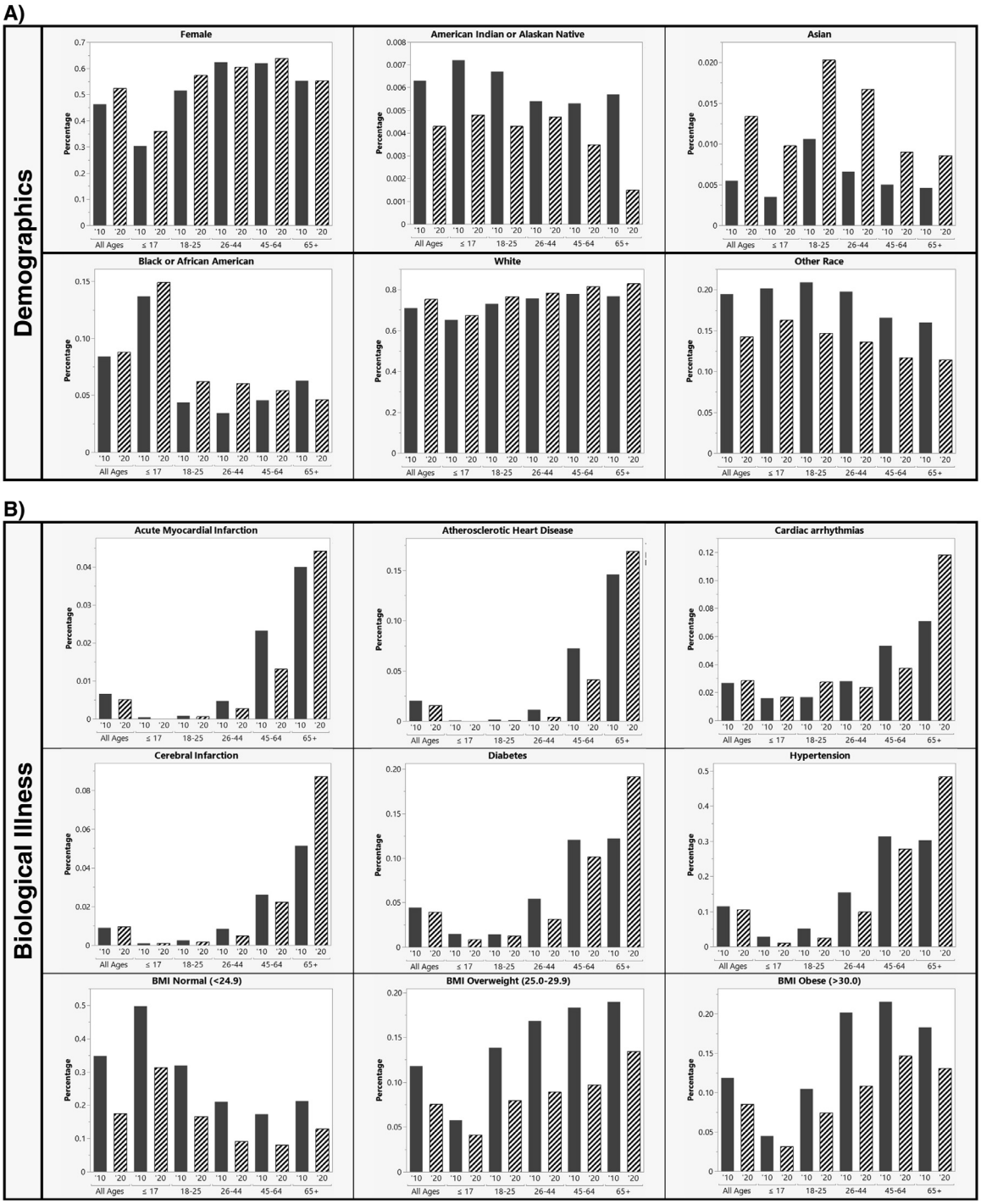

Figure 2. Age stratified trends in biopsychosocial characteristics of patients newly prescribed an amphetamine in the United States in 2010 vs. 2020.

'10 refers to 2010 and '20 refers to 2020.

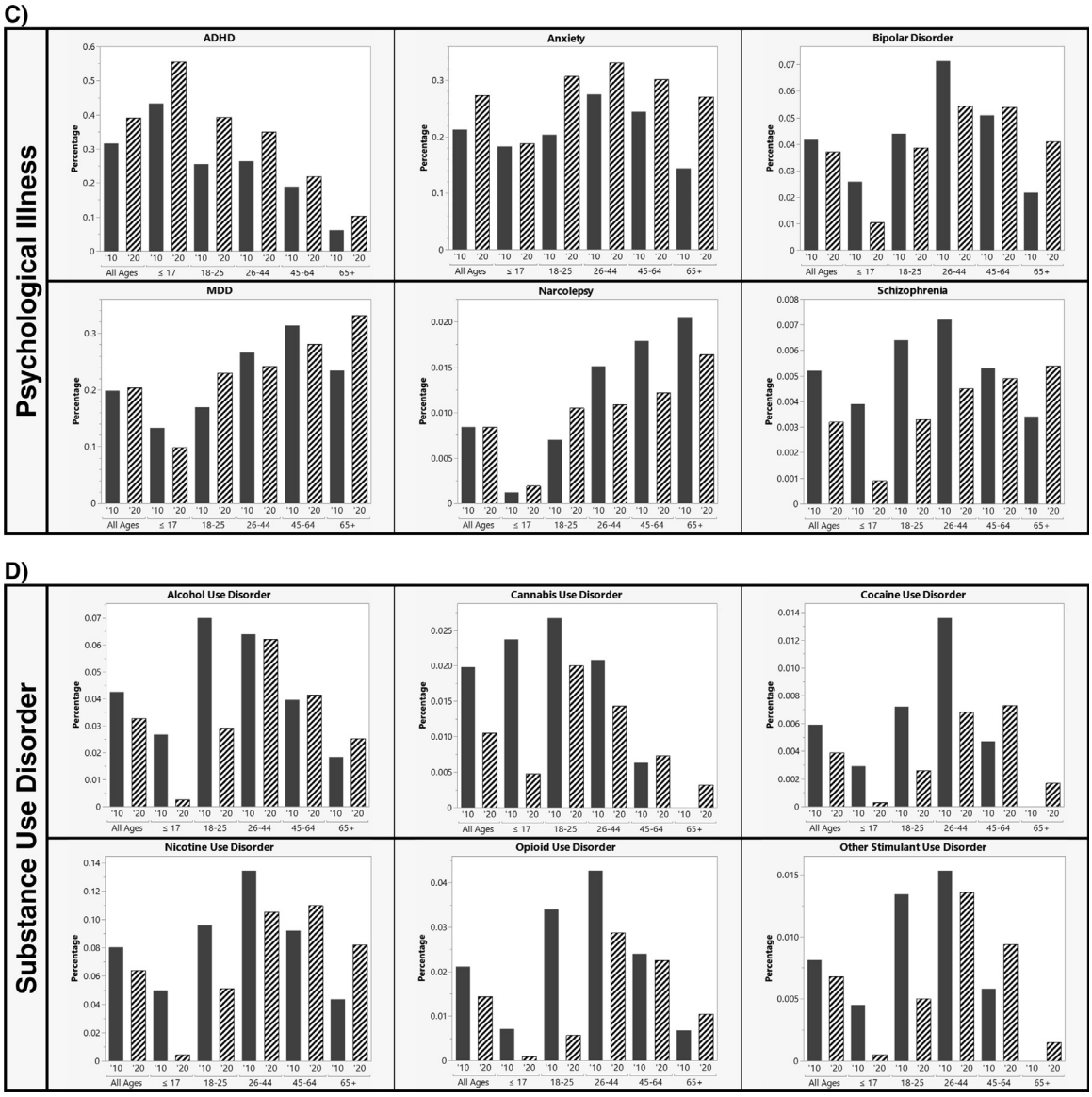

Figure 2 Continued.

also the least likely to receive a prescription after documentation of BMI greater than 30.

Psychological diagnoses

The only psychological comorbidities with an increase in stimulant prescriptions for all ages included anxiety disorders (OR 1.39 CI 1.35-1.44) and ADHD (OR 1.39 CI 1.35-1.44). There were fewer prescription stimulants in 2020 compared to 2010 for those with a diagnosis of bipolar disorder (0R 0.89 CI 0.82-0.95) and Schizophrenia (OR 0.63 CI 0.51-0.77).

In 2010, people who were 17 and younger received the majority of prescriptions after a diagnosis of ADHD, those who were 26-44 received the most prescriptions after a diagnosis of anxiety disorder, and bipolar disorder, while people 65 and older received the majority of prescriptions after diagnosis of narcolepsy. In 2020, these trends persisted however individuals 65 and older received more stimulant prescriptions than all other age groups with diagnosis of major depressive disorder.

Substance use disorders

Finally, there was lower odds of stimulant prescriptions for people with substance use disorders in 2020 compared to 2010 without dramatic variability by age group.

When we assess prescriptions distributed to people with substance use disorders by age group in 2010, individuals that were 65 and older who received stimulant prescriptions were the least likely to have a diagnosis of alcohol use disorder, cannabis use disorder, cocaine use disorder, nicotine use disorder, or opioid use disorder. However, in 2020, individuals that were 65 and older with a diagnosis of cocaine use disorder, nicotine use disorder, opioid use disorder and other stimulant disorders had higher prevalence of prescription stimulants than pediatric populations. Individuals 26-44 remained the most likely to receive stimulant prescriptions with a diagnosis of opioid use disorder and other stimulant use disorder while those 45-64 were the most often prescribed stimulants with an existing diagnosis of nicotine use disorder and cocaine use disorder.

Discussion

This study demonstrates that new stimulant prescriptions have been dispensed to increasingly older individuals since 2010. Moreover, there are trends that suggest increase in new prescriptions to people with known cardiovascular and mental health comorbidities that may be exacerbated by stimulant use. At the same time, there were notable reductions in prescriptions to people with substance use disorders and cardiovascular risk factors in most age groups. However, trends towards liberalization of prescription stimulants were most pronounced among individuals older than sixty-five. The trend that there has been an increase in new prescription stimulants to older individuals over the past 10 years is notable given recent evidence that prescriptions in geriatric populations is associated with more than a six-fold increased risk of cardiovascular events.[21] It is well established that stimulants increase heart rate and blood pressure among all age demographics.[26,27] However, the clinical relevance of this has been questioned.[28] In a youthful cardiovascular system, the persistent elevation in catecholamines produced by stimulants may not have a tremendous impact on cardiovascular risk, but a more mature cardiovascular system may be vulnerable. As the cardiovascular system ages, natural elevation in levels of atherosclerosis, atrophy of pacemaker cells, damage to the bundle of His, and interstitial fibrosis, may enhance susceptibility to adverse outcomes from stimulants. While the aforementioned conditions may appear pathologic, these changes are expected.[29,30] Indeed one post-mortem study showed that more than 60% of individuals older than 60 years of age had atherosclerosis[31] while a separate study demonstrated an expected loss of 50%-75% of all pacemaker cells by age 50.[8] In addition, responsiveness to beta agonist stimulation decreases, while levels of circulating catecholamines increase through the lifespan.[29,32] Given that stress dose levels of stimulants (i.e. methamphetamine and cocaine) can result in adverse outcomes in a youthful cardiovascular system such as arrhythmia, myocardial infarction, and stroke, one can imagine that prescription level stimulants may result in adverse outcomes for a vulnerable cardiovascular system.[33–35]

There are a number of variables that may contribute to the increase in stimulant prescriptions generally and also to vulnerable demographics evaluated in this study. Considering the socio-ecological model, we can imagine individual, relational, institutional, and societal factors intersecting to influence the witnessed trends.[36] First, awareness of ADHD and comfort with treatment continues to grow among patients and families across the country.[37] This may contribute to the increase in prescription stimulants seen across all ages of our dataset. Second, health care has placed increased financial pressure on the patient-provider relationship which is often measured in terms of patient satisfaction.[38] Given the benefits that prescription stimulants may provide for efforts with weight loss, increased energy, and improved mood, they may be more commonly requested by patients than other medications; providers may experience invisible or even institutionalized pressure to comply with such requests despite reservations.

From a community standpoint, there is increased recognition in medical communities that medications can be effective in treatment of obesity. There have also been multiple studies that demonstrate the effectiveness of stimulants in treatment of geriatric depression.[5,39] These factors may influence the increased BMI seen among people who receive stimulant prescriptions and the increase in older adults with depression that received this medication. Finally, societal factors such as legislation and CDC guidelines related to the opioid epidemic, and cannabis legislation may have influenced stimulant prescription trends.[40] Prescription opioids have reduced in recent years due macro-level and institutional influences[41,42] There is evidence that when individuals are not given access to one substance, they will often engage with a separate substance.[43–45] So it is plausible that reduced access to opioids has increased patient level desire for stimulants. There is also evidence that cannabis liberalization has been associated with an increase in non-cannabis related substance use.[46] It is possible that patients utilize the increased focus and energy provided by stimulants to counteract the sedating and cognitively clouding side effects of cannabis.[47] Additionally, benzodiazepine[48] and gabapentin[49] prescriptions have increased dramatically over the past 10-15 years. Their use for chronic pain, anxiety, and/or recreation, may have an impact on desire for stimulants similar to alleviate sedation and cognitive dulling. Finally, as mentioned there is a non-linear trend in many of the variables assessed in this study and a notable bulge in prescriptions from 2016-2018. There may be a number of factors that influence these dynamics, however, some have attributed the dramatic rise in stimulant

prescriptions leading up to 2016 to targeted marketing. From 2013 to 2018, there was an estimated 20 million dollars spent on direct payments to more than 55,000 physicians that were tied to prescription stimulants.[50]

Given that prescriptions to adults have outpaced those to pediatric populations, and multiple studies demonstrate increased risk of cardiovascular events in older adults,[21,51] the public health consequences of this fundamental shift in prescribing trends remains unclear. However, the impact may not be experienced evenly among demographic groups. The observation that stimulant prescriptions to older adults were primarily dispensed to people identified as white may be due to bias among prescribers and could disproportionately impact cardiovascular events among white older adults. Similar trends were witnessed in prescription opioids and resulted in disproportionate overdose deaths among Caucasian people when compared to other demographics.[52] However, in addition to the cardiovascular risks associated with stimulants, they also carry significant potential to influence mental health outcomes. Stimulants are associated with increased risk of insomnia, anxiety, and psychosis.[53–56] While the neurobiology that connects stimulants to sleep is not well elucidated, multiple studies have demonstrated increased sleep latency, elevated sleep disturbance, and increased nighttime wakings among people who use stimulants.[57,58] (Although multiple studies assess the influence of stimulants on pediatric sleep, fewer studies assess this relationship in adults. One large study demonstrated increased sleep latency and night time wakings among adults with ADHD, but a thorough review on this topic explained there is insufficient data on adults to describe this relationship in older age groups.[59] While there is limited information regarding sleep in adults, there are copious reports of anxiety[56] and even psychosis (characterized by hallucinations and delusions) related to stimulant administration.[60] The neurobiological mechanism for the conditions centers on dopamine regulation and GABA receptor activation.[53] While stimulants broadly exacerbated feelings of anxiety, it is challenging to predict who might experience psychosis. Still, cases are attributed to both genetic predisposition and the inherent properties of the substance.[61] So it is not surprising that previous studies have shown a relationship between underlying depression and anxiety with stimulant induced psychosis.[62] The increase in stimulant prescriptions dispensed over the past 10 years to people with mood disorders and the notable increase in psychiatric admissions through the COVID pandemic may give clinicians pause and warrant further investigation by public health experts.[63]

Despite negative consequences associated with stimulants, there are multiple studies that suggest potential therapeutic value for severe depression and cognitive impairment, particularly in older individuals. A systematic review of this topic published in 2020 suggests that 81.5% of studies demonstrated clinical improvement in geriatric depression and/or cognitive function with utilization of stimulants.[3] A separate systematic review published in 2021 concluded that methylphenidate was effective in all five studies of geriatric depression, particularly when combined with citalopram.[39] They have also demonstrated effectiveness in treatment of obesity and binge eating disorders.[64–66] Interestingly, people seventeen or younger were the least likely to receive a stimulant prescription in this study. Given established safety profiles for stimulants in pediatric patients along with surging levels of juvenile obesity and diabetes, the relatively low level of prescriptions to this demographic may represent a clinical and public health opportunity.

While we feel these data offer necessary perspective regarding prescribing patterns for an important class of medications, there are several limitations to consider. First, while the overall sample size was robust, the number of health care organizations increased from 2010 to 2020 as more systems converted to using electronic health records. Furthermore, our dataset consisted of people who received stimulant prescriptions, so we report raw numbers and percentages among those who received stimulant prescriptions, rather than percentages of a more comprehensive sample, across the study period.

In addition, all data retrieved was based on ICD codes that had been documented for each patient. There are inherent limitations with EHR studies predicated on ICD-10 codes including inaccurate coding and incomplete coding. For example, substance use disorders are often under-reported by patients[67] and thus may not be accurately coded by providers. In addition, stimulant prescriptions vary by geographic region[22] and our EHR based data set does not provide geographic location nor insurance payer type. Moreover, these data reflect population trends specific to the 52 Federated Health Centers that contribute to the TriNetX dataset and it may not be a perfectly representative sample of the United States. In addition, the Covid-19 pandemic may have impacted prescribing patterns in the latter part of this study due to the variety of changes within healthcare systems and changes in patient utilization of health care resources.

Though these limitations are evident, we feel these data remain important as we are not aware of other recent studies that describe these trends. Moreover, we feel it relevant to highlight that although we are not able to verify the geographic distribution of our sample, the trends we observed align with other studies that sought to address similar questions. For example, one study that included prescriptions provided across the United States from 2007 to 2011 from 38,000 retail pharmacies and a separate study that focused on prescriptions to pediatric populations in Michigan through use of the state's online drug monitoring program, both

demonstrated an increase in prescription stimulants over their respective study periods.[68,69] Finally, a study that utilized data from the IMS Health (now known as IQVIA) National Prescription Audit (NPA), (which purports to report on 92% of all outpatient prescriptions sold in the United States) assessed trends in prescription from 2014 to 2019[70] and detected a significant increase in overall stimulant prescriptions, an increase in prescriptions to people identified as female, and an increase in prescriptions to older adults including people older than 60. We feel the alignment of our data with these population level US studies suggests that our results may generalize across the United States.

The trends that we are witnessing in stimulant prescriptions mirror trends seen with the opioid epidemic; raising awareness for providers was critical tool to influence prescribing patterns. We feel it is notable that prescriptions have increased to older adults, individuals with anxiety, and people with hypertension while physical and mental health consequences of stimulant use in these populations are either concerning or unclear. Future studies that include geospatial analysis, studies that assess the impact of Medicaid status on prescription stimulants, and those that draw from an ideally representative US sample (such as the National Health and Nutrition Examination Survey) may be warranted to further characterize trends in prescriptions for stimulants.

Prescription stimulant dispensing may have liberalized during the study period as a greater number of new prescriptions were dispensed to individuals with risk of adverse outcomes (i.e. older individuals, obese individuals, and geriatric patients with CV risk factors) between 2010 and 2020. Investigation into patient and provider motivation for stimulant prescriptions as well as their perception of stimulant related risks, should be pursued. Further research is also needed to quantify stimulant related risks in sub-populations to better inform patient and provider decision making.

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Contributors

Shannon Brumbaugh: conceptualization; writing – original draft; writing – reviewing and editing.
Wen Jan Tuan: data curation; formal analysis; methodology; project administration; supervision; writing – reviewing and editing.
James R. Latronica: writing – original draft; writing – reviewing and editing; project administration.
Curtis Bone: conceptualization; visualization; methodology; supervision; project administration; writing – original draft; writing – reviewing and editing.

Data sharing statement

The anonymized patient data collected for the study from the TriNetX database will be made available, upon request, pending publication of the manuscript. Data will be shared for the purposes of further study or alternative analyses of the same data, and provided via electronic delivery. Data will be made available for one calendar year after the publication of the manuscript.

Declaration of interests

Shannon Brumbaugh, Wen Jan Tuan DHA, Alyssa Scott, James R. Latronica, and Curtis Bone attest that that they have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101524.

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